Université de Montréal

Cardiovascular effects of a medetomidine constant rate infusion at different dose levels in anaesthetized dogs

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a été évalué par un jury composé des personnes suivantes

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Résumé

Les effets cardiovasculaires des alpha$_2$ agonistes, particulièrement importants chez les chiens, limitent leur utilisation en pratique vétérinaire. La perfusion à débit constant (PDC) de ces drogues, comme la médétomidine (MED) permettrait un contrôle plus précis de ces effets. Les effets hémodynamiques de plusieurs doses de MED en PDC ont été évalués chez le chien.

Lors de cette étude prospective, réalisée en double aveugle, 24 chiens en santé, ont reçu de façon aléatoire une des 6 doses de MED PDC (4 chiens par groupe). Les chiens ont été ventilés mécaniquement pendant une anesthésie minimale standardisée avec de l'isoflurane dans de l'oxygène. Une dose de charge (DC) de médétomidine a été administrée aux doses de 0.2, 0.5, 1.0, 1.7, 4.0 ou 12.0 μg/kg pendant 10 minutes, après laquelle la MED PDC a été injectée à une dose identique à celle de la DC pendant 60 minutes. L'isoflurane a été administré seul pendant une heure après l'administration d'une combinaison d'ISO et de MED PDC pendant 70 minutes. La fréquence cardiaque (FC), la pression artérielle moyenne (PAM) et l'index du débit cardiaque (IC) ont été mesurés. Des prélèvements sanguins ont permis d'évaluer le profil pharmacocinétique. D'après ces études, les effets hémodynamiques de la MED PDC pendant une anesthésie à l'isoflurane ont été doses-dépendants. L'IC a diminué progressivement alors que la dose de MED augmentait avec: 14.9 (12.7), 21.7 (17.9), 27.1 (13.2), 44.2 (9.7), 47.9 (8.1), and 61.2 (14.1) % respectivement. Les quatre doses les plus basses n'ont provoqué que des changements minimes et transitoires de la FC, de la PAM et de l'IC. La pharmacocinétique apparaît clairement dose-dépendante. De nouvelles expériences seront nécessaires afin d'étudier l'utilisation clinique de la MED PDC.

Mots-clés: Médétomidine, Perfusion à Débit Constant (PDC), Sédation, Analgésie, Anesthésie, Chien

Abstract

The cardiovascular effects of alpha-$_2$ agonists, particularly pronounced in dogs, limit their use in veterinary practice. The use of these drugs, namely medetomidine (MED), by constant rate infusion (CRI), could allow more precise control of the cardiovascular effects. The haemodynamic responses of MED CRI at several dosages in dogs were investigated.

In a prospective, blinded study, 24 healthy beagles randomly received one of 6 MED CRI regimens (4 dogs per regimen). Dogs were mechanically ventilated to maintain stable low-level isoflurane (ISO) anaesthesia in oxygen. A loading MED infusion was administered at 0.2, 0.5, 1.0, 1.7, 4.0 or 12.0 $\mu g \cdot kg^{-1}$ for 10 min, followed by maintenance CRI for 60 min providing identical dose amounts for all dogs (total duration for MED and ISO: 70 min). Isoflurane was then administered alone for an additional hour. Heart rate (HR), mean arterial blood pressure (MAP), and cardiac index (CI) were recorded. Blood sampling was performed to establish pharmacokinetic profiles.

Based on this study, the hemodynamic effects of MED CRI during ISO anaesthesia were found to be dose-dependent. Baseline CI decreased dose-dependently as MED dose increased by: 14.9 (12.7), 21.7 (17.9), 27.1 (13.2), 44.2 (9.7), 47.9 (8.1), and 61.2 (14.1) % respectively. The four lowest dosages created limited and transient changes in HR, MAP, and CI. Pharmacokinetics were dose-dependent. Further investigations for perioperative use are warranted.

Keywords: Medetomidine, Constant rate infusion (CRI), Sedation, Analgesia, Anaesthesia, Dog

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List of abbreviations

α = alpha

AV = atrioventricular

β = beta

bpm = beats per minute

C^o = Celcius degree

CI = cardiac index

Cl = clearance

CNS = central nervous system

CO = cardiac output

CO_2 = carbon dioxide

CRI = constant rate infusion

CVP = central venous pressure

DAP = diastolic arterial pressure

DMED = dexmedetomidine

ECG = electrocardiogram

ET-CO_2 = end-tidal carbon dioxide concentration

ET-ISO = end-tidal isoflurane concentration

f_u = free fraction

h = hour

HCO_3^- = bicarbonate

HR = heart rate

IM = intramuscularly

IPPV = intermittent positive pressure ventilation

IV = intravenously

ISO = isoflurane

kg = kilogram

L =litre

LC = locus ceruleus

LiCl = lithium chloride

LiDCO = lithium dilution cardiac output

LMED = levomedetomidine

m^2 = square metre

MAC = minimal alveolar concentration

MAP = mean arterial pressure

MED = medetomidine

µg = microgram

µmol = micromole

mg = milligram

min = minute

mL = millilitre

mmol = millimole

mmHg = mercurymillimetre

ng = nanogram

NSAID = non-steroidal anti-inflammatory drug

$PaCO_2$ = arterial partial pressure of carbon dioxide

PaO_2 = arterial partial pressure of oxygen

PCO_2= partial pressure of carbon dioxide

pH = potential hydrogen

PO_2 = partial pressure of oxygen

$PvCO_2$ = venous partial pressure of carbon dioxide

PvO_2 = venous partial pressure of oxygen

REM = rapid eye movement

RR = respiratory rate

SAP = systolic arterial pressure

SC = subcutaneously

SD = standard deviation

SVR = systemic vascular resistance

$T_{½}$ = elimination half-life

TV = tidal volume

UDP = uridine diphosphate

Vss = volume of distribution at steady state

"Of course it's trivial, but then again, most things are." –John Malkovich

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Introduction

In recent years, pain management in veterinary medicine has become increasingly important. Pain assessment and alleviation is now a discipline, and is particularly developed in small animal practice. It brings together an increasing number of veterinarians and technicians devoted to the promotion, enhancement, and advancement of pain management in animals.

Analgesic agents that are widely used in clinical practice, include opioids and non-steroidal analgesic drugs (NSAIDs). In North-America opioids are the major players for systemic analgesia in veterinary medicine with butorphanol being one of the most popular analgesic drugs currently used in Canadian small animal practices. However, potential risks exist for adverse and at times deleterious effects in patients with opioid administration which may include constipation, urinary retention, respiratory depression, bradycardia, dysphoria, and opioid-induced hyperalgesia.

Alpha-$_2$ agonists, namely medetomidine (the most commonly used alpha-$_2$ agonist in small animal practice in Canada; Kaartinen *et al*., 2007), could provide an alternative or additive effect to opioid protocols used in peri-operative analgesia. Medetomidine is a potent analgesic, sedative, muscular relaxant, and is anxiolytic as well as reversible. It is primarily used for sedation and pre-medication prior to general anaesthesia. However, in spite of its claimed analgesic potency, it has not been used to its full extent as a peri-operative analgesic adjunct. Concerns about the cardiovascular side effects of alpha-$_2$ agonists after one bolus injection, especially in dogs, have somewhat prevented full adoption of these agents in veterinary practice.

The use of medetomidine through constant rate infusion (CRI) in dogs is a relatively new approach, although not thoroughly explored. With the use of CRI, the cardiovascular side effects may be minimized and plasma concentrations are more stable than with frequent bolus injections.

The objective of this study was to investigate an alternative or supplemental analgesic drug protocol to opioids, by intravenous delivery of medetomidine at CRI in dogs. The hypothesis of this study was to identify a dosage level of medetomidine CRI

causing minimal hemodynamic changes usually associated to alpha-$_2$ agonists whilst allowing precise control of both sedation and analgesia duration.

FIRST CHAPTER – LITERATURE REVIEW

1.0 PHYSIOLOGY AND PHARMACOLOGY OF THE ALPHA-$_2$ AGONISTS

1.1 Agonists

Alpha-$_2$ agonists act on alpha-$_2$-adrenoceptors by inhibiting the sympathetic tone (decreased release and turnover of noradrenaline) and increasing the parasympathetic tone (Cullen, 1999). This leads to characteristic hemodynamic effects (*e.g*. decreased heart rate and cardiac output) as well as a range of anxiolytic, sedative, and analgesic effects.

The alpha-$_2$ agonists available for clinical use in veterinary medicine are xylazine, medetomidine, detomidine, and romifidine. Medetomidine is mostly used in small animal practice and is licensed for use in dogs, in Canada. Medetomidine is a highly selective alpha-$_2$ agonist. The chemical structure is shown in figure 1. It is supplied in a racemic mixture of two optical enantiomers (dexmedetomidine and levomedetomidine). Dexmedetomidine is the active enantiomer (Virtanen, 1989; Murrell and Hellebrekers, 2005; Kuusela *et al*., 2000). The pure form of dexmedetomidine has recently been launched for the veterinary market but was unavailable in Canada in 2009. Dexmedetomidine is the most potent alpha-$_2$ agonist available for clinical use in veterinary medicine. It has a very high affinity for alpha-$_2$ adrenoceptors where it acts as a full agonist. It has a selectivity ratio of 1620/1 (α_2/α_1) which is 5 to 10 times higher than that of xylazine (α_2/α_1 ratio 160/1) and detomidine (260/1) (Virtanen, 1989; Cullen, 1996). Thus, medetomidine and dexmedetomidine have a very low affinity to alpha-$_1$ adrenoceptors, compared to other alpha-$_2$ agonists, such as xylazine and clonidine. Medetomidine seems to provide better sedation and analgesia than xylazine, possibly due to its higher selectivity (Tyner *et al*., 1997).

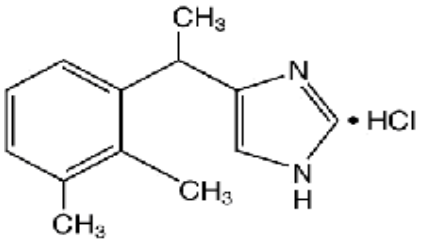

Figure 1. Chemical structure of medetomidine. (From Orion Pharmos Inc. info brochure of medetomidine.)

Medetomidine, dexmedetomidine and detomidine are the only clinically available alpha-$_2$ agonists in veterinary practice that have an imidazole ring in their structure enabling these compounds to also interact with the imidazoline receptor (Murrell and Hellebrekers, 2005). Xylazine and romifidine do not possess this property. Studies with dexmedetomidine have shown that one of its cardiovascular properties was also mediated *via* these receptors. Interestingly it was demonstrated to have a cardioprotective effect; an antiarrhythmic effect *via* imidazoline receptors in the CNS as well as enhancing vagal tone (Kamibayashi *et al*., 2000; Kamibayashi *et al*., 1995A & B).

Medetomidine can be given intramuscularly (IM), intravenously (IV) or subcutaneously (SC). After IM administration, the drug is rapidly absorbed and peak plasma levels are reached within 30 minutes. When given IV, the onset of action is rapid but the peripheral effects on the cardiovascular system are more pronounced than when given IM. After SC administration in dogs, the absorption time of the drug is slow and extremely variable which makes this route of administration less favourable (England and Clarke, 1989).

In North-America, the recommended dosage range of medetomidine in healthy dogs is 10-40 µg/kg (Paddleford and Harvey, 1999). Earlier studies searching for optimal dosage of medetomidine in clinical practice suggested 30-40 µg/kg for dogs (Vähä-Vahe, 1989A), 750 µg/m^2 IV and 1000 µg/m^2 IM (Hamlin and Bernarski, 1989). Although clinically difficult, it has been suggested by the manufacturer that dosages calculated as µg per body surface area would be more accurate than those calculated per body weight.

In a clinical study, the optimal dosage recommended for medetomidine was 15-20 µg/kg for radiological examinations and a dosage of 30-40 µg/kg was necessary for sufficient restraint and analgesia for clinical examinations or minor interventions (Nilsfors *et al*., 1989). The highest dosage of medetomidine recommended for dogs was 80 µg/kg (Vainio, 1989A).

However, much lower doses may be adequate for perioperative use when given with other anaesthetic and analgesic drugs, since the sedative and analgesic effects of medetomidine are very potent (Bergström, 1988). Low dose bolus administration and low dose infusion are now preferred in clinical practice.

1.2 Receptors

Alpha-$_2$-adrenoceptors are widely distributed throughout tissues and organs where they mediate the effects of endogenous catecholamines. Receptors are located both presynaptically and postsynaptically. Postsynaptic alpha-$_2$-adrenoceptors in peripheral blood vessels mediate vasoconstriction leading to increased blood pressure. Presynaptic alpha-$_2$-adrenoceptors regulate the release of noradrenaline, the sympathetic neurotransmitter from adrenergic nerve endings. These receptors control the concentration of catecholamines in the extracellular space of nerve endings. If these receptors are occupied by a synthetic alpha-$_2$ agonist (ex. medetomidine) the nerve impulses through the synapse are decreased resulting in sympatholysis (decrease in central noradrenergic tone). Sedation and analgesia occur along with a centrally mediated decrease in heart rate and attenuation of vasoconstriction leading to reduced blood pressure. The overall hemodynamic response to systemically administered alpha-$_2$ agonists may be determined by receptors within the central nervous system (CNS) and spinal cord (Aantaa and Jalonen, 2006). However, it was also suggested that this response in dogs depends on the initial status of vessel tone (Lin *et al*., 2008).

Other physiological functions have been found for alpha-$_2$-adrenoceptors located postsynaptically, for example, in renal, hepatic, pancreatic, adipose and ocular tissues, and in thrombocytes, as well as vascular smooth muscle (Murrell and Hellebrekers, 2005).

Adrenoceptors are classified in three main classes (β-, α_1-, and α_2-adrenoceptors). In general, the sedative and anxiolytic effects of alpha-$_2$ agonists are mediated by activation of supraspinal autoreceptors (receptors located on noradrenergic neurons) located in the pons (locus ceruleus; LC; Figure 2). Analgesic effects are mediated by activation of spinal heteroceptors (receptors located on non-noradrenergic neurons) located in the dorsal horn of the spinal cord (Lemke, 2004A). However, the supraspinal autoreceptors located in the pons also play a prominent role in descending modulation of nociceptive input (Lemke, 2004B; Cullen, 1996; Ossipov *et al*., 1990).

Three distinct alpha-$_2$ receptor subtypes (A, B and C) have been identified (Maze and Fujinaga, 2000). Alpha-$_{2A}$ receptors mediate sedation, analgesia, hypotension, and bradycardia. Alpha-$_{2B}$ receptors mediate the initial increase in vascular resistance, hypertensive action, and reflex bradycardia. Alpha-$_{2C}$ receptors mediate the hypothermia that may accompany administration of alpha-$_2$ agonists. Centrally located alpha-$_{2C}$ receptors also mediate anxiolysis. Drugs acting via these receptors may have therapeutic value in decreasing the stress response, for example in the case of post-traumatic stress disorders (Kamibayashi *et al*., 2000).

Alpha-$_2$ receptors are cell membrane proteins that trigger cellular responses to ligands by interacting with intracellular G-proteins (Aantaa *et al.*, 1995). These receptors are capable of interacting with all types of pertussis toxin-sensitive G-proteins, although the most important interactions are with the inhibitory G-proteins G_i and G_o. Intracellular second-messenger pathways include inhibition of adenylate cyclase and modulation of ion channels.

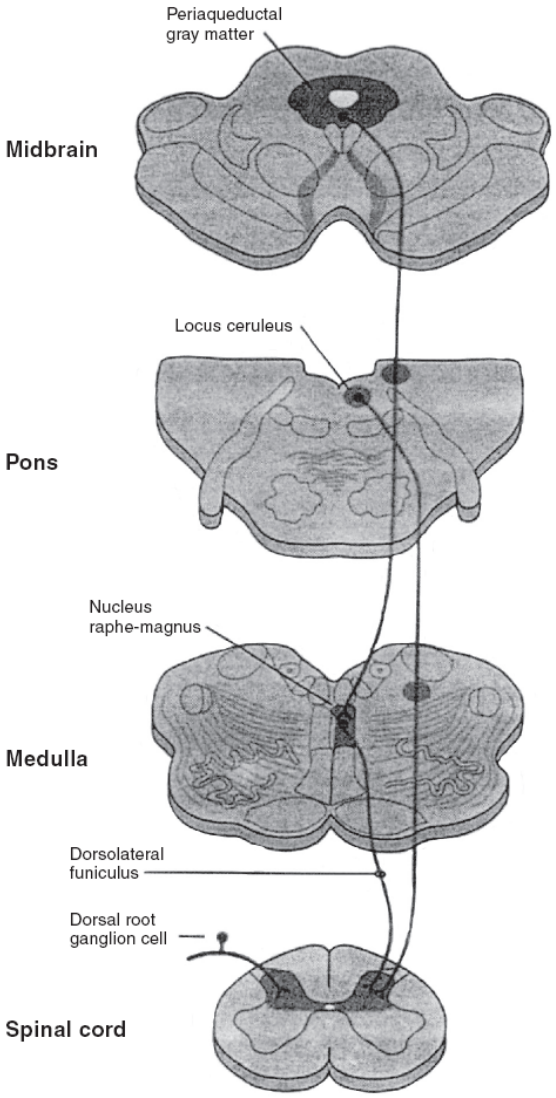

Figure 2. Descending antinociceptive pathways. Noradrenergic neurons project from supraspinal levels to the neurons in the dorsal horn of the spinal cord. (From Kandel Schwartz and Jessel, *Principles of Neural Science*, 4th edition, 2000, McGraw-Hill.)

1.3 Pharmacokinetics

Pharmacokinetic studies have shown that absorption occurs rapidly following medetomidine (IM) administration in dogs. Plasma protein binding of medetomidine is very high (92-95%) (Salonen, 1989). Thus, medetomidine is present in the circulation mostly in its inactive protein-bound form. Medetomidine, a weak organic base, when given

at high dosage (80 µg/kg) presented a low free fraction (f_u) estimated at 15% in dogs, cats, and rats. Binding of the drug to α-proteins (globulins, lipoproteins, glycoproteins) was hypothesized. Due to high lipid solubility, there is rapid distribution, systemic diffusion, and clearance. In a pharmacokinetic study with radioactively labelled ^{3}H-medetomidine, serum peak concentration (approximately 20 ng/ml) was obtained 30 minutes after administration at a dosage of 80 µg/kg (Salonen, 1989). The volumes of distribution at steady state (Vss), the clearances (Cl), and half-lives of elimination ($T_{½}$) after IV and IM administration of this dosage are shown in Table I. Similar pharmacokinetic data were shown in a study by Kuusela *et al*. (2000), in which they compared pharmacokinetics of medetomidine, levomedetomidine, and dexmedetomidine after IV bolus administration. The data are included in Table I.

	Vss (l/kg)	Cl (l/h/kg)	$T_{½}$ (h)
Medetomidine IM 80 µg/kg Medetomidine IV 80 µg/kg (Salonen, 1989)	3.0 2.8	1.65 (27.5 ml/min/kg) 2.00 (33.4 ml/min/kg)	1.28 0.97
Medetomidine IV 40 µg/kg	1.28	1.26	0.96
Dexmedetomidine IV 20 µg/kg	0.86	1.24	0.78
Levomedetomidine IV 20 µg/kg (Kuusela *et al*., 2000)	2.68	4.07	0.63

Table I. Pharmacokinetic parameters of medetomidine, dexmedetomidine, and levomedetomidine (information obtained from Salonen, 1989; and Kuusela *et al*., 2000). Vss = volume of distribution at steady state, Cl = clearance, $T_{½}$ = elimination half-life.

The clearance of levomedetomidine appears more rapid than dexmedetomidine or racemic medetomidine in dogs (Table I; Kuusela *et al*., 2000). In addition, levomedetomidine has been shown to interfere with the metabolism of other anesthetic drugs in the liver, such as slowing ketamine metabolism (Kharasch *et al*., 1992).

In healthy human adults, dexmedetomidine pharmacokinetic profile includes a rapid distribution phase, $T_{½}$ of 2 h, and Vss of 118 L (Dyck and Shafer, 1993). Based on

available pharmacokinetic data, the $T_{½}$ after bolus administration suggests more rapid elimination in dogs compared to humans, while the Vss with 40 μg/kg (IV) in dogs is similar to weight-adjusted results in humans.

Dexmedetomidine and medetomidine undergoes hepatic metabolism with limited unchanged drug excreted in the urine or feces. Medetomidine is mainly (80-90%) metabolized by hepatic hydroxylation followed by glucuronidation in dogs, involving several biotransformation pathways (Salonen, 1992). Phase I reaction proceeds with a rate sufficient for rapid removal of the drug from the animal's body and is therefore regulated mainly by hepatic blood flow. Phase II glucuronidation of medetomidine with glucuronic acid is accomplished by different UDP-glucuronosyltransferases presenting different affinity, regio-and stereo-selectivity in human and canine liver microsomes. N-glucