HYPOTENSION IN HEALTHY DOGS UNDERGOING ELECTIVE DESEXING

Submitted by

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DECLARATION

I declare that this thesis is my own account of my research and contains as its main content work which has not previously been submitted for a degree at any tertiary education institution.

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Renata Sampaio Costa

2014

DISCLAIMER

This Master in Philosophy (MPhil) thesis consists of chapters that have been prepared as stand-alone manuscripts. These manuscripts have either been published or have been submitted for publication. As a consequence, there may be some repetition between chapters and differences in formatting.

The manuscript "Frequency of hypotension in a historical cohort of anaesthetised dogs undergoing elective desexing" has been published in the Australian Veterinary Practitioner in June, 2013:

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GENERAL ABSTRACT

Hypotension is the most common complication during anaesthesia of dogs and contributes to anaesthetic-related morbidity. The frequency of hypotension reported in anaesthetised dogs is quite variable due to the lack of a standardised definition of hypotension and the number of different factors present in each study that could influence the results. In addition, there is no study in the veterinary literature that has attempted to identify animal factors that may influence perioperative mean arterial blood pressure (MAP).

The aims of this thesis were to document the proportion of healthy dogs developing hypotension during elective desexing at Murdoch University Veterinary Hospital (MUVH) and investigate patient factors influencing perioperative MAP during a surgical plane of anaesthesia. To achieve these aims, a historical cohort study and two prospective studies were performed. These studies were approved by the Murdoch University Animal Ethics Committee (AEC R239611).

The historical cohort study reviewed anaesthetic records from dogs desexed in general practice (GP) between 2007 and 2011. The aim was to determine the frequency of hypotension and explore associations between gender, age, body mass, heart rate and anaesthetic drugs with MAP. Hypotension was defined as MAP <60 mmHg for ≥10 minutes. Records from 188 dogs were included, 87/188 developed hypotension and the frequency of hypotension was higher in younger dogs. However, this study had limitations such as the use of a non-invasive technique for measuring MAP and various anaesthetic protocols were utilised. Prospective studies were thus performed to clarify the previous findings. These studies used invasive blood pressure monitoring (the most accurate method of measuring blood pressure) and a standardised anaesthetic protocol.

A prospective study was performed in dogs undergoing elective desexing in student neutering clinics between 2011 and 2012. To determine the proportion of hypotensive dogs, the average of 10 consecutive MAP measurements were recorded every five minutes. Hypotension was defined as above. To investigate factors that influenced MAP, the area under the MAP*time curve (AUC) from 10 minutes before to 40 minutes after the start of surgery was calculated using the trapezoidal method. Association of explanatory variables including gender, age, body mass, urine specific gravity (USG), packed cell volume and total solids with the AUC were explored using regression models. Thirty five of 71 dogs developed hypotension. The combination of age and USG best explained the MAP with age being positively and USG being negatively associated with MAP.

A second prospective study was performed to determine if the findings of the previous study could be corroborated in dogs undergoing desexing in GP, where dogs were hospitalised for a shorter period and surgery was performed by experienced veterinarians. As duration of anaesthesia was shorter, the AUC was calculated from 5 minutes before to 30 minutes after the start of surgery. Association of explanatory variables with AUC were explored. The proportion of hypotensive dogs was higher than in student neutering clinics with 17 of 24 dogs developing hypotension. Urine specific gravity was also found to be negatively associated with MAP, which was consistent with the previous study.

The observed proportions of hypotensive dogs support the recommendation for blood pressure monitoring during anaesthesia in healthy young dogs and the presence of subclinical dehydration suggested by increases in USG support the administration of intravenous fluids.

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ABBREVIATIONS

ACP	Acepromazine
AEC	Animal Ethics Committee
ANP	Atrial natriuretic peptide
ASA	American Society of Anesthesiologists
ATP	Adenosine triphosphate
AUC	Area under the curve
BM	Body mass
BSA	Body surface area
CI	Confidence interval
CO_2	Carbon dioxide
$ETCO_2$	End-tidal carbon dioxide
GP	General practice
HR	Heart rate
HZ	Hertz
IBP	Invasive blood pressure
IM	Intramuscular
IV	Intravenous
l	Length
MAP	Mean arterial blood pressure
mmHg	Millimetres of Mercury
MUVH	Murdoch University Veterinary Hospital
η	Blood viscosity
NIBP	Non-invasive blood pressure
NO	Nitric oxide
O_2	Oxygen

P	Pressure
PCV	Packed cell volume
pH	Potential of hydrogen
Qt	Cardiac output
r	Radius
R	Resistance
SAP	Systolic blood pressure
SpO_2	Oxyhaemoglobin saturation
SV	Stroke volume
SVR	Systemic vascular resistance
T	Ventricular wall tension
TS	Total solids
USG	Urine specific gravity
α	Alpha
β	Beta
π	Constant 3.14

CHAPTER 1 – LITERATURE REVIEW

Introduction

Morbidity and mortality associated with small animal general anaesthesia has increasingly been the focus of investigation. In dogs categorised as ASA I and II (American Society of Anesthesiologists health status classification), the reported rate of anaesthetic-related death has seemingly decreased from 0.12% in earlier studies (Clarke and Hall 1990) to 0.067% (Dyson et al. 1998) to 0.05% (Brodbelt et al. 2007). The reduction in mortality can be attributed to more comprehensive monitoring techniques and equipment, better trained practitioners and the development of safer drugs (Tuman 1991, Wagner and Hellyer 2000). However the frequency of mortality in dogs remains much higher than that reported in people, 0.01%-0.005% (Biboulet et al. 2001, Newland et al. 2002, Braz et al. 2006), supporting the need for further improvements to anaesthetic techniques (Dyson et al. 1998, Gaynor et al. 1999, Redondo et al. 2007, Brodbelt 2009, Bille et al. 2012). In order to improve the safety of anaesthesia in dogs, a greater understanding of the factors that contribute to anaesthetic related morbidity and mortality is required.

Hypotension has been identified as an important contributing factor to anaesthetic related mortality in people. A 3.6% increase in mortality risk in people within one year of anaesthesia for every minute of perioperative hypotension defined as systolic arterial blood pressure (SAP) <80 mmHg was reported (Monk et al. 2005). Hypotension has been identified as the most common cardiovascular complication in anaesthetised dogs (Gaynor et al. 1999, Redondo et al. 2007) and is likely to contribute to anaesthetic morbidity and mortality in this species (Redondo et al. 2007, Brodbelt 2009).

Studies in anaesthetised dogs demonstrate a wide variation in the frequency of hypotension from 7% (Gaynor et al. 1999) to 37.9% (Redondo et al. 2007). The reasons for this wide variation are not readily apparent. Both studies included animals that received different types of anaesthetic drugs and underwent a variety of procedures. The contribution of these factors to the development of hypotension was not investigated. In addition, the effect of patient health was not assessed and thus it is not known whether animals with lower ASA classification are more or less likely to develop hypotension. An additional factor that could have contributed to the differences in the frequency of hypotension in these studies is the definition of hypotension used. The definition of hypotension has been reported to cause the calculated frequency of perioperative hypotension to vary between 5% and 99% (Bijker et al. 2007). The lack of a consistent definition in anaesthetised dogs may help explain discrepancies in findings between studies.

Based on the limitations of the current studies, it is clear that further studies on the frequency and causes of hypotension in anaesthetised dogs are warranted. In order to appropriately investigate the frequency and causes of hypotension, it is essential to have an in-depth understanding of i) definition of normal and abnormal arterial blood pressure ii) the regulation of arterial blood pressure and iii) factors present in the perianaesthetic period that have the potential to alter regulation of blood pressure. These aspects are discussed in the following sections.

Definition of normal and abnormal blood pressure

There are a number of studies that provide a reference range for blood pressure in healthy conscious dogs (Kick et al. 1993, Hall et al. 2001, Redondo et al. 2007). In conscious dogs, normal blood pressure has been reported to be mean arterial blood

pressure (MAP) between 80 and 120 mmHg and/or systolic arterial blood pressure (SAP) between 100 and 160 mmHg, while hypotension is defined as MAP <60 mmHg and/or SAP <80 mmHg (Haskins 1993, Littman and Drobatz 1995, Gaynor et al. 1999, Hall et al. 2001). In contrast, the definition of hypotension under anaesthesia varies considerably between studies. This reflects in part the lack of information of what is considered an acceptable blood pressure in anaesthetised dogs. A summary of the definitions of hypotension in different studies is provided in Table 1.

Table 1. Summary of the definition of hypotension used in anaesthetised dogs

Definition of hypotension	References
SAP <90 mmHg or MAP <60 mmHg	Miyake et al. (2005)
SAP <80 mmHg or MAP <60 mmHg	Gaynor et al. (1999) Redondo et al. (2007)
SAP <80 mmHg	Muir and Wiese (2004) Aarnes et al. (2009)
MAP <70 mmHg	Gimenes et al. (2011)
MAP <60 mmHg	Ambros et al. (2008)

Systolic arterial blood pressure (SAP), mean arterial blood pressure (MAP)

The inconsistencies in the definition of hypotension probably reflect the lack of clear evidence linking a particular blood pressure to organ damage in the anaesthetised patient. There are also inconsistencies between authors as to whether the MAP or the SAP is the most important, although the majority of literature focuses on the importance of MAP for organ perfusion. It is generally considered that a MAP >60-65 mmHg is required to maintain perfusion to vital organs such as the brain and the kidneys (LeDoux

et al 2000, Muir and Mason 1996). At a MAP of <70-80 mmHg the kidney loses its ability to autoregulate the blood supply and, as a result, renal blood flow decreases linearly with decreases in MAP. Eventually this decrease in renal blood flow will result in ischaemic renal damage (Rosen et al. 1972, Mason 1993, Guyton and Hall 2000, DiBartola 2006) however the point at which clinically significant damage occurs has not been clearly determined.

Regulation of blood pressure

To appreciate how patient factors and anaesthesia affect blood pressure, it is essential to have in-depth understanding of how blood pressure is regulated. For the purposes of this thesis, discussion of blood pressure regulation will focus on MAP.

Mean arterial blood pressure is the product of systemic vascular resistance (SVR) and cardiac output (Qt) (MAP = SVR × Qt). Cardiac output is the product of heart rate and stroke volume (Qt = HR × SV) and represents the volume of blood ejected into the arteries per minute. These factors are discussed in more detail in the following sections.

Systemic vascular resistance

Systemic vascular resistance is influenced by the diameter of vessels, particularly the radius of arterioles (Hagen-Poiseuille equation: $R = 8 \times 1 \times \eta / \pi r^4$; where R is resistance, l is length, η is blood viscosity, π is the constant 3.14, and r is the vessel radius). As vessel radius increases and vessel length and blood viscosity decrease, vascular resistance decreases (Muir and Mason 1996) resulting in vasodilation and reductions in blood pressure. The radius of small arteries and arterioles is altered by relaxation and contraction of the vascular smooth muscle cells and this, in turn, is regulated by several local and systemic factors (Mayet and Hughes 2003). Relaxation of

vascular smooth muscle in most tissues is mediated by decreases in circulating cathecholamine, oxygen (O_2) tension and potential of hydrogen (pH), histamine, carbon dioxide (CO_2) tension, local temperature, atrial natriuretic peptide (ANP), adenosine triphosphate (ATP) and nitric oxide (NO). In certain organs such as skeletal muscle and liver, increases in circulating epinephrine mediate relaxation of vascular smooth muscle via stimulation of β adrenergic receptors. Conversely, contraction of vascular smooth muscle is mediated by increases in circulating catecholamines (except epinephrine in skeletal muscle and liver) and decreases in local temperature (Muir and Mason 1996, Sjaastad et al. 2003).

Blood viscosity can also affect SVR but the effect is limited, except in severe anaemia or polycythaemia (>65%) (Thomas 2002). Blood viscosity is affected by haematocrit concentration, elongation and aggregation of red blood cells and plasma viscosity (Zhao et al. 2009, Hoffman 2011). Plasma viscosity mainly depends on the concentration of high-molecular weight proteins (Koppensteiner 1996). Hyperproteinemia and increase plasma viscosity may occur during dehydration due to inadequate water intake or excessive water loss (i.e. severe vomiting, diarrhoea) (Muir and Mason 1996). Increases in blood viscosity lead to increases in shear stress on the endothelium and NO production which causes vasodilation due to relaxation of smooth muscle cells. This decreased resistance to blood flow results in decreases in MAP (Salazar Vazquez et al. 2010). Decreased blood viscosity has been reported due to dilution of plasma proteins during administration of large volumes of intravenous (IV) fluids (Muir et al. 2011).

As well as influencing blood pressure directly, SVR also alters arterial blood pressure by altering cardiac afterload and therefore Qt. The effects of afterload on Qt are discussed in more detail below.

Stroke volume

Stroke volume is determined by three factors: myocardial contractility, afterload and preload (Muir and Mason 1996, Miyake 2005, Mark and Slaughter 2005). A reduction in contractility, preload or an increase in afterload decrease SV and thus Qt.

Myocardial contractility is the intrinsic ability of the heart to develop force for a given muscle length (James and Jonas 2009). The generation of contractile force depends on the interaction between thick (myosin) and thin (actin) filaments and the degree of binding between these filaments depends on the concentration of calcium ions in the cell (Muir and Mason 1996). Changes in the concentration of this ion play an important role in the control of myocardial contractile force (Rusy and Komai 1987, Muir and Mason 1996). Sympathetic stimulation and release of catecholamines activates β adrenergic receptors in the heart leading to phosphorylation of calcium membrane channels, increasing calcium entry into the myocyte (Sher et al. 2008). Increase in intracellular calcium triggers the release of calcium (calcium-induced calcium release) from the sarcoplasmic reticulum resulting in an increase in intracellular calcium ion concentration. Calcium promotes actin-myosin interactions which cause an increase in myocardial contractility (Rusy and Komai 1987, Muir and Mason 1996). Conversely, decreases in intracellular calcium will decrease contractility and may result in decreased Qt and thus MAP.

Afterload is the tension generated in the myocardium of the left ventricle during cardiac ejection (Muir and Mason 1996, Sjaastad et al. 2003). Ventricular wall tension (T) is dependent on pressure gradient (P) and radius (r) (Laplace's law; $T = Pr$). If SVR increases, pressure gradient or resistance to ejection of blood increases resulting in decreased stroke volume and thus Qt. This results in an increase in end-systolic volume

and afterload (Sjaastad et al. 2003). Increased afterload also decreases Qt by decreasing the velocity of fibre shortening and thus contractile force (Muir and Mason 1996). However, this is in part offset by increases in preload (see below) that result from more blood remaining in the ventricle thus helping SV and Qt return to normal (Klabunde 2011).

Preload represents left ventricular end-diastolic volume which in turn influences the resting or pre-contraction fibre length (Frank-Starling's law) and the inherent state of activity of the contractile apparatus (actin and myosin filaments) within the myocyte (Prys-Roberts et al. 1972). Preload is affected by blood volume returning to the heart (venous return) and the stiffness in the cardiac muscle wall (Muir and Mason 1996, Sjaastad et al. 2003). Venous return depends on the pressure gradient between the peripheral and central veins, which is influenced by absolute changes in blood volume or by an alteration in the size or capacitance of the vessels. Within a certain range, an increase in end-diastolic volume increases the length of the cardiac muscle fibre and allows more cross-bridges to form between the actin and myosin filaments, subsequently allowing a greater force to be generated during myocardial contraction and an increased SV (Mazzaferro and Wagner 2001, Sjaastad et al. 2003). A decrease in preload will reduce SV and subsequently Qt (Mazzaferro and Wagner 2001).

Heart rate

Hear rate is primarily regulated by the autonomic nervous system. Alterations in heart rate are usually due to changes in activity of both sympathetic and parasympathetic activities. An increased heart rate is normally the result of reduced parasympathetic activity combined with increased sympathetic activity while a reduced heart rate is caused by the reverse changes (Sjaastad et al. 2003). Decreases in heart rate or

bradycardia decrease Qt by decreasing the number of times the heart pumps every minute and thus the total amount of blood pumped per minute. Conversely, severe tachycardia can also decrease Qt by decreasing ventricular filling time.

Intrinsic cardiovascular reflexes

There are several intrinsic cardiovascular reflexes that act to modify blood pressure. Baroreceptors and stretch receptors present in the aortic and carotid arteries detect changes in wall tension. The decrease in wall tension that accompanies decreased blood pressure results in decreased parasympathetic activity and increased sympathetic neural activity. The increase in sympathetic nerve system activity leads to increases in heart rate, myocardial contractility and systemic vasoconstriction. The opposite occurs when increased blood pressure causes an increase in wall tension (Kirchheim 1976, Jordan et al. 2002, Moranville et al. 2011).

There are a variety of cardiopulmonary reflexes that also aid in the stabilization of MAP by controlling blood volume and vascular tone. Atrial mechanoreceptors with myelinated vagal afferents are stimulated by increases in atrial volume and/or pressure resulting in vasodilation and tachycardia (Bainbridge reflex). Ventricular mechanoreceptors in the left ventricle and coronary arteries are stimulated by increases in ventricular diastolic pressure and afterload, resulting in vasodilation Ventricular chemoreceptors are stimulated by bradykinin and prostaglandins released during ischaemia or in response to administration of some intravenous drugs, resulting in increased parasympathetic activity, decreased sympathetic activity and subsequently bradycardia, vasodilation and hypotension (Bezold-Jarisch effect) (Muir and Mason 1996, Constanzo 1998).

Chemoreceptors, located in the carotid and aortic bodies, are activated by changes in pH (i.e. acidosis), hypocapnia and decreases in blood oxygen that occur during the reduction in perfusion that accompanies decreases in blood pressure. The chemoreceptor reflexes mainly act to increase ventilation but also increase blood pressure through the sympathetic stimulation of cardiovascular system which results in constriction of arterioles (mainly skeletal muscle), splanchnic venoconstriction and increases in heart rate (Muir and Mason 1996, Constanzo 1998).

Factors influencing blood pressure regulation during anaesthesia

Arterial blood pressure can be altered by changing any of the regulatory mechanisms of blood pressure discussed previously. During anaesthesia, many factors have the potential to reduce MAP by acting either alone or in combination. These include pharmacological factors (anaesthetic agents) and physiological factors (animal characteristics).

Anaesthetic agents

The most common cause of hypotension during anaesthesia of people is the anaesthetic drugs (Morris et al. 2005). Similar studies have not been performed in dogs. However, nearly all of the commonly used sedative, analgesic and anaesthetic agents are capable of altering cardiovascular function in the perianaesthetic period (Parry et al. 1982, Nakamura et al. 1992, Grimm et al. 2001) and thus predisposing to hypotension. Alterations in cardiovascular function are mediated by altering SVR, myocardial contractility, afterload preload and/or heart rate (Sebel and Lowdon 1989, Valverde et al. 2006, Monteiro et al. 2007).

A discussion of the reported effects of some of the most commonly used anaesthetic agents (acepromazine, morphine, methadone, propofol, alfaxalone, diazepam, ketamine and isoflurane) on cardiovascular function is presented below.

Decreased systemic vascular resistance

Decreased SVR during anaesthesia is due to drug mediated arteriolar vasodilation. Vasodilation is caused by many sedative and anaesthetic agents, including acepromazine (ACP), propofol, alfaxalone and isoflurane.

Acepromazine is a phenothiazine tranquiliser commonly used for premedication in dogs, usually in combination with an opioid analgesic agent. Acepromazine causes peripheral vasodilation by antagonising α_1-adrenoreceptors (Parry et al. 1982), resulting in decreases in blood pressure which tends to increase with increasing doses (Brock 1994, Monteiro et al. 2008). Occasionally, the decrease in blood pressure is accompanied by a compensatory tachycardia (Soma 1971, Ludders 1983, Monteiro et al. 2007).

Propofol (2, 6-diisopropylphenol) is a nonbarbiturate IV hypnotic agent widely used for induction and maintenance of anaesthesia in small animal patients. Administration of propofol, particularly at high doses and rapid IV infusion is associated with significant alteration in blood pressure (Scheepstra et al. 1989, Nakamura et al. 1992, Nakaigawa et al. 1995). However, this mechanism is not completely understood. The decrease in blood pressure associated with propofol administration has been attributed to vasodilation and decreased SVR (Sebel and Lowdon 1989, Fusellier et al. 2007) mediated via the release of nitric oxide by the vascular endothelium (Petros et al. 1993). However mechanism has been refuted by *in vitro* studies which have failed to

demonstrate a direct vasodilator effect of propofol in isolated canine peripheral arteries at clinical concentrations (Nakamura et al. 1992). Regardless of how propofol causes hypotension, it is known that its effect is dose-related (Nakaigawa et al. 1995, Xu et al. 2000) and can be more pronounced in patients with reduced blood volume (Marik 2004).

Alfaxalone (3 a-hydroxy-5 a-pregnane-11, 20-dione) is a synthetic neuroactive steroid that produces a rapid and smooth induction of anaesthesia in dogs and cats (Ferre et al. 2006, Muir et al. 2008). Decreases in MAP after induction of anaesthesia in dogs receiving therapeutic doses of alfaxalone have been attributed in part to peripheral vasodilation (Muir et al. 2008).

Inhaled anaesthetics are commonly used for maintenance of general anaesthesia (Valverde et al. 2006, Moppett 2008). Isoflurane is one of the most widely used volatile anaesthetic agents. Most studies show that isoflurane causes dose dependent reduction in MAP due to a decrease in SVR (Skovsted and Sapthavichaikul 1977, Van Aken et al. 1986, Gaynor et al. 1999, Tomiyasu et al. 1999, Valverde et al. 2006).

Decreased myocardial contractility

Myocardial contractility may be reduced due to the direct effect of some anaesthetic drugs, such as isoflurane, propofol and ketamine (Muir and Mason 1996, Mazzaferro and Wagner 2001). The reduction in contractility associated with the anaesthetic agents will exacerbate decreases in blood pressure associated with vasodilation.

Isoflurane has been reported to cause dose dependent decreases in myocardial contractility in dogs (Conzen et al. 1989) by reducing the calcium influx or calcium

reuptake by the sarcoplasmic reticulum (Rusy and Komai 1987, Muir and Mason 1996). However, the myocardial depression is less profound than that reported for other inhalants such as halothane and enflurane (Tarnow et al. 1977, Valverde et al. 2006, Moppett 2008).

Ketamine (2-[o-chlorophenyl]-2-[methlyamino] Cyclohexanone) is a nonbarbiturate phencyclidine derivative with potent sedative, hypnotic and analgesic properties (Hostetler and Davis 2002, Ng and Ang 2002). It is commonly used for induction of anaesthesia in combination with diazepam. In dogs, ketamine alone or in combination with diazepam may depress myocardial contractility (Diaz et al. 1976), increase heart rate and left ventricle work (Haskins et al. 1985, Haskins and Patz 1990). In people, IV ketamine administered alone results in increases in heart rate and significant decreases in cardiac contractility (Waxman et al. 1980). However, the indirect sympathomimetic effect of ketamine is assumed to dominate over its direct negative inotropic properties, resulting in reduced risk of hypotension (Tobias and Rasmussen 1994).

Alterations in afterload

Afterload may be affected by SVR, ventricular chamber size and wall thickness. The effect of anaesthetic agents on afterload is predominantly through changes in SVR which has been discussed in detail above.

Alterations in preload

Anaesthetic agents can also decrease blood pressure by altering preload predominantly by venodilation and decreased amount of venous blood returning to the heart. Propofol administration is believed to decrease blood pressure in anaesthetised dogs (Goodchild

and Serrao 1989) and people (Muzi et al. 1992) by a direct effect on venous smooth muscle tone resulting in venodilation.

Alterations in heart rate

Sedative, analgesic and anaesthetic agents can affect blood pressure during anaesthesia by altering the heart rate directly through alterations in autonomic nervous system activity or by decreasing baroreflex sensitivity and inhibiting changes in heart rate that compensate for changes in blood pressure (Kruse-Elliot 2002, Miyake 2005).

Opioid analgesic agents such as morphine and methadone may decrease the heart rate and thus Qt due to an increase in parasympathetic nervous system activity (Stanley et al. 1980, Maiante et al. 2009, Garofalo et al. 2012). Premedication with morphine has been reported to decrease heart rate during isoflurane-anaesthesia (Cahalan et al. 1987). This effect can override the effects of other anaesthetic drugs on the heart rate.

Drug induced inhibition of the baroreceptor reflex activity can prevent the reflex changes in heart rate in response to decreases in blood pressure preventing MAP from returning to normal (Morris et al. 2005). Thus any agent that inhibits this reflex will increase the risk of prolonged hypotension. In dogs, lack of a reflex increase in heart rate during isoflurane-induced hypotension has been reported (Davis and Avner 1989, Aarnes et al. 2009). Also, propofol-induced hypotension was also observed in conjunction with an unchanged heart rate in dogs (Nakaigawa et al. 1995), rabbits (Xu et al. 2000) and people (Claeys et al. 1988), suggesting that there is no increase in heart rate to partially compensate the decrease in SVR.

Animal characteristics

Age, gender, body mass, body condition score and temperament have been reported to influence cardiac function (Page et al. 1993, Vollmar 1999, Schober and Fuentes 2001, Muzzi et al. 2006) and blood pressure measurements in awake and anaesthetised dogs (Bodey and Michell 1996, Bodey and Rampling 1999, Bright and Dentino 2002, Sanan and Arslan 2007). Abnormalities in physiological function such as hydration may also contribute to decreases in MAP during general anaesthesia. These factors may influence the risk of an animal developing hypotension when certain anaesthetic agents are used. These contributing factors are discussed in more detail below.

Gender

In a study of conscious dogs, gender differences in blood pressure were reported with higher blood pressures being observed in male dogs than in females (Mishina et al. 1997). However, another study reported that gender did not have a significant effect on blood pressure (Sanan and Arslan 2007). Also, in people, no differences between induction doses of propofol and related side effects, such as hypotension, were observed between males and females (Scheepstra et al. 1989) but similar studies have not been done in dogs.

Age

Both young and very old patients have alterations in the cardiovascular system that increase the risk of decreases in MAP during anaesthesia. A greater degree of cardiovascular depression was observed in anaesthetised foals in comparison to adult horses (Read et al. 2002, Craig et al. 2007). Studies in people have also demonstrated a higher frequency of hypotension during anaesthesia of healthy children in comparison to adults (Morris et al. 2005). While similar studies in anaesthetised dogs have not been

performed, studies in conscious dogs have demonstrated developmental changes in cardiovascular function and blood pressure that could contribute to lower blood pressure in younger dogs during anaesthesia. Studies in healthy conscious dogs have reported lower MAP in younger (<12 months old) dogs compared to older (>12 months old) dogs (Bodey and Michell 1996, Sanan and Arslan 2007). Bodey and Michell (1996) reported that 6 months old dogs have mean MAP of 79.2 mmHg (standard error of 1.76) compared to mean MAP of 92.9 mmHg (standard error of 0.83) in dogs aged 12 to 24 months. It has been reported that right ventricle contractile performance improves greatly from 3 to 9 months of age due to increases in number of sarcomeres with twice as many sarcomeres present by 9 months of age. Cardiac function is also improved by the presence of a greater intercellular adhesive strength in the right ventricular myocytes and contractility (Urthaler 1978). In puppies (21 to 40 days of age) development of the sympathetic nervous system is incomplete which may compromise the regulation of cardiac function and blood pressure in this age group (Mace and Levy 1983). Sympathetic nervous system activity improves as the animal ages. The immaturity of the cardiovascular nervous system and the sympathetic nervous system may explain the lower MAP observed in younger dogs when compared with older dogs.

Geriatric dogs have reduced cardiopulmonary reserves that could contribute to decreased capacity to respond to the depressant effects of anaesthetic agents (Meyer 1999). Minimal studies have been done comparing changes in blood pressure in geriatric patients with younger cohort however studies did demonstrate a higher frequency of hypotension in geriatric people (60 to 85 years old) after induction of anaesthesia with propofol when compared to younger patients aged between 18 to 35 years old (Kirkpatrick et al. 1988, Kazama et al. 1999).

Body mass and body condition score

Body condition and body mass are important factors influencing cardiac function in dogs. In conscious dogs, higher body condition score is reported to reduce filling of the left atrium and left ventricle (Schober and Fuentes 2001). It has been reported that extremes of dog weight are associated with increased anaesthetic related mortality (Brodbelt et al. 2008). An overweight dog may be at a greater risk of having complications during anaesthesia due to a reduction in cardiovascular reserves, impaired venous return to the heart and prolonged recovery (Hall et al. 2001). In people anaesthetised with propofol, no significant differences in patients' body mass and propofol-related decreases in blood pressure and heart rate were found (Kazama et al. 1999, Ishiyama et al. 2003), but similar studies have not been done in dogs nor evaluate other drugs and their cardiovascular effects.

Temperament

An animal's temperament may influence the effects of some drugs on the cardiovascular system. Greater decreases in blood pressure have been reported in anxious animals receiving ACP when compared to calm animals. This is attributed to the increase in circulating catecholamines (norepinephrine and epinephrine) that occur in stressed animals (Brock 1994, Vaisanen et al. 2002). Although, norepinephrine and high dose epinephrine typically cause α-adrenergic receptor mediated vasoconstriction, epinephrine can also produce vasodilation at lower concentrations due to β-2 effects on skeletal muscle leading to "orthostatic" hypotension. When α-1 activity is blocked by acepromazine, β-2 activity can prevail, resulting in additional vasodilation and thus greater decreases in blood pressure than that caused by ACP alone (Dugdale 2010).

Physiological abnormalities

In clinically normal animals, it is unlikely that physiological abnormalities associated with disease processes contribute to decreases in MAP during anaesthesia. However, there is a significant increase in the frequency of hypotension as the anaesthetic risk increases (Redondo et al. 2007). Dogs and cats classified as ASA III, IV and V have a worse prognosis and higher risk of anaesthetic related death than ASA I and II animals (Brodbelt et al. 2008, Bille et al. 2012).

The most common abnormality expected to affect blood pressure in a healthy animal is absolute hypovolaemia due to blood loss secondary to surgical complications. Absolute hypovolaemia can also be caused by dehydration (James and Jonas 2009, Moranville et al. 2011). Dehydration is defined as a decrease in total body water and can be caused by increased water loss due to illness (causing vomit or diarrhoea) and reduced water intake. Typically, dehydration exceeding 10% of body water significantly impacts blood volume and blood pressure in conscious animals (Hinton 1987). This degree of dehydration is unlikely to be present in a healthy animal requiring anaesthesia for an elective procedure.

Subclinical dehydration could be present in clinically healthy animals. Whether this level of dehydration could negatively impact cardiovascular function during anaesthesia is not known. A possible cause of subclinical dehydration in healthy animals requiring anaesthesia is reduction in water intake due to fasting and/or reduced intake during hospitalisation. Food deprivation has been shown to decrease water intake in several species, including dogs (Morris and Collins 1967, Kutscher 1969). As animals are routinely fasted prior to anaesthesia to reduce the risk of vomiting and regurgitation, this could contribute to a reduction in water intake preoperatively. Decreases in water intake

of 25 to 50% of the normal volume in dogs have been reported after a one day fast (Chew 1965).

In people, preoperative fasting results in a fluid deficit of approximately 1 litre (Holte and Kehlet 2002). Prolonged preoperative fasting can result in decreases in total body water and circulating blood volume as a result of ongoing urine production and insensible perspiration. If an animal is hospitalised for an extended period prior to anaesthesia, the stress associated with the unfamiliar environment may further reduce food and water intake. Animals with subclinical dehydration may not present with overt clinical signs, but the reduction in total body water could alter the ability to compensate for the effects of anaesthetic agents on MAP.

Summary and Aims

The reported frequency of hypotension is variable and none of the current studies have attempted to ascertain the factors that influenced the frequency of hypotension in their study group. It is clear that many factors have the potential to contribute to the development of hypotension during anaesthesia. The most notable of these factors are the effects of pharmacologic agents used for premedication, induction and maintenance of anaesthesia. However, it is unclear why administration of these agents causes hypotension in some dogs but not others. This raises the question as to whether there are other factors that may influence the occurrence of hypotension in some dogs.

The aims of this thesis were to document the proportion of healthy (ASA I) dogs with hypotension (MAP<60 mmHg) during elective desexing at Murdoch University Veterinary Hospital (MUVH) and to investigate patient factors that may influence the measured perioperative MAP during a surgical plane of anaesthesia. To achieve these aims, a historical cohort study of healthy anaesthetised dogs desexed in general practice and two prospective studies of healthy dogs undergoing elective desexing in student neutering clinics and in general practice were performed.

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CHAPTER 2 – FREQUENCY OF HYPOTENSION IN A HISTORICAL COHORT OF ANAESTHETISED DOGS UNDERGOING ELECTIVE DESEXING

Abstract

The aim of this study was to determine the frequency of hypotension (based on mean arterial pressure measurements; MAP) in healthy dogs that were anaesthetised for elective desexing at Murdoch University Veterinary Hospital (MUVH). The secondary aim was to explore any association between gender, age, body mass, heart rate and anaesthetic induction agent with MAP. We hypothesised that MAP less than 60 mmHg would occur in at least 40% of healthy anaesthetised dogs. A historical cohort study was performed using anaesthetic records from dogs desexed by clinicians in the general practice service at MUVH between 2007 and 2011. Each dog was categorised according to the following criteria: I) hypotension - the lowest MAP present for at least two consecutive measurements was less than 60 mmHg, II) mild hypotension - the lowest MAP present for at least two measurements was between 60–79 mmHg and III) normotension - all MAP measurements were between 80–120 mmHg. The frequency of each category (point estimate, 95% confidence interval - CI) was calculated. Records from 188 dogs were included with 87/188 (0.46; 95% CI 0.39-0.53) categorised as hypotensive, 72/188 (0.38; 95% CI 0.31-0.45) as mildly hypotensive and 29/188 (0.15; 95% CI 0.10-0.21) as normotensive. Normotensive dogs were significantly older than hypotensive and mildly hypotensive dogs (P=0.0003 and 0.009 respectively) and hypotensive dogs had significantly lower body mass than mildly hypotensive dogs and normotensive dogs (P=0.008 and P=0.015 respectively). The frequency of hypotension

was significantly higher when acepromazine and methadone was administered compared to acepromazine and morphine. The frequency of hypotension observed in the current study was at least as high as hypothesised at approximately 40%. This supports the concern that the development of hypotension is not infrequent and monitoring and managing blood pressure in healthy dogs is important. The significantly higher frequency of hypotension in younger and smaller dogs suggests modification of anaesthetic techniques may be warranted. *Aust Vet Pract* 2013;43(2):414-419.

Introduction

The frequency of anaesthetic related mortality in healthy (American Society of Anesthesiologists health status classification - ASA I) dogs has been reported to be 0.05%[1], 0.067%[2] and 0.12%.[3] Major causes of perioperative death in small animals include cardiovascular complications.[1,4] Hypotension is reported to be the most common cardiovascular complication observed during small animal anaesthesia.[1,4,5] Currently there are limited studies investigating hypotension in small animals. These studies demonstrate a wide variation in frequency of hypotension from 7%[5] to 37.9%.[4] Reasons for the wide variation between these studies are not readily apparent. Both studies included animals that received different types of anaesthetic drugs and underwent a variety of procedures. The contribution of these different factors to the development of hypotension was not investigated. In addition, these studies included animals with a wide variety of ASA classifications and the effect of this on the frequency of hypotension was also not assessed.

Assessment of the association of hypotension in small animals with ASA scoring may be helpful in developing anaesthetic protocols. Investigation of the contribution of animal factors and different anaesthetic agents to the frequency of hypotension is

needed. This information can then be used to develop anaesthetic techniques that will reduce the frequency of hypotension in anaesthetised animals.

The aim of the study was to identify the lowest mean arterial pressure (MAP) recorded during anaesthesia of healthy dogs (ASA I) undergoing elective desexing and estimate the frequency of hypotension (MAP <60 mmHg), mild hypotension (MAP 60–79 mmHg) and normotension (MAP 80–120 mmHg). It was hypothesised that at least 40% of healthy anaesthetised dogs at MUVH would be categorised as hypotensive. An additional aim was to explore any difference in age and body mass across MAP categories or any association between animal factors such as gender and agents used for premedication and induction of anaesthesia, with MAP. The presence of abnormalities in other physiologic variables such as heart rate and temperature was also recorded.

Materials and methods

Anaesthetic records

Anaesthetic records from healthy dogs (ASA I) undergoing anaesthesia for elective desexing in general practice at MUVH between 2007 and 2011 were reviewed. Information obtained from anaesthetic records included the signalment (gender, age and body mass), type and dose of premedicant, and the type and dose of induction agent used.

Premedication included acepromazine (ACP2, Ceva Animal Health) combined with morphine (Hospira Australia) or methadone (Ilium methadone - Troy Labs). Anaesthetic induction agents included propofol (Fresofol 1% - Fresenius Kabi Australia), alfaxalone (Alfaxan, Jurox) and diazepam (Ilium diazepam, Troy Labs) combined with ketamine (Parnell Australia). The maintenance anaesthetic agent used in

all cases was isoflurane (ISO, Veterinary Companies of Australia) vaporised into 100% oxygen.

Data for blood pressure and heart rate were also retrieved from the anaesthetic records. The blood pressure and heart rate had been recorded using the Surgivet V9203 multivariable monitor (Polymount GCX® Corporation, CA, USA). The Surgivet measures arterial blood pressure using the non-invasive oscillometric technique.

Data analysis

The dogs in this study were categorised according to the following criteria: I) hypotension - the lowest MAP recorded on the anaesthetic record for at least two consecutive measurements was <60 mmHg; II) mild hypotension - the lowest MAP recorded for at least two consecutive measurements was between 60–79 mmHg; and III) normotension - all MAP measurements were between 80–120 mmHg. As oscillometric methods for measuring blood pressure can be affected by animal and environmental factors, two consecutive measurements were used to define the categories to increase the likelihood that the measurement reflected the true physiologic state of the animal. Since physiologic variables were noted on the anaesthetic record at five minute intervals, this equated to at least 10 minutes. The criteria used to define each category was based in part on published normal and abnormal blood pressure measurements.[6-9]

Hypotension was defined as MAP <60 mmHg since this is the value that is consistently reported to increase the risk of organ damage, particularly the kidneys. Normotension was defined using the reported reference interval for conscious dogs. Mild hypotension was defined between the minimally acceptable value of 60 mmHg and the lower end of normal at 80 mmHg. Mild hypotension was included as any decrease in MAP below

normal will result in a decrease in renal blood flow[10] although the clinical implications of these decreases on organ function have not been established. The proportion of dogs within each MAP category was the response of interest and the point estimate and the 95% confidence interval (CI) was calculated using methods for proportions. Statistical software (SAS v9.3, SAS Institute, Cary, NC) was used for the calculations.

For hypotensive and mildly hypotensive dogs, the heart rate was calculated as the mean of the heart rate measurements that coincided with the MAP measurements used to define the blood pressure category. The mean heart rate recorded at this time was calculated and then categorised according to the following criteria based on published normal and abnormal heart rates[5,11]: I) low - heart rate <80 beats per minute (bpm); II) normal - heart rate 80–150 bpm; III) high - heart rate >150 bpm. For dogs that remained normotensive throughout the anaesthetic, heart rates recorded for the duration of anaesthesia were assessed to determine if the heart rate was observed to fall into one of the above categories for two or more consecutive readings. If the heart rate varied, for example, normal and low heart rate for more than two consecutive readings, the dog would be included in the low heart rate category. The same protocol was used if the dog had normal and high heart rate during the procedure; the dog would be included in the high heart rate category.

Age and body mass were summarised for each MAP category as median and range. The age and body mass were compared across categories using the Kruskal-Wallis rank sum test with the two-sided null hypothesis of no difference rejected at $P<0.05$. Post-hoc comparisons across MAP categories were made using the Kruskal-Wallis procedure with significance determined at a Bonferroni-adjusted $P<0.017$. The MAP categories were stratified according to possible explanatory variables including gender, heart rate,

premedicant and induction agent. The proportion of dogs in each MAP category was reported across the explanatory strata. The association between the possible explanatory variables and MAP category was explored using univariate analysis. A Fisher's exact test was performed for each explanatory variable with the two-sided null hypothesis of no association rejected at $P < 0.05$. The doses of premedicants and induction agents across body mass (kg) were graphed for visual assessment of any dispersion. Statistical software (SAS) was used for the analyses.

Results

A total of 188 anaesthetic records from healthy dogs desexed in the general practice at MUVH between 2007 and 2011 were suitable for inclusion. A total of 87/188 (0.46; 95% CI 0.39-0.53) dogs were categorised as hypotensive, 72/188 (0.38; 95% CI 0.31-0.45) dogs were categorised as mildly hypotensive and 29/188 (0.15; 95% CI 0.10-0.21) dogs were categorised as normotensive.

There was a significant difference between MAP categories for age (P=0.001) and body mass (P=0.008). Normotensive dogs were significantly older than hypotensive and mildly hypotensive dogs (P=0.0003 and 0.009 respectively). Dogs with hypotension had significantly lower body mass than dogs with mild hypotension (P=0.008) (Table 1). There was no association of gender with MAP categories (P=0.319).

All 188 dogs included in this study received acepromazine in combination with a μ opioid agonist. The opioid agonists were morphine in 133 dogs and methadone in 55 dogs. Premedication was administered by intramuscular injection before induction of anaesthesia in all dogs. There was a significant association of premedicant and MAP category (P=0.012). There was a significantly higher frequency of administration of

methadone and acepromazine in hypotensive dogs and significant lower frequency in normotensive dogs (Tables 2 and 3). There was considerable variation of the dose of acepromazine across body mass (Figure 1).

Table 1. Signalment (gender, age and body mass) of 188 healthy dogs undergoing desexing. Dogs were categorised according to mean arterial pressure recorded during anaesthesia (hypotension, MAP <60 mmHg; mild hypotension, MAP 60-79 mmHg; normotension, MAP 80-120 mmHg). Frequencies are reported with proportions in parentheses and age and mass are summarised as median (range). *Indicates significantly different from other MAP categories (P ≤0.017, Bonferroni-adjusted)

		Hypotension	Mild hypotension	Normotension	Total
Gender	All	87 (0.46)	72 (0.38)	29 (0.15)	188
	Male	31 (0.53)	21 (0.36)	6 (0.10)	58 (0.31)
	Female	56 (0.43)	51 (0.39)	23 (0.18)	130 (0.69)
Age (months)	All	6 (6-91)	7 (6-70)	12 (6-60)*	
	Male	7 (6-84)	9 (6-49)	24 (7-60)	
	Female	6 (6-91)	7 (6-70)	12 (6-48)	
Body mass (kg)	All	9.6 (1.5-30.2)*	13.8 (2-30.5)	7.2 (3.3-27.9)	
	Male	7.6 (3.3-27.5)	10.8 (2-30)	8 (3.3-22.7)	
	Female	11.8 (1.5-30.2)	14.2 (2.3-30.5)	7 (3.7-27.9)	

Out of 188 anaesthetic records reviewed, the anaesthetic induction agent was recorded in 142 records and 110/142 dogs (0.77) received propofol, 12/142 (0.08) received alfaxalone and 20/142 (0.14) received diazepam/ketamine (Table 2).There was no significant association between induction agent and MAP category (P=0.252). Collapsing induction categories to propofol versus other showed no association with MAP category (P=0.130).

Only 3/188 (0.02) dogs had a heart rate < 80 bpm and two of these dogs were hypotensive. No association was found between heart rate and MAP category (P=0.142). Measurements of body temperature were incomplete with only 27 records containing information on body temperature and in the majority of these cases, temperature was only measured at the end of surgery. No statistical analysis was performed on the body temperature data.

Table 2. Anaesthetic drugs (premedicants and induction agents) used and heart rate of 188 healthy dogs undergoing desexing. Dogs have been categorised according to mean arterial blood pressure recorded during anaesthesia (hypotension, MAP<60 mmHg; mild hypotension, MAP 60-79 mmHg; normotension, MAP 80-120 mmHg). Frequencies are reported with proportions in parentheses. bpm = beats per minutes

		Hypotension	Mild Hypotension	Normotension	Total
Premedicant	ACP+morphine	54 (0.41)	53 (0.40)	26 (0.20)	133 (0.71)
	ACP+methadone	33 (0.60)	19 (0.35)	3 (0.05)	55 (0.29)
	Number of records	87	72	29	188
Induction agent	Propofol	52 (0.47)	37 (0.34)	21 (0.19)	110 (0.77)
	Alfaxalone	5 (0.42)	7 (0.58)	0	12 (0.08)
	Diazepam/ Ketamine	11 (0.55)	7 (0.35)	2 (0.10)	20 (0.14)
	Number of records	68	51	23	142
Heart rate (bpm)	Normal (80–150)	62 (0.42)	60 (0.41)	25 (0.17)	147 (0.78)
	High (>150)	23 (0.61)	11 (0.29)	4 (0.11)	38 (0.20)
	Low (<80)	2	1	0	3
	Number of records	87	72	29	188

Table 3. Median (range) dose of premedicants and induction agents (mg/kg) used for 188 healthy dogs undergoing desexing surgery. Dogs have been categorised according to mean arterial blood pressure recorded during anaesthesia (hypotension, MAP <60 mmHg; mild hypotension, MAP 60-79 mmHg; normotension, MAP 80-120 mmHg). ACP = acepromazine

			Hypotension n = 87	Mild hypotension n = 72	Normotension n = 29
Premedicant	ACP + Morphine	ACP	0.04 (0.01–0.09)	0.05 (0.01–0.09)	0.05 (0.01–0.09)
		Morphine	0.3 (0.1–0.4)	0.3 (0.2–0.4)	0.3 (0.07–0.5)
	ACP + Methadone	ACP	0.05 (0.02–0.07)	0.05 (0.02–0.08)	0.04 (0.04–0.07)
		Methadone	0.3 (0.08-0.4)	0.3 (0.3–0.4)	0.3 (0.3–0.4)
Induction agent	Propofol		3.5 (1–6)	3.4 (2–7)	3.8 (1–7)
	Alfaxalone		1.6 (1–2)	1.3(1–2)	-
	Diazepam + Ketamine	Diazepam	0.2 (0.1–0.3)	0.3 (0.1–0.2)	0.2 (0.1–0.2)

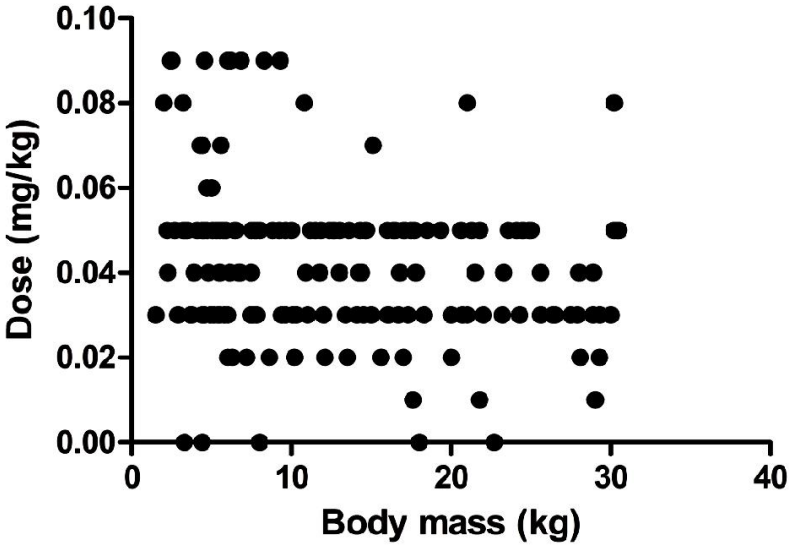

Figure 1. Dose of acepromazine (mg/kg) across body mass (kg) in 188 healthy dogs undergoing desexing

Discussion

This study reviewed 188 anaesthetic records from dogs desexed in the general practice at MUVH between 2007 and 2011. Using specific criteria for assessing blood pressure, we found a frequency of hypotension at least as high as the hypothesized estimate of 40%. Only a small proportion of dogs remained normotensive during anaesthesia. Mean arterial blood pressure less than 60 mmHg is associated with inadequate perfusion of vital organs such as kidney and brain.[5-7,9] It is concerning that such a large number of dogs had blood pressure measured below 60 mmHg in the current study and that very few dogs had normal blood pressure. Although a MAP between 60–79 mmHg is usually considered sufficient to prevent serious organ damage during anaesthesia, there is a linear decrease in renal blood flow as blood pressure decreases within this range.[8,10] Thus, discounting blood pressure within this range as not harmful is possibly careless and it should be interpreted as having potential to reduce organ function.

Our estimated proportion of dogs with hypotension is much higher than a previous report of 7% (179 of 2,556) of anaesthetised dogs.[5] This discrepancy may be due to the different definitions of hypotension used, the method used to measure arterial blood pressure, differences in animal characteristics, drugs used and procedures performed. Gaynor[5] defined hypotension as MAP less than 60 mmHg or systolic arterial blood pressure less than 80 mmHg and did not specify the duration of the decrease in blood pressure measurement. In our study, hypotension was defined as MAP less than 60 mmHg required for 10 minutes or more. This is a strict definition compared to other studies and unlikely to have resulted in overestimation.

Gaynor[5] used both the Doppler and invasive blood pressure techniques to measure blood pressure. In anaesthetised dogs, the Doppler technique is reported to overestimate systolic arterial pressure compared to invasive measurements.[12] This could result in a false diagnosis of normotension in some dogs and could have contributed to the lower frequency of hypotension reported in that study. Unfortunately, those authors did not indicate how many measurements were obtained using the Doppler and thus it is not possible to ascertain the influence this may have had on the estimation of the frequency of hypotension in their study. In our study, the Surgivet V9203 was used to measure blood pressure non-invasively via the oscillometric technique. This method can underestimate MAP compared to invasive measurements[13] and may have overestimated hypotension. However, the frequency of hypotension reported in 485 (37.9%) dogs undergoing several types of procedures was similar to that in our study despite using various techniques for measuring blood pressure.[4] This suggests that the method for measuring blood pressure may not be the sole cause of differences between studies.

Other factors that could contribute to discrepancies in the frequency of hypotension reported could include variations in animal characteristics, drugs used and procedures performed. Our study investigated hypotension in young healthy dogs undergoing routine desexing procedures. In contrast, previous studies included animals with variable ASA classification, ages and procedures. Unfortunately, the effect of these different characteristics on frequency of hypotension was not determined thus preventing comparisons between studies.

Animal factors explored in our study included age and body mass which were significantly associated with MAP category. The frequency of hypotension was significantly higher in younger animals. This is consistent with results of studies investigating hypotension in anaesthetised people. Hypotension during anaesthesia of ASA I patients demonstrated a higher frequency of hypotension during anaesthesia of children than adults.[14] The higher frequency of hypotension in younger animals may be attributed to an immature cardiovascular system. Cardiac contractility and thus cardiac function is reported to increase in dogs from three to nine months of age.[16] This is comparable to the median age of the dogs in the hypotensive and mildly hypotensive categories which were six to seven months and six to nine months, respectively. This immaturity in development of the cardiovascular system reduces the ability of younger animals to compensate for decreases in arterial blood pressure.[15-18]

The body mass of dogs was also found to be significantly associated with MAP category. The body mass of dogs with hypotension was significantly lower than body mass of dogs with mild hypotension. This finding may reflect confounding effects of drug dose administered on a dose per kg basis rather than a dose per m^3 body surface area basis. There was considerable disparity in the dose of acepromazine administered

to dogs with different body mass with many smaller animals getting some of the highest relative doses of acepromazine. Acepromazine causes dose dependant decreases in blood pressure[19,20] and higher doses may have contributed to the higher frequency of hypotension in dogs with low body mass. The dose used may have been influenced by confounding factors such as temperament, breed, type and duration of procedure. It has been reported that the effects of acepromazine on the cardiovascular system are influenced by temperament.[22] Greater decreases in blood pressure have been reported in anxious animals receiving acepromazine when compared to calm animals. This is attributed to the increase in circulating catecholamines that occur in stressed animal which exacerbate the peripheral vasodilation associated with acepromazine.[21,22]

When the type of drugs used for premedication were investigated it was found that the administration of acepromazine and methadone was associated with a higher proportion of hypotensive dogs and lower proportion of normotensive dogs when compared to acepromazine and morphine. Possible reasons could include differences in the effect of methadone and morphine on the cardiovascular system and or differences in the doses of the different agents that were used. Administration of intravenous methadone is reported to cause a significantly greater decrease in blood pressure than intravenous morphine in conscious[23] and anaesthetised[24] dogs. However, this decrease in blood pressure is associated with a decrease in heart rate (and cardiac index). Of note, although the decrease in blood pressure was greater following intravenous methadone, none of the dogs developed hypotension defined as MAP less than 60 mmHg.[23,24] In our study, records were not assessed for decreases in heart rate from baseline, however heart rate was defined as above or below normal. Bradycardia defined as heart rate less than 80 bpm was observed in only two of the hypotensive animals making it less likely that bradycardia associated with administration of methadone was responsible for the higher

frequency of hypotension observed in dogs receiving this combination. The lack of apparent influence of methadone on heart rate in the current study could be explained by administration of methadone intramuscularly which would be expected to produce lower peak serum concentrations and a less profound decrease in heart rate. The changes associated with these premedicant protocols may reflect variations in the acepromazine dose as explained previously.

There was no significant association of induction agent with MAP category. This is consistent with recent studies in dogs that failed to detect significant differences in cardiovascular function when anaesthesia was induced and maintained with propofol or alfaxalone[25-28]or propofol or diazepam-ketamine.[29] It is important to point out that, in the current study, a relatively small number of dogs received alfaxalone and diazepam/ketamine for induction of anaesthesia compared to dogs receiving propofol. Data from a larger number of dogs receiving each of the different induction agents are needed to confirm the findings of this study.

To interpret the results of this study it is important to understand the limitations of its design. The main limitation of this study was the use of the oscillometric method for measuring arterial blood pressure. The oscillometric technique is reported to underestimate blood pressure values[13,30] which could have overestimated the frequency of hypotension. However, our requirement for a recording over 10 minutes was quite restrictive so may have tempered this possible overestimation. Studies using direct methods of measuring blood pressure are advised to confirm the findings in this study. Other limitations of this study was the reliance of historical data and the large number of confounding variables that are likely present which cannot be clearly accounted for.

This study reports the frequency of hypotension in healthy dogs undergoing elective desexing in general practice at Murdoch University Veterinary Hospital was at least as high as 40%. This high frequency of hypotension justifies monitoring blood pressure during anaesthesia in healthy dogs. Factors that influenced the frequency of hypotension were age, body mass and type of premedicant used. Prospective studies using standardised anaesthetic protocols and direct methods of blood pressure monitoring would be worthwhile to further investigate the role of explanatory factors.

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CHAPTER 3 – HYPOTENSION IN ANAESTHETISED DOGS UNDERGOING ELECTIVE DESEXING IN STUDENT NEUTERING CLINICS

Abstract

Objectives - To document the proportion of dogs with perioperative hypotension and explore the association between gender, age and body mass and indices of hydration with mean arterial blood pressure (MAP) in a cohort of healthy anaesthetised dogs maintained at an appropriate depth of anaesthesia for desexing.

Methods - Dogs were anaesthetised with a standardised protocol. Proportion of dogs with invasive MAP <60 mmHg for ≥10 min was recorded. The area under the MAP*time curve (AUC) was calculated for a standard perioperative period (10 minutes before to 40 minutes after start of surgery). The association of explanatory variables including gender, age, body mass and indices of hydration (urine specific gravity (USG), packed cell volume (PCV) and total solids (TS), measured prior to surgery, with the AUC was explored using regression models and analysis of variance.

Results - Thirty five of 71 (0.49; 95% confidence interval 0.37-0.61) dogs developed hypotension. Regression analysis showed that age and USG was the best subset to explain the AUC. Analysis of variance of the subset found a positive association between age and AUC and a negative association between USG and AUC.

Conclusion - The results from this study support the recommendation for blood pressure monitoring and intravenous fluid administration during anaesthesia in healthy young dogs.

Key words - hypotension, anaesthesia, invasive blood pressure, dog.

Introduction

Hypotension is the most common cardiovascular complication reported in small animal anaesthesia (Gaynor et al. 1999, Redondo et al. 2007, Brodbelt 2009). The reported frequency of hypotension in anaesthetised dogs varies from 7% (Gaynor et al. 1999), 22% (Gordon and Wagner 2006) to 46% (Costa et al. 2013). Varying frequencies may, in part, be due to the lack of a standard definition for hypotension. Hypotension is commonly defined as mean arterial blood pressure (MAP) <60 mmHg (Littman and Drobatz 1995, LeDoux et al. 2000, Hall et al. 2001). However other definitions used in anaesthetised dogs include systolic arterial blood pressure (SAP) <80 mmHg (Muir and Wiese 2004, Aarnes et al. 2009), MAP <70 mmHg (Gimenes et al. 2011) and SAP <90 mmHg and/or MAP <60 mmHg (Miyake et al. 2005). The use of either non-invasive (oscillometric and Doppler) or invasive techniques may also contribute to variation in frequency as inaccurate measurements, particularly from non-invasive methods, could result in inaccurate estimation of hypotension. Further variability in the anaesthetic drugs administered and the subjects' characteristics, particularly American Society of Anaesthesiologists (ASA) health status classification, could also contribute to discrepancies between studies. Unfortunately none of the cited studies investigated the influence of these factors on hypotension.

The first aim of our study was to document the proportion of dogs developing hypotension (MAP <60 mmHg using invasive blood pressure techniques - IBP) in a cohort of ASA I dogs undergoing elective desexing. Our second aim was to explore the association between patient factors including signalment (gender, age, body mass) and hydration status (assessed using simple indices: PCV, TS and USG) with perioperative MAP in dogs anaesthetised according to a standardised protocol designed to maintain anaesthesia at an appropriate depth for desexing.

We hypothesised that the proportion of dogs developing hypotension would be at least 0.40. We also hypothesised that when dogs were maintained at an appropriate depth of anaesthesia for the desexing procedure, younger age and lower body mass would be positively associated with perioperative MAP and high values for indices of hydration including urine specific gravity (USG), packed cell volume (PCV) and total solids (TS) would be negatively associated with MAP.

Materials and methods

Animals

Data were collected from dogs being desexed by supervised undergraduate veterinary students in student neutering clinics at Murdoch University Veterinary Hospital (MUVH) between 2011 and 2012. This study was approved by the Murdoch University Animal Ethics Committee (AEC R239611).

All dogs included in this study were classified as ASA I. Based on pre-anaesthetic assessment, dogs were excluded if their temperament prohibited blood sample collection without excessive restraint or use of the standard anaesthetic protocol, their body condition score prevented accurate estimation of ideal body mass (>6/9), dehydration was evident (≥5%), PCV <0.30 L/L or TS <45 g/L. Data were also excluded if marked changes in cardiopulmonary function were observed during anaesthesia and persisted despite decreasing administration of isoflurane. Abnormalities included respiratory rate <10 breaths per minute, end-tidal carbon dioxide ($ETCO_2$) >60 mmHg (8 kPa), heart rate <60 beats per minute, body temperature <34^{o}C and oxyhaemoglobin saturation (SpO_2) <96%.

Data collection

Data collected prior to anaesthesia

The dogs were admitted to hospital the day before surgery and gender, age and body mass recorded. Clinical examination and collection of urine and blood samples were performed on admission (day 1) and repeated prior to premedication on the day of surgery (day 2). Preoperative hydration was classified according to clinical examination and laboratory tests (Muir and DiBartola 1983).

Urine was collected by free catch. If the dog did not urinate on day 2, a sample was collected immediately following induction of anaesthesia by manually expressing the urinary bladder. Urine specific gravity was determined using a refractometer (Reichert VET 360 Reichert Inc.; NY, USA).

Blood for measurement of PCV and TS was collected from the jugular or cephalic vein and placed directly into heparinised microcapillary tubes (Chase scientific glass Inc. Rochwood; TN, USA), which were centrifuged at 50 Hz for 5 minutes (Jouan CR3i multifunction centrifuge, Keywrite-D thermo scientific; USA). Following centrifugation, PCV was measured using a microhaematocrit reader (Clements; AUS). The concentration of TS in the plasma was measured using a refractometer (Reichert VET 360, Reichert Inc.; NY, USA).

Anaesthesia

All dogs were premedicated with 0.03 mg kg^{-1} of acepromazine (ACP2, Ceva Animal Health Pty Ltd.; AUS) and 0.3 mg kg^{-1} of morphine (DBL® Morphine Sulfate Injection, Hospira Australia Pty Ltd.; AUS) administered intramuscularly (IM) 30 minutes prior to placement of a venous catheter. A 22-20 gauge catheter (BD Insyte™, 0.9 x 25 mm,

Becton Dickinson Infusion Therapy Systems Inc.; Utah, USA) was placed in the cephalic vein for administration of anaesthetic drugs and intravenous (IV) crystalloid fluids. Anaesthesia was induced using 4-6 mg kg^{-1} of propofol IV (Fresofol 1%, Fresenius Kabi Australia Pty Limited; AUS) titrated until sufficient depth of anaesthesia allowed intubation of the trachea without a response. Anaesthesia was maintained with isoflurane (ISO, Veterinary Companies of Australia; AUS) vaporised into 100% oxygen using a non-rebreathing system for animals below 10 kg and a rebreathing system for animals above 10 kg. The isoflurane vaporizer setting was adjusted to achieve the minimum % in each dog that would maintain appropriate depth of anaesthesia during the surgical procedure characterised by ventral eye position, absent palpebral reflex, absence of jaw muscle tone but presence of corneal reflex (Ribeiro et al. 2009). Vaporiser settings were reduced if decreases in respiratory rate (<10 breaths per minute) and/or increases in $ETCO_2$, and decreases in blood pressure or in heart rate (<60 bpm) were observed. The vaporiser setting required to maintain anaesthesia in each dog was recorded.

Hartmann's solution (Baxter Compound Sodium Lactate, Baxter Healthcare Corporation) was administered at 10 mL kg^{-1} h^{-1} IV and increased if the MAP was <60 mmHg for ≥10 minutes despite decreasing the inspired concentration of isoflurane or starting surgery. Active warming of all dogs was performed using warm air blowers.

The multivariable monitor (Surgivet V9203 PolymountGCX® Corporation; California, USA) was used to record heart rate, respiratory rate, SpO_2, $ETCO_2$ and body temperature (oesophageal probe), in addition to invasive blood pressure (IBP). Meloxicam (Metacam®, Boehringer Ingelheim Vetmedica Inc.; MO, USA) at 0.2 mg kg^{-1} was administered subcutaneously at the end of anaesthesia.

Instrumentation

Blood pressure was measured using an arterial catheter connected via fluid filled extension tubing to a transducer (DTXPlus^{TM}, Becton Dickinson Critical Care Systems Pte Ltd; Singapore) which was interfaced with the multivariable monitor. Prior to the start of anaesthesia, the transducer was checked for linearity using a water manometer.

Depending on the dog's size, a 20-22 gauge catheter (BD Insyte^{TM}, Becton Dickinson Infusion Therapy Systems Inc.; Utah, USA) was placed in the metatarsal artery after induction and stabilisation of anaesthesia. The transducer was positioned at the thoracic inlet, the approximate position of the heart base in dorsal recumbency, and zeroed to atmospheric pressure. Prior to commencement of measurement, a rapid flush test was performed to subjectively assess the level of damping of the measurement system. Invasive measurement of MAP was commenced after the dog was moved into the operating room. Blood pressure calculated from the average of 10 consecutive MAP measurements was recorded every 5 minutes. At the end of anaesthesia, the transducer was reopened to the atmosphere to confirm absence of baseline drift during the study.

Data analysis

Frequency and onset of hypotension

Hypotension was considered present if MAP was <60 mmHg for ≥10 minutes (at least two consecutive measurements) despite decreasing the vaporiser setting or increasing surgical stimulation. The proportion of dogs classified as hypotensive was the response of interest and the point estimate and its 95% confidence interval (CI) was calculated using methods for proportions (Statistical software, SAS v9.3, SAS Institute; NC, USA). For each dog, the time at which hypotension was first recorded relative to the start of surgery was identified and the mean and 95% CI was determined.

Administered dose of isoflurane

To provide an approximation of dose of isoflurane administered in each dog, the area under the isoflurane concentration versus time curve (AUC_{iso}) during the standardised perioperative period common to males and females (10 minutes before start of surgery to 40 minutes after start of surgery) was calculated using the trapezoidal method (GraphPad prism 5, GraphPad Software; California, USA). The AUC_{iso} was then divided by duration to determine the time averaged AUC (AUC_{iso} $minute^{-1}$) and the mean (95% CI) were calculated. The proportion of animals using a rebreathing (Circle) breathing system or non-rebreathing (bain) breathing system was also determined.

Patient factors associated with mean arterial blood pressure

Animal characteristics

All data collected were tested for normality using D'agostino and Pearson omnibus normality test (GraphPad prism 5). When data were normally distributed, the mean and 95% CI was calculated and when data were not normally distributed, median and interquartile interval were calculated. For the purpose of analysis, USG was modified according to the formula: (USG - 1) x 1000, therefore an USG of 1.040 would be 40. The mean USG, PCV and TS were compared across day 1 and day 2 using a paired T-test with significance determined at $P \leq 0.05$ (GraphPad prism 5).

Exploration of factors associated with mean arterial blood pressure

To investigate factors that influenced MAP during anaesthesia, the area under the MAP versus time curve (AUC_{-10-40}) during the standardised perioperative period common to males and females (see above) was calculated using the trapezoidal method (GraphPad prism 5).

Significant association of explanatory variables, including gender, age, body mass, USG (day 2), PCV (day 2) and TS (day 2) with the AUC_{-10-40} were explored using regression models. If data for day 2 were missing, USG, PCV and TS for day 1 were used as default. The best model was selected based on the smallest C(p) with the least bias, that is, the C(p) closest to p, where p is the number of variables in the model (Neter et al. 1985). The simplest explanatory subsets that explained the outcome were chosen. Where several subsets fit the selection criteria, the final model was chosen based on residual analysis, the highest coefficient of determination (r^2) and biologic plausibility. The C(p) and the r^2 were reported.

Further assessment of the best explanatory subset was provided by visual assessment of plots, analysis of the selected regression model and analysis of variance. A simple linear regression was applied if this appeared to best suit the data pattern. The regression analysis allowed the relationship between the explanatory variables and the outcome to be characterised. Variables were considered significantly associated with the outcome at $P \leq 0.15$ to avoid premature exclusion of possible associations between variables and outcome. Using a more lenient criterion (P value) for significance is justified in exploratory studies, such as ours, to increase power and thus reduce type II error (Cohen 1988). This reduces our chance of prematurely dismissing a factor that may have an effect, simply because our confidence in that decision is slightly reduced, 85%, versus the accepted standard of 95%.

Results

Seventy one healthy dogs desexed at MUVH between 2011 and 2012 were included in this study.

Frequency and onset of hypotension

The mean start time for recording blood pressure was 30 minutes (95% CI 28-31) after the induction of anaesthesia, which was 10 minutes (95% CI 9-11) prior to start of surgery. The mean (95% CI) of anaesthesia and surgery duration are reported in Table 1.

Of the 71 dogs, 34 (0.48) were males and 37 (0.52) were females. A total of 35/71 (0.49; 95% CI 0.37-0.61) dogs developed hypotension during general anaesthesia. Of the 35 dogs with hypotension, 15 (0.43; 95% CI 0.27-0.59) were males and 20 (0.57; 95% CI 0.41-0.73) were females.

Of the 35 dogs with hypotension, 32 were hypotensive before the start of surgery while three dogs developed hypotension after the start of surgery. For all but three of the 32 dogs this coincided with the start of IBP measurements. Twenty of these 32 dogs remained hypotensive after the start of surgery for 20 minutes (95% CI 10-32). An additional five dogs developed a second episode of hypotension 31 minutes (95% CI 23-39) after start of surgery. For the three dogs that only developed hypotension during surgery, the onset was 5, 10 and 45 minutes after start of surgery.

Administered dose of isoflurane

The isoflurane vaporiser settings expressed as the mean (95% CI) for AUC_{iso} minute-^{1} are reported in Table 1. The AUC_{iso} minute^{-1} is presented for all animals and for males

and females separately. Circle breathing system was used in 56 of 71 dogs (79%) with a standard fresh gas flow of 2L/min and a bain breathing system was used in the remaining dogs (21%). As a circle breathing system was used in the majority of the dogs, we acknowledge that the inspired concentration may be slightly lower than the vaporiser setting in these dogs.

Factors associated with mean arterial blood pressure

Animal characteristics

Signalment data were available for all dogs. Median (interquartile interval) for age and body mass is reported in Table 1. There were some missing data points for USG, PCV and TS. Urine specific gravity data were available in 40 dogs (27 males and 13 females) on day 1 and 60 dogs (32 males and 28 females) on day 2 as some dogs did not urinate prior to anaesthesia and there was no urine present in the bladder immediately following induction of anaesthesia. Measurement of PCV and TS was obtained in 58 dogs (28 males and 30 females) on day 1 and 65 dogs (30 males and 35 females) on day 2 (Table 2) due to haemolysis of some samples. The mean (95% CI) for USG, PCV and TS from these animals are presented in Table 1. The mean (95% CI) for AUC_{-10-40} for all dogs are also presented in Table 1.

For paired data only, there was no significant difference between day 1 and day 2 for PCV (P=0.586, n=58) and TS (P=0.258, n=58) but USG on day 2 was significantly higher than USG on day 1 (P <0.001, n=60).

Exploration of patient factors associated with mean arterial blood pressure

A complete data set including gender, age, body mass, USG, TS and PCV was available in 60 of the 71 dogs (30 males, 30 females). For six dogs, default data for PCV, TS or

USG from day 1 were used. The AUC_{-10-40} was used for analyses as it was calculated over the time period common to all procedures. It is also worth pointing out, in the dogs defined as hypotensive, at least one episode of hypotension was observed during this period. Regression analysis showed the model that included age and USG best explained the AUC_{-10-40} (C(p)=1.692, r^2=0.140) (Table 3). Analysis of variance of the best subset found a positive association between age and AUC_{-10-40} (P=0.038, r=0.319) and a negative association between USG and AUC_{-10-40} (P=0.126, r=-0.224). This relationship was confirmed by visual assessment of fit plot AUC_{-10-40} versus age (Figure 1) and USG (Figure 2).

Table 1. Median (interquartile interval) of age and body mass and mean (95% confidence interval) of anaesthesia duration, surgery duration, dose of isoflurane and cumulative mean arterial blood pressure calculated from 10 minutes before to 40 minutes after start of surgery (AUC_{-10-40}) of 71 healthy dogs undergoing elective desexing in student neutering clinics at Murdoch Veterinary Hospital

	Total (n=71)	**Males** (n=34)	**Females** (n=37)
Age (month)	13 (8-30)	12 (8-36)	14 (8-29)
Body mass (kilogram)	17.5 (7.3-22.7)	18.4 (8-22.6)	17.4 (7-23)
Anaesthesia duration (minute)	119 (111-127)	92 (84-100)	144 (135-153)
Surgery duration (minute)	91 (83-99)	65 (58-72)	120 (111-129)
AUC_{iso} minute^{-1} (% minute^{-1})	1.6 (1.5-1.7)	1.6 (1.5-1.7)	1.6 (1.5-1.7)
AUC_{-10-40} (mmHg*minute)	3524 (3388-3659)	3473 (3261-3686)	3570 (3396-3744)

Table 2. Mean (95% confidence interval) of urine specific gravity (USG), packed cell volume (PCV) and total solids (TS) of healthy dogs undergoing elective desexing in student neutering clinics at Murdoch Veterinary Hospital

	Day 1	**Day 2**
USG	1.035 (1.032-37) n=40	1.041[a] (1.038-43) n=60
PCV (L/L)	0.41 (0.40-0.42) n=58	0.41 (0.39-0.42) n=65
TS (g/L)	74 (72-76) n=58	76 (74-78) n=65

[a]Significantly different from day 1 ($P<0.001$)

Table 3. Best subset regression models explaining the cumulative mean arterial blood pressure calculated from 10 minutes before to 40 minutes after start of surgery (AUC_{-10-40}) in 60 dogs undergoing elective desexing in student neutering clinics at Murdoch Veterinary Hospital. The complete subset included age, gender, body mass (BM), urine specific gravity (USG), packed cell volume (PCV) and total solids (TS). The model including age and USG was considered the best fit subset based on C(p), r^2 and biologic plausibility

Variables in Model	p	C(p)	R-Square
Age	1	2.047	0.103
Age USG	**2**	**1.692**	**0.140**
Age USG BM	3	2.492	0.158
Age USG gender TS	4	3.143	0.179
Age USG BM gender TS	5	4.385	0.191
Age USG BM gender TS PCV	6	6.161	0.194

Figure 1. Fit plot for age and cumulative mean arterial blood pressure calculated from 10 minutes before surgery to 40 minutes after surgery (AUC_{-10-40}) (P=0.038, r=0.319) in 60 dogs undergoing elective desexing in student neutering clinics at Murdoch University Veterinary Hospital. The regression line (solid line) and the 95% confidence interval (dotted lines) of the fitted line is depicted

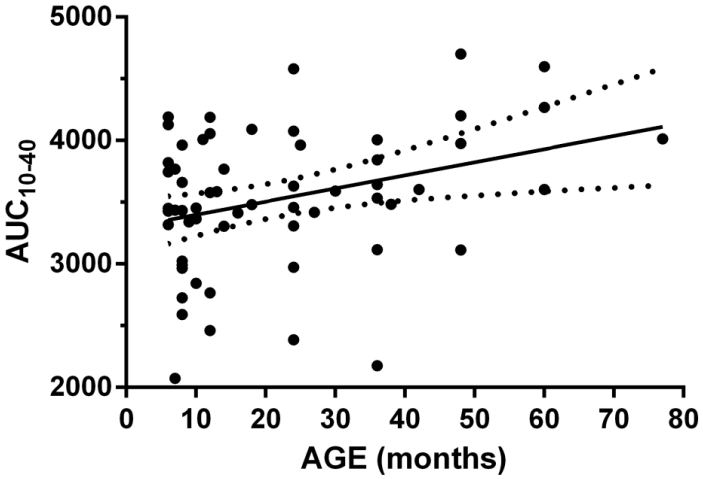
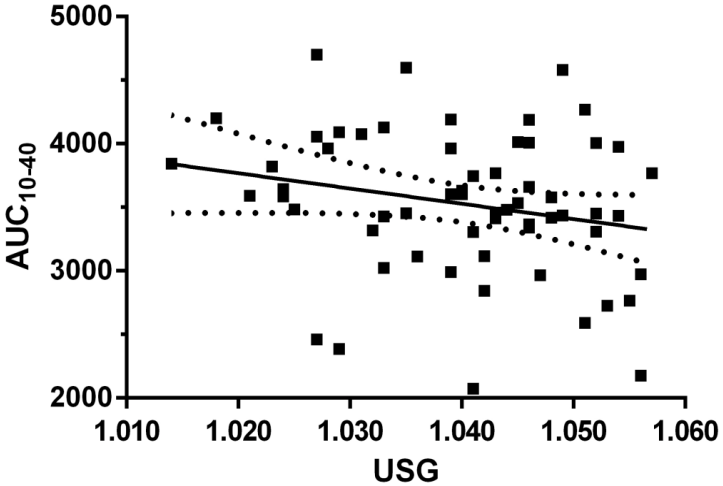


Figure 2. Fit plot for urine specific gravity (USG) and cumulative mean arterial blood pressure calculated from 10 minutes before surgery to 40 minutes after surgery (AUC_{-10-40}) (P=0.126, r=-0.224) in 60 dogs undergoing elective desexing in student neutering clinics at Murdoch University Veterinary Hospital. The regression line (solid line) and the 95% confidence interval (dotted lines) of the fitted line is depicted



Discussion

This study investigated the frequency of perioperative hypotension in ASA I dogs and factors that influenced MAP measurements during general anaesthesia. The proportion of dogs with hypotension was similar to the hypothesised estimate of 0.40 and the combination of age and USG best explained the cumulative MAP over the perioperative period.

The proportion of dogs with hypotension in our study was similar to many of the previous studies (Miyake et al. 2005, Chen et al. 2007, Redondo et al. 2007, Costa et al. 2013) in anaesthetised dogs. Two studies report lower frequencies of 7% (Gaynor et al. 1999) and 22% (Gordon and Wagner 2006). Factors such as different definitions of hypotension used (Bijker et al. 2007) and the methods utilised to measure MAP during anaesthesia may have contributed to the discrepancies between studies. Gordon and Wagner (2006) defined hypotension as SAP <90 mmHg and MAP <60 mmHg, while Gaynor et al. (1999) defined hypotension as SAP <80 mmHg. The latter study used the Doppler technique as well as invasive techniques to measure SAP. As the Doppler device is reported to overestimate SAP compared to the invasive measurement (Seliskar et al. 2013), this could underestimate the frequencies of hypotension particularly if a large number of the measurements within the study were made with the Doppler technique. In our study, MAP was measured invasively in all dogs as this method is considered more accurate than non-invasive techniques, especially for hypotensive animals (Stepien et al. 2000, Bosiack et al. 2010, Shih et al. 2010), thus minimising inaccurate estimation of the proportion of dogs with hypotension in our study.

Other factors that could contribute to discrepancies in the frequency of hypotension include variations in animal characteristics and drugs administered. In our prospective

clinical study, we attempted to reduce variability by using a cohort of young healthy dogs undergoing an elective procedure using a standardised anaesthetic protocol. In contrast, previous studies failed to specify the animals' age and included animals with variable ASA classifications undergoing several types of procedures (Gaynor et al. 1999) and receiving different premedicant and induction agents (Gaynor et al. 1999, Gordon and Wagner 2006). Any of these factors could have resulted in a frequency of hypotension different from the one reported in our study.

Exploration of patient factors that influence MAP in our study revealed a positive association between age and perioperative MAP. Such an association is consistent with reports of higher frequency of anaesthesia related hypotension in younger dogs (Costa et al. 2013) and children (Morris et al. 2005) compared to older patients. Greater cardiovascular depression is also reported during anaesthesia of foals when compared to adult horses (Read et al. 2002, Craig et al. 2007). Studies in conscious dogs also report lower MAP in younger (<12 months) dogs compared to older (>12 months) dogs (Bodey and Michell 1996, Sanan and Arslan 2007). Bodey and Michell (1996) reported that 6 month old dogs have mean MAP of 79.2 mmHg compared to mean MAP of 92.9 mmHg in dogs aged 12-24 months. These findings could be caused by age related changes in cardiovascular system function. In puppies (21 to 40 days old) development of the sympathetic nervous system is incomplete which may compromise the regulation of cardiac function and MAP (Mace and Levy 1983). Sympathetic nervous system activity improves as the animal ages. Cardiac contractility thus cardiac function is also reported to increase in dogs from 3 to 9 months of age (Urthaler et al. 1978). Reduced cardiac function may exacerbate the cardiovascular effects of sedatives and anaesthetic agents resulting in lower blood pressures during anaesthesia in younger animals

compared to older animals (Urthaler et al. 1978, Templeton et al. 1979, Vollmar 1999, Yamashita et al. 2009).

Urine specific gravity was observed to have a negative relationship with perioperative MAP. In addition, a significant increase in USG between admission and the day of surgery was observed, which suggests the development of subclinical dehydration in these dogs (DiBartola 2005). It is probable that water intake was reduced during hospitalisation resulting in reduced urinary water excretion in an attempt to preserve body water. Typically, small decreases in body water associated with subclinical dehydration would not be expected to impact blood volume significantly. However, when combined with drug induced vasodilation and increased vascular volume and an immature cardiovascular system, it is possible that even small decreases in total body water could contribute to reduced blood volume and thus blood pressure (Machado et al. 2005). Reduced water intake can be attributed to the stress of an unusual environment and fasting. At least 70% of the total water intake is consumed just before, during and immediately after meals (Fitzsimons 1979) thus overnight fasting could contribute to dehydration (Holte and Kehlet 2002).

It is important to note that the missing data for some variables could impact the association between these variables and perioperative MAP. The inclusion of data for six dogs from day 1 allowed us to maximise the number of dogs in the analysis and is, if anything, likely to have biased the result away from our hypotheses. Although there was no difference in PCV or TS between day 1 and day 2, USG was significantly lower on day 1. Thus, the influence of USG on MAP may have been underestimated.

In our study, the calculation of AUC allowed for a global assessment of the MAP across time and created one response variable for analysis. This avoids finding spurious results at multiple, individual, arbitrary time-points, a consequence of increased type I error. The AUC assessed the cumulative MAP over the common time period of -10 to 40 minutes which allowed standardised comparison across males and females. Gender was included in the regression analysis to account for any differences that the procedures (stimulus, open abdomen) might have on the MAP but no association was found. It was also considered likely that this period represented the time in which MAP would be more likely to be influenced by patient factors and not factors related to effects of prolonged anaesthesia such as decreasing body temperature and increasing evaporative water losses from the pulmonary system (Wilkes 2001) and peritoneum (females only) (Lamke et al 1977). It is also important to note that, of the dogs that developed hypotension, all developed hypotension at least once during this standardised period, therefore, data collected after the standard 40 minutes would likely not add much information.

To interpret the findings of this study, it is also important to understand its limitations. Firstly, measurement of IBP commenced after the dogs were moved into the operating room thus no data were obtained in the preparation room. This could have resulted in underestimation of the frequency or duration of hypotension. Secondly, all dogs with MAP <60 mmHg for ≥10 minutes were treated with increased rates of IV fluid administration which should increase MAP over time. While this may have reduced the ability to detect associations between MAP and the explanatory variables, it is more likely that this would have underestimated the importance of variables such as age and USG.

A further limitation of this study was the inability to measure inspired and end-tidal isoflurane due to unavailability of specific equipment. Thus the dose of isoflurane required to produce an appropriate depth of anaesthesia for the surgical procedure being performed in this study could not be determined. As isoflurane is known to produce dose related cardiovascular system changes with decreasing blood pressure being observed with increasing concentrations (Skovsted and Sapthavichaikul 1977, Tomiyasu et al. 1999), we cannot discount the possibility that variation in the dose of isoflurane required to produce a surgical plane of anaesthesia influenced the recorded MAP. However the purpose of the study was to determine patient factors that could influence blood pressure during a surgical plane of anaesthesia. The results of our study show that when anaesthesia is maintained at an appropriate depth for the desexing procedure, age and USG were the patient factors that had some influence on the measured MAP.

This study reports the proportion of healthy dogs undergoing elective desexing at MUVH that developed hypotension was at least as high as that hypothesised of 0.40. Of the patient factors assessed in this study, the combination of age and USG best explained the cumulative MAP observed during anaesthesia maintained at an appropriate depth for the desexing procedure. The combination of an immature cardiovascular system confounded by the minor reduction in total body water that occurs during subclinical dehydration could increase the sensitivity of these animals to the depressant effects of anaesthetic agents. The results from this study support the use of blood pressure monitoring in healthy young dogs and the use of intravenous fluid therapy to offset reduction in water intake and subclinical dehydration that may occur due to fasting and/or stress of hospitalisation.

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CHAPTER 4 – HYPOTENSION IN ANAESTHETISED DOGS UNDERGOING ELECTIVE DESEXING IN GENERAL PRACTICE

Abstract

Objective - To document the proportion of healthy dogs with perioperative hypotension, explore the association between gender, age and body mass and indices of hydration with mean arterial blood pressure (MAP) in dogs undergoing desexing in a general practice and to compare the results with those reported in dogs undergoing desexing in student neutering clinics (Chapter 3).

Methods - Dogs were anaesthetised with a standardised protocol. Proportion of dogs with invasive MAP <60 mmHg for ≥10 minutes was recorded. The area under the MAP*time curve (AUC) was calculated for a standard perioperative period (5 minutes before to 30 minutes after start of surgery). The association of explanatory variables including gender, age, body mass and indices of hydration (urine specific gravity (USG), packed cell volume and total solids) with the AUC was explored using regression models and analysis of variance.

Results - Seventeen of 24 (0.71; 95% CI 0.53-0.89) dogs developed hypotension. Regression analysis showed that USG was the best subset to explain the AUC. Analysis of variance of the subset found a negative association between USG and AUC.

Conclusion - The results from this study support the use of blood pressure monitoring and intravenous fluid administration during anaesthesia in healthy dogs.

Key words: hypotension, anaesthesia, invasive blood pressure, dog

Introduction

Hypotension is reported to be the most common cardiovascular complication observed in anaesthetised dogs (Gaynor et al. 1999, Redondo et al. 2007 Brodbelt 2009). Mean arterial blood pressures (MAP) below 60 to 65 mmHg can compromise perfusion to vital organs such as the brain and the kidneys (LeDoux et al. 2000). A study in people reported a 3.6% increase in one-year mortality for every minute of perioperative hypotension (Monk et al. 2005). Currently, however, there are limited studies investigating hypotension in anaesthetised dogs.

Our recent historical cohort study (Costa et al. 2013) reported a frequency of 0.46 for hypotension (MAP <60 mmHg for ≥10 minutes) in healthy anaesthetised dogs. Of 188 dogs, 87 developed perioperative hypotension. Although the use of oscillometric methods of measuring blood pressure may have overestimated the frequency of hypotension in the study by Costa et al. (2013), a prospective study in healthy dogs desexed in student neutering clinics (Chapter 3) at Murdoch University Veterinary Hospital (MUVH) revealed a similar frequency, 0.49 (35 of 71) of perioperative hypotension. The prospective study also investigated factors that influenced blood pressure and found that age and urine specific gravity (USG) best explained the changes in MAP with age being positively and USG being negatively associated with MAP.

The aim of this study was to document the proportion of dogs with perioperative hypotension (MAP <60 mmHg using invasive blood pressure techniques - IBP) in a cohort of healthy dogs (American Society of Anaesthesiologists health status classification - ASA I) undergoing elective desexing in general practice. Our second aim was to explore the association between patient factors including signalment (gender, age, body mass) and hydration status (assessed using simple indices: USG,

PCV and TS) with perioperative MAP in dogs anaesthetised according to a standardised protocol designed to maintain anaesthesia at an appropriate depth for the surgical procedure. Our final aim was to compare these results to the findings from the prospective study performed in student neutering clinics (Chapter 3).

We hypothesised that the proportion of dogs developing hypotension would be lower than 0.49 (lower than in student neutering clinics (Chapter 3) due to experienced veterinarians performing the surgeries, shorter duration of surgery and hospitalisation). We also hypothesised that when anaesthesia was maintained at appropriate depth for desexing, age would be positively associated with perioperative MAP and urine specific gravity (USG) would be negatively associated with perioperative MAP.

Materials and methods

Animals

Data were collected from dogs being desexed by experienced veterinarians in general practice at MUVH between February and July, 2012. This study was approved by the Murdoch University Animal Ethics Committee (AEC R239611).

All dogs included in this study were classified as ASA I. Based on pre-anaesthetic assessment, dogs were excluded if their temperament prohibited blood sample collection without excessive restraint or use of the standard anaesthetic protocol, their body condition score prevented accurate estimation of ideal body mass (>6/9), dehydration was evident (≥5%), PCV <0.30 L/L or TS <45 g/L. Data were also excluded if marked changes in cardiopulmonary function were observed during anaesthesia and persisted despite decreasing administration of isoflurane. Abnormalities included respiratory rate <10 breaths per minute, end-tidal carbon dioxide ($ETCO_2$) >60

mmHg (8 kPa), heart rate <60 beats per minute, body temperature <34^{o}C and oxyhaemoglobin saturation (SpO_2) <96%.

Data collection

Data collected prior to anaesthesia

The dogs were admitted on the day of surgery and gender, age and body mass were recorded. Clinical examination and collection of blood and urine samples were performed prior to premedication on the same day. Preoperative hydration was classified according to clinical examination and laboratory tests (Muir and DiBartola 1983).

Urine was collected by free catch. If the dog did not urinate prior to anaesthesia, a sample was collected immediately following induction of anaesthesia by manually expressing the urinary bladder. Urine specific gravity was analysed using a refractometer (Reichert VET 360 Reichert Inc.; NY, USA).

Blood for measurement of PCV and TS was collected from the jugular or cephalic vein and placed directly into heparinised microcapillary tubes (Chase scientific glass Inc. Rochwood; TN, USA) which were centrifuged at 50 Hz for 5 minutes (Jouan CR3i multifunction centrifuge, Keywrite-D thermo scientific; USA). Following centrifugation, PCV was measured using a microhaematocrit reader (Clements; AUS). The concentration of TS in the plasma was measured using a refractometer (Reichert VET 360, Reichert Inc.; NY, USA).

Anaesthesia

All dogs were premedicated with 0.03 mg kg^{-1} of acepromazine (ACP2, Ceva Animal Health Pty Ltd.; AUS) and 0.3 mg kg^{-1} of morphine (DBL® Morphine Sulfate Injection, Hospira Australia Pty Ltd.; AUS) administered intramuscularly (IM) 30 minutes prior to placement of a venous catheter. A 22-20 gauge catheter (BD Insyte™, Becton Dickinson Infusion Therapy Systems Inc.; Utah, USA) was placed in the cephalic vein for administration of anaesthetic drugs and intravenous (IV) crystalloid fluids. Anaesthesia was induced using 4-6 mg kg^{-1} of propofol IV (Fresofol 1%, Fresenius Kabi Australia Pty Limited; AUS) titrated until sufficient depth of anaesthesia allowed intubation of the trachea without a response. Anaesthesia was maintained with isoflurane (ISO, Veterinary Companies of Australia; AUS) vaporised into 100% oxygen using a non-rebreathing system for animals below 10 kg and a rebreathing system for animals above 10 kg. The isoflurane vaporizer setting was adjusted to achieve the minimum % in each dog that would maintain appropriate depth of anaesthesia characterised by ventral eye position, absent palpebral reflex, absence of jaw muscle tone but presence of corneal reflex (Ribeiro et al. 2009). Vaporiser settings were reduced if decreases in respiratory rate (<10 breaths per minute) and/or increases in $ETCO_2$, and decreases in blood pressure or in heart rate (<60 bpm) were observed. The vaporiser setting required to maintain anaesthesia in each dog was recorded.

Hartmann's solution (Baxter Compound Sodium Lactate, Baxter Healthcare Corporation) was administered at 10 mL kg^{-1} h^{-1} IV and increased if the MAP was <60 mmHg for ≥10 minutes despite decreasing the inspired concentration of isoflurane or starting surgery. Active warming of all dogs was performed using warm air blowers.

The multivariable monitor (Surgivet V9203 PolymountGCX® Corporation; California, USA) was used to record heart rate, respiratory rate, SpO_2, $ETCO_2$ and body temperature (oesophageal probe), in addition to invasive blood pressure (IBP). Meloxicam (Metacam®, Boehringer Ingelheim Vetmedica Inc.; MO, USA) at 0.2 mg kg^{-1} was administered subcutaneously at the end of anaesthesia.

Instrumentation

Blood pressure was measured using an arterial catheter connected via fluid filled extension tubing to a transducer (DTXPlus™, Becton Dickinson Critical Care Systems Pte Ltd; Singapore) which was interfaced with the multivariable monitor. Prior to the start of anaesthesia, the transducer was checked for linearity using a water manometer.

Depending on dog's size, a 20-22 gauge catheter (BD Insyte™, Becton Dickinson Infusion Therapy Systems Inc.; Utah, USA) was placed in the metatarsal artery after induction and stabilisation of anaesthesia. The transducer was positioned at the thoracic inlet, the approximate position of the heart base in dorsal recumbency, and zeroed to atmospheric pressure. Prior to commencement of measurement, a rapid flush test was performed to subjectively assess the level of damping of the measurement system. Invasive measurement of MAP was commenced after the dog was moved into the operating room. Blood pressure calculated from the average of 10 consecutive MAP measurements was recorded every 5 minutes. At the end of anaesthesia, the transducer was reopened to the atmosphere to confirm absence of baseline drift during the study.

Data analysis

Frequency and onset of hypotension

Hypotension was considered present if MAP was <60 mmHg for ≥10 minutes (at least two consecutive measurements) despite decreasing the vaporiser setting or increasing surgical stimulation. The proportion of dogs classified as hypotensive was the response of interest and the point estimate and its 95% confidence interval (CI) was calculated using methods for proportions (Statistical software, SAS v9.3, SAS Institute; NC, USA). For each dog, the time at which hypotension was first recorded relative to the start of surgery was identified and the mean and 95% CI was determined.

Administered dose of isoflurane

To provide an approximation of the dose of isoflurane administered in each dog, the area under the isoflurane concentration versus time curve (AUC_{iso}) during the standardised perioperative period common to males and females (5 minutes before start of surgery to 30 minutes after start of surgery) was calculated using the trapezoidal method (GraphPad prism 5, GraphPad Software; California, USA). The AUC_{iso} was then divided by duration to determine the time averaged AUC (AUC_{iso} $minute^{-1}$) and the mean (95% CI) were calculated. The proportion of animals using a rebreathing (Circle) breathing system or non-rebreathing (bain) breathing system was also determined

Factors associated with mean arterial blood pressure

Animal characteristics

All data were tested for normality using D'agostino and Pearson omnibus normality test (GraphPad prism 5). When data were normally distributed, the mean and 95% CI were calculated and when data were not normally distributed, median and interquartile

interval were calculated. For the purpose of analysis, USG was modified according to the formula: (USG - 1) x 1000, therefore an USG of 1.040 would be 40.

Exploration of patient factors associated with mean arterial blood pressure

To investigate patient factors that influenced MAP during anaesthesia, the area under the MAP versus time curve (AUC_{-5-30}) during the standardised perioperative period common to males and females (see above) was calculated using the trapezoidal method (GraphPad prism 5).

Significant association of explanatory variables, including gender, age, body mass, USG, PCV and TS with the AUC_{-5-30} were explored using regression models. The best model was selected based on the smallest C(p) with the least bias, that is, the C(p) closest to p, where p is the number of variables in the model (Neter et al. 1985). The simplest explanatory subsets that explained the outcome were chosen. Where several subsets fit the selection criteria, the final model was chosen based on residual analysis, the highest coefficient of determination (r^2) and biologic plausibility. The C(p) and the r^2 were reported.

Further assessment of the best explanatory subset was provided by visual assessment of plots, analysis of the selected regression model and analysis of variance. A simple linear regression was applied if this appeared to best suit the data pattern. The regression analysis allowed the relationship between the explanatory variables and the outcome to be characterised. Variables were considered significantly associated with the outcome at $P \leq 0.15$ to avoid premature exclusion of possible associations between variables and outcome. Using a more lenient criterion (P value) for significance is justified in exploratory studies, such as ours, to increase power and thus reduce type II error (Cohen

1988). This reduces our chance of prematurely dismissing a factor that may have an effect, simply because our confidence in that decision is slightly reduced, 85%, versus the accepted standard of 95%.

If the best model and explanatory subset observed in this study differed from the ones in student neutering clinics (Chapter 3), an unpaired t-test (GraphPad prism 5) was performed (significance defined as $P < 0.05$) to determine if there was any difference between the cohorts that could explain the discrepancy.

Results

Twenty four healthy dogs desexed at MUVH between February and July 2012 were included in this study.

Frequency and onset of hypotension

The mean start time for recording blood pressure was 24 minutes (95% CI 21-27) after the induction of anaesthesia and 7 minutes (95% CI 4-9) prior to start of surgery. The mean (95% CI) of anaesthesia and surgery duration are reported in Table 1.

Of the 24 dogs, 8 (0.33) were males and 16 (0.67) were females. A total of 17/24 (0.71; 95% CI 0.53-0.89) dogs developed hypotension during general anaesthesia. Of the 17 dogs with hypotension, 5 (0.29; 95% CI 0.07-0.51) were males and 12 (0.71; 95% CI 0.49-0.93) were females.

Of the 17 dogs with hypotension, 13 were observed to be hypotensive before the start of surgery while three dogs developed hypotension after the start of surgery. Two of these 13 dogs remained hypotensive for 33 minutes (95% CI 22.61-43.39). An additional 10

dogs developed a second episode of hypotension at 22 minutes (95% CI 18.08-25.92) after start of surgery. For the three dogs that only developed hypotension during surgery, the onset was at 5, 20 and 25 minutes after start of surgery.

Administered dose of isoflurane

The isoflurane vaporiser settings expressed as the mean (95% CI) for AUC_{iso} minute-^{1} are reported in Table 1. The AUC_{iso} minute^{-1} is presented for all animals and for males and females separately. Circle breathing system was used in 18 of 24 dogs (75%) with a standard fresh gas flow of 2L/min and a brain breathing system was used in the remaining 25%. As a circle breathing system was used in the majority of the dogs, we acknowledge that the inspired concentration may be slightly lower than the vaporiser setting in these dogs.

Exploration of patient factors associated with mean arterial blood pressure

Animal characteristics

Signalment data were available for all dogs. Median (interquartile interval) for age and body mass is reported in Table 1. There were some missing data points for USG, PCV and TS. Urine specific gravity data were available in 20 dogs (eight males and 12 females) as some dogs did not urinate prior to anaesthesia and there was no present urine in the urinary bladder immediately following induction of anaesthesia. Measurement of PCV and TS was obtained in 20 dogs (seven males and 13 females) (Table 2) due to haemolysis of some samples. Mean and 95% CI for USG, PCV and TS from these animals are presented in Table 1. AUC_{-5-30} is presented in Table 1.

Exploration of patient factors associated with mean arterial blood pressure

A complete data set including gender, age, body mass, USG, PCV and TS, was available in 16 (seven males and nine females) of the 24 dogs. The mean age of these 16 dogs was 8 months (95% CI 5-10). Regression analysis of all possible explanatory subsets showed the model that included USG best explained the AUC_{-5-30} (C(p)= -3.504; r^2=0.417) (Table 3). Analysis of variance showed a negative association between USG and AUC_{-5-30} (P=0.007; r=-0.649) and this relationship was confirmed by visual assessment of fit plot (Figure 1).

An unpaired t-test comparing the age of the dogs in this study with the ones desexed in student neutering clinics (Chapter 3) revealed that, in the former, dogs were significantly younger (P=0.005) than dogs in the latter. In the present study, 18 of the 24 dogs were less than 12 months of age.

Table 1. Median (interquartile interval) of age and body mass and mean (95% confidence interval) of anaesthesia duration, surgery duration, dose of isoflurane and cumulative mean arterial blood pressure calculated from 5 minutes before to 30 minutes after start of surgery (AUC_{-5-30}) of 24 healthy dogs undergoing elective desexing in general practice at Murdoch University Veterinary Hospital

	Total (n=24)	**Males** (n=8)	**Females** (n=16)
Age (months)	7 (6-12) [a]	7 (5-11)	7 (6-13)
Body mass (kilogram)	16.2 (6.2-21.3)	18.7 (9.6-25.1)	15.7 (4.6-20.1)
Anaesthesia duration (minutes)	67 (61-73)	57 (49-65)	73 (67-79)
Surgery duration (minutes)	42 (36-48)	38 (24-38)	47 (41-53)
AUC_{iso} minutes^{-1} (% minutes^{-1})	1.7 (1.6-1.8)	1.6 (1.5-1.7)	1.7 (1.6-1.8)
AUC_{-5-30} (mmHg*minutes)	2365 (2203-2527)	2344 (2145-2543)	2376 (2150-2601)

[a]Significantly different from student neutering clinics (Chapter 3) (P=0.005)

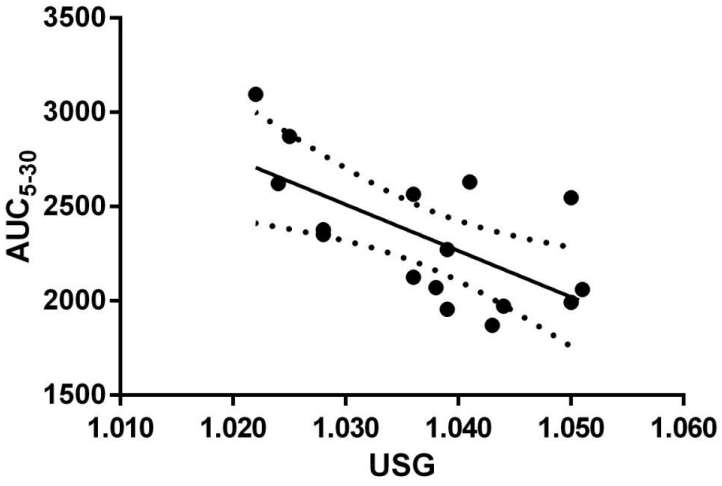
Table 2. Mean (95% confidence interval) of urine specific gravity (USG), packed cell volume (PCV) and total solids (TS) of healthy dogs undergoing elective desexing in general practice at Murdoch Veterinary Hospital

	Total	**Males**	**Females**
USG	1.035 (1.033-1.039) n=20	1.039 (1.033-1.045) n=8	1.033 (1.028-1.037) n=12
PCV (L/L)	39 (36-41) n=20	38 (33-43) n=7	39 (36-41) n=13
TS (g/L)	68 (65-70) n=20	69 (65-72) n=7	67 (64-70) n=13

Table 3. Best subset regression models explaining the cumulative mean arterial blood pressure calculated from 5 minutes before to 30 minutes after start of surgery (AUC_{-5-30}) in 16 dogs undergoing elective desexing in general practice at Murdoch University Veterinary Hospital. The complete subset included age, gender, body mass (BM), urine specific gravity (USG), packed cell volume (PCV) and total solids (TS). The model including USG was considered the best fit subset based on C(p), r^2 and biologic plausibility

Variables in Model	p	C(p)	R-Square
USG	**1**	**-3.504**	**0.417**
Age USG	2	-1.605	0.424
Age USG BM	3	0.424	1.262
Age USG gender TS	4	0.433	3.111
Age USG BM gender TS	5	0.436	5.072
Age USG BM gender TS PCV	6	0.440	7.000

Figure 1. Fit plot for urine specific gravity (USG) and cumulative mean arterial blood pressure calculated from 5 minutes before to 30 minutes after start of surgery (AUC_{-5-30}) in 16 dogs undergoing elective desexing in at Murdoch University Veterinary Hospital. The regression line (solid line) and the 95% confidence interval (dotted lines) of the fitted line is depicted



Discussion

This study investigated the proportion of ASA I dogs with hypotension during general anaesthesia, the patient factors that influenced perioperative MAP and assessed whether the results obtained in this study corroborated the findings from student neutering clinics (Chapter 3). The proportion of dogs with hypotension was higher in the dogs desexed in the general practice when compared to those desexed in student neutering clinics (Chapter 3). For dogs desexed in general practice, only USG was found to be associated with MAP compared to the combination of USG and age in the dogs desexed in student neutering clinics (Chapter 3).

The proportion of dogs with hypotension in this study was much higher than in previous reports of anaesthetised dogs where frequencies varied from 7% to 46% (Gaynor et al.

1999, Miyake et al. 2005, Gordon and Wagner 2006, Chen et al. 2007, Redondo et al. 2007, Costa et al. 2013). Factors that could contribute to the discrepancies between studies such as different definitions of hypotension used, methods utilised to measure MAP during anaesthesia and variations in drugs administered have been discussed in the previous study performed in student neutering clinics (Chapter 3).

The higher proportion of hypotensive dogs observed in general practice (0.71) in comparison to student neutering clinics (Chapter 3) (0.49) was unexpected and was not consistent with the hypothesis. When factors associated with MAP were assessed, USG but not age was found to be significantly associated with AUC. This result differs somewhat from student neutering clinics (Chapter 3) where both age and USG were associated with AUC. Further investigation revealed that dogs desexed in this study were significantly younger (median age of 7 months; interquartile interval 6-13) than dogs in student neutering clinics (median age of 13 months; interquartile interval 8-30) (Chapter 3). In fact 18 of the 24 dogs desexed in the general practice were <12 months of age. Hence, age may have been a confounding factor influencing the result of this study but it was not significant in the data analysis because the majority of dogs were young compared to the wider range of age (6 to 77 months) of dogs in the student neutering clinics (Chapter 3). Therefore, in this study, no age differential across the cohort could be detected. Additionally, as the majority of dogs included in this study were <12 months, it is likely that age-related immaturity in cardiovascular function (Urthaler et al. 1978, Templeton et al. 1979, Vollmar 1999, Yamashita et al. 2009) accounted for the higher frequency of hypotension documented.

As discussed above, USG was found to be associated with perioperative MAP with a negative relationship being detected. This is consistent with the results from student

neutering clinics (Chapter 3). In student neutering clinics (Chapter 3), it was postulated that this association could be caused by reduced water intake due to a combination of stress associated with being hospitalised overnight and fasting. In contrast to dogs desexed in student neutering clinics (Chapter 3), dogs desexed in this study were admitted on the day of surgery and did not experience prolonged hospitalisation. Thus fasting was most likely the major factor contributing to reduced water intake and subclinical dehydration in this cohort (Holte and Kehlet 2002) although owners may have inappropriately restricted water intake as well.

In our study, the AUC assessed the cumulative MAP over the common time period of -5 to 30 minutes which allowed standardised comparison across males and females. Gender was included in the regression analysis to account for any differences that the procedures (stimulus, open abdomen) might have on the MAP but no association was found. Of the dogs that developed hypotension, all developed hypotension at least once during this standardised period. Furthermore the mean surgery duration of 42 minutes (95% CI 36-48) was only marginally longer than this standardised period. Therefore, data collected after the standard 30 minutes were unlikely to add much information.

To interpret the findings of this study, it is important to understand its limitations. Firstly, the measurement of IBP commenced after the dogs were moved into the operating room thus no data were obtained in the preparation room. This could have resulted in underestimation of the frequency or duration of hypotension. Secondly, all dogs with MAP <60 mmHg for ≥10 minutes were treated with increased rates of IV fluid administration which would increase MAP over time. While, this may have reduced the ability to detect associations between lower MAP and the explanatory

variables, it is more likely that this would have underestimated the importance of variables such as USG.

A further limitation of this study was the inability to measure inspired and end-tidal isoflurane due to unavailability of specific equipment. Thus the dose of isoflurane required to produce an appropriate depth of anaesthesia for the surgical procedure being performed in this study could not be determined. As isoflurane is known to produce dose related cardiovascular system changes with decreasing blood pressure being observed with increasing concentrations (Skovsted and Sapthavichaikul 1977, Tomiyasu et al. 1999), we cannot discount the possibility that variation in the dose of isoflurane required to produce a surgical plane of anaesthesia influenced the recorded MAP. However the purpose of the study was to determine patient factors that could influence blood pressure in anaesthetised animals undergoing desexing. The results of our study show that when anaesthesia is maintained at an appropriate depth for the desexing procedure, USG was the patient factor that had some influence on the measured MAP.

This study reports that the proportion of hypotensive dogs undergoing elective desexing was higher than that reported in student neutering clinics (Chapter 3) which may be due to differences in the age of the cohorts. Of the factors assessed in this study, USG best explained the cumulative perioperative MAP and the importance of USG is supported by results of Chapter 3. The results from this study support the recommendation for diligent monitoring of blood pressure and the need for intravenous fluid administration during anaesthesia in healthy young dogs.

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CHAPTER 5 – GENERAL DISCUSSION AND CONCLUSIONS

This thesis investigated the proportion of dogs with perioperative hypotension and explored patient factors influencing mean arterial blood pressure (MAP) in cohorts of healthy anaesthetised dogs undergoing elective desexing at Murdoch University Veterinary Hospital (MUVH). In our first study of an historical cohort (Chapter 2), anaesthetic records from dogs desexed in the general practice were reviewed. In our second and third studies, data from healthy dogs undergoing elective desexing in student neutering clinics (Chapter 3) and in the general practice (Chapter 4) were collected and analysed.

The proportion of dogs with hypotension in the historical cohort study (Chapter 2) and student neutering clinics (Chapter 3) were similar to the hypothesised estimate of 0.40. Our findings are consistent with a previous report where perioperative hypotension was observed in 36% ASA II dogs (Chen et al. 2007). Similar results were also reported in dogs with unspecified ASA classification, 38% (Redondo et al. 2007) and 32% (Miyake et al. 2005). Two other studies reported lower frequencies of hypotension, 7% (Gaynor et al. 1999) and 22% (Gordon and Wagner 2006). This discrepancy may be due to different definitions of hypotension used (Bijker et al. 2007) and the techniques used to measure blood pressure. Gordon and Wagner (2006) defined hypotension as systolic blood pressure (SAP) <90 mmHg and MAP <60 mmHg, while Gaynor et al. (1999) defined hypotension as SAP <80 mmHg. In our studies, hypotension was defined as MAP <60 mmHg for ≥10 minutes. This is a strict definition compared to other studies and unlikely to have resulted in overestimation. Additionally, Gaynor et al. (1999) used

the Doppler technique as well as invasive techniques to measure SAP. As the Doppler device is reported to overestimate SAP compared to the invasive measurement (Seliskar et al. 2013), this could have underestimated the frequency of hypotension particularly if a large number of the measurements within the study were made with the Doppler technique. In student neutering clinics (Chapter 3), MAP was measured invasively in all dogs as this method is considered more accurate than non-invasive techniques, especially for hypotensive animals (Stepien et al. 2000, Bosiack et al. 2010, Shih et al. 2010), thus minimising inaccurate estimation of the proportion of dogs with hypotension in our study. Further variability in the anaesthetic drugs administered and animal's characteristics, including ASA classification and age, could have also contributed to discrepancies between studies. Unfortunately none of the cited studies investigated the influence of each of these factors on hypotension.

In the general practice (Chapter 4), the proportion of hypotensive dogs was much higher (0.71) than observed in our previous studies. The proportion of hypotensive dogs was higher than in the historical cohort study (Chapter 2) despite the fact that both studies were performed in the same environment (general practice). Comparisons between data collected in the general practice (Chapter 4) with historical data collected in the historical cohort study (Chapter 2) are difficult due to the number of confounding variables present including different drugs used and the reliance on accurate record keeping. Differences in animal characteristics were considered to be one possible reason for the discrepancies, however, examination of the data failed to support this as a cause. Although age was reported differently between studies, preventing direct comparisons, the dogs in the historical cohort study (Chapter 2) appeared to be younger than dogs in the general practice (Chapter 4). Findings from our previous Chapters (2 and 3) suggest that younger animals are more predisposed to developing lower MAP during general

anaesthesia. Thus, if age was playing a role, the proportion of dogs with hypotension in the historical cohort study (Chapter 2) should be higher. Another possible reason could be due to different techniques used to measure MAP. In the historical cohort study (Chapter 2), MAP was measured non-invasively by an oscillometric technique which may underestimate MAP in comparison to invasive techniques (Deflandre and Hellebrekers 2008, Drynan and Raisis 2012) which does not help explain the results. However, the accuracy of MAP measurements via the oscillometric technique may be affected by many factors including cuff size and site of cuff placement. Unfortunately, this information was not present in the anaesthetic records reviewed. However if small cuffs relative to limb circumference were used and/or cuffs were positioned below the level of the right atrium, blood pressure measurements would be overestimated (Geddes et al. 1980, Bodey et al. 1996) resulting in underestimation of the frequency of hypotension in the historical cohort study (Chapter 2).

The higher proportion of dogs with hypotension in the general practice (Chapter 4) in comparison to that reported in the student neutering clinics (Chapter 3) was unexpected. As both studies used the same standardised anaesthetic protocol and measured MAP invasively via the metatarsal artery, it was hypothesised that shorter hospitalisation would have resulted in a smaller proportion of dogs with hypotension being desexed in the general practice (Chapter 4). Possible reasons for this discrepancy may be due to differences in sample size and animal characteristics. The cohort desexed in the general practice (Chapter 4) was considerably smaller (n=24) than in student neutering clinics (Chapter 3) (n=71). This could have influenced the result because the accuracy of an estimate from a *probability sample* is strongly influenced by the size of the sample itself. Smaller cohorts produce less accurate estimates whereas larger cohorts provide more precise estimates (Morgan 2008). Furthermore, differences in animal

characteristics may have influenced perioperative MAP measurements thus contributing to the discrepancy between studies. Dogs in the general practice (Chapter 4) were significantly younger than in student neutering clinics (Chapter 3). It has been reported that sympathetic nervous system activity is incomplete in puppies (21 to 40 days old) which may compromise the regulation of cardiac function and MAP (Mace and Levy 1983), but it improves as the animal ages. In addition, cardiac contractility, and thus cardiac function, is reported to increase in dogs from 3 to 9 months of age (Urthaler et al. 1978). Therefore, age related immaturity in the cardiovascular system may have reduced their ability to compensate for anaesthetic drug related decreases in blood pressure. This difference in age could help explain the higher proportion of hypotensive dogs observed in general practice (Chapter 4) compared to student neutering clinics (Chapter 3).

In the historical cohort study (Chapter 2), factors such as body mass and age were found to be associated with a higher frequency of hypotension in ASA I dogs. Dogs with lower body mass were found to have a significantly higher frequency of hypotension than dogs with higher body mass. The reason for this was not readily apparent. It has been suggested that dosing of many drugs may be more accurate if calculated using body surface area (BSA) rather than body mass. However as larger dogs have a relatively smaller BSA than smaller dogs, it would be expected that larger dogs are more likely to receive higher doses and thus are more likely to suffer dose related depression of cardiovascular systems than smaller dogs. Interestingly, many of the smaller dogs received the higher doses of acepromazine, which suggests that other confounding factors expected in smaller breeds, such as temperament, may have influenced selection of drug doses in these dogs. As acepromazine causes dose dependent decreases in blood pressure (Parry et al. 1982, Monteiro et al. 2007), higher

doses may have contributed to the higher frequency of hypotension in dogs with lower body mass. Due to the large number of confounding variables likely to be present in this historical cohort study (Chapter 2), factors influencing perioperative MAP were investigated further in student neutering clinics (Chapter 3) and in general practice (Chapter 4) where a standardised anaesthetic protocol was used and more accurate direct measurements of MAP were obtained. Under these experimental conditions, no association between body mass and perioperative MAP was observed further suggesting that the association between lower body mass and higher frequency of hypotension actually reflected another confounding factor that was not evident in the study results.

Younger dogs were also found to have a higher frequency of hypotension and older dogs a lower frequency of hypotension in the historical cohort study (Chapter 2). This finding was corroborated by the results in student neutering clinics (Chapter 3) where age was one of the factors found to be associated with perioperative MAP with a positive relationship observed. Such an association is consistent with reports of higher frequency of anaesthesia related hypotension in children compared to adults (Morris et al. 2005). Greater cardiovascular depression is also reported during anaesthesia of foals when compared to adult horses (Read et al. 2002, Craig et al. 2007). As mentioned previously, this can be explained by age related changes in cardiovascular system function. Studies in conscious dogs have reported lower MAP in younger (<12 months) dogs compared to older (>12 months) dogs (Bodey and Michell 1996, Sanan and Arslan 2007). Bodey and Michell (1996) reported that 6 month old dogs have mean MAP of 79.2 mmHg compared to mean MAP of 92.9 mmHg in dogs aged 12-24 months. Therefore, immaturity in development of the cardiovascular system and sympathetic nervous system that regulates the cardiovascular system may reduce the ability of younger dogs to compensate for decreases in blood pressure.

In contrast to student neutering clinics (Chapter 3), in general practice (Chapter 4), age was not found to be significantly associated with AUC. Further investigation revealed that dogs desexed in the general practice were significantly younger median age of 7 months; interquartile interval 6-13) than dogs in student neutering clinics (median age of 13 months; interquartile interval 8-30) (Chapter 3). In fact 18 of the 24 dogs desexed in the general practice (Chapter 4) were <12 months of age. Hence, age may have been a confounding factor influencing the result of this study but it was not significant in the data analysis because the majority of dogs were young compared to the wider range of age (6 to 77 months) of dogs in the student neutering clinics (Chapter 3). Therefore, in the general practice (Chapter 4), no age differential across the cohort could be detected.

Urine specific gravity (USG) was also found to be associated with perioperative MAP in both prospective studies (Chapters 3 and 4) with a negative relationship observed. In addition, a significant increase in USG between admission and the day of surgery was observed in dogs desexed in student neutering clinics (Chapter 3). In the student neutering clinics (Chapter 3), it was postulated that this association could be caused by reduced water intake due to a combination of stress associated with being hospitalised overnight and fasting. In contrast to dogs desexed in the student neutering clinics (Chapter 3), dogs desexed in the general practice (Chapter 4) were admitted on the day of surgery and did not experience prolonged hospitalisation. Thus fasting was most likely the major factor contributing to reduced water intake and subclinical dehydration in this cohort (Holte and Kehlet 2002) although owners may have inappropriately restricted water intake as well. As total water intake is influenced by food intake (Fitzsimons 1979), overnight fasting may have contributed to the development of subclinical dehydration, resulting in the production of more concentrated urine as a mechanism to preserve body water (DiBartola 2005). Although small decreases in body

water associated with subclinical dehydration would not be expected to impact blood volume significantly, when combined with increases in vascular volume due to anaesthetic drug induced vasodilation and an immature cardiovascular system, it is possible that even small decreases in total body water could contribute to reduced blood volume and thus MAP (Machado et al. 2005).

To interpret the results from student neutering clinics (Chapter 3) and general practice (Chapter 4), it is also important to understand their limitations. Firstly, measurement of MAP commenced after the dogs were moved into the operating room thus no data were obtained in the preparation room. This could have resulted in underestimation of the frequency or duration of hypotension and thus resulted in calculation of higher AUC. Secondly, all dogs with MAP <60 mmHg for ≥10 minutes were treated with increased rates of intravenous fluid administration, which would increase MAP over time. While this may have reduced the ability to detect associations between MAP and the explanatory variables, it is more likely that this would have underestimated the importance of variables such as age and USG. A further limitation of these studies was the inability to measure inspired and end-tidal isoflurane due to unavailability of specific equipment. Thus the dose of isoflurane required to produce an appropriate depth of anaesthesia for the surgical procedure being performed could not be determined. As isoflurane is known to produce dose related cardiovascular system changes with decreasing blood pressure being observed with increasing concentrations (Skovsted and Sapthavichaikul 1977, Tomiyasu et al. 1999), we cannot discount the possibility that variation in the dose of isoflurane required to produce a surgical plane of anaesthesia influenced the recorded MAP. However the purpose of our studies was to determine patient factors that could influence blood pressure in anaesthetised dogs when depth of anaesthesia was maintained at appropriate depth for desexing.

In student neutering clinics (Chapter 3) and in general practice (Chapter 4), our exploratory criterion for significance ($P \leq 0.15$) was justified to avoid premature exclusion of possible associations between variables and outcome. Although using a more lenient criterion (higher P value) for significance is justified in exploratory studies to increase power and thus reduce type II error (Cohen 1988), further studies with larger cohorts are warranted to verify at a higher confidence level, the associations between factors such as age and USG with perioperative MAP.

Our studies report that the proportion of hypotensive dogs undergoing elective desexing at MUVH was as at least as high as hypothesised. In Chapter 2, age was significantly associated with the frequency of hypotension and the influence of age on perioperative MAP was supported directly and indirectly by the results observed in student neutering clinics (Chapter 3) and in the general practice (Chapter 4), respectively. Urine specific gravity was also found to be associated with cumulative perioperative MAP in student neutering clinics (Chapter 3) and in the general practice (Chapter 4).

The observed proportion of dogs developing hypotension supports the recommendation for blood pressure monitoring and the presence of subclinical dehydration suggested by increases in USG support the administration of intravenous fluids during anaesthesia of young healthy dogs.

Further work

Based on our findings, further work exploring the association between animal characteristics and indices of hydration with perioperative MAP in dogs undergoing other elective procedures such as elective orthopaedics is warranted to determine if the same factors affect different cohorts. It would be worthwhile to perform studies to determine the proportion of hypotensive ASA I cats and factors influencing MAP during general anaesthesia. Additionally, it may be worth investigating whether shorter periods of fasting could reduce problems such as subclinical dehydration without increasing surgical risk to the animal. Furthermore, the high proportion of hypotensive dogs observed in our studies justifies prospective studies evaluating the relevance of hypotension (defined as MAP <60 mmHg for ≥10 minutes) in relation to possible organ damage, such as kidney injury.

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APPENDICES

Appendix 1. American Society of Anesthesiologists (ASA) health status classification

ASA	Definition
I	Normal healthy patient
II	Patient with mild systemic disease
III	Patient with severe systemic disease
IV	Patient with severe systemic disease that is a constant threat to life
V	Moribund; not expect to survive without surgery

Appendix 2. Hydration status categories

Characteristics	Dehydration
0%	No clinical signs and normal urine specific gravity
<5%	No clinical signs, increased urine specific gravity
5-6%	Tacky-dry oral mucous membranes, subtle loss of skin elasticity and reduced tear film
6-8%	Dry mucous membranes, definite delay in return of skin to normal position, eyes possibly sunken in orbits No clinical signs, increased urine specific gravity
10-12%	Tented skin stands in place, definite prolongation of capillary refill time, possibly signs of shock (tachycardia, cool extremities, rapid and weak pulses)
12-15%	Definite signs of shock, death imminent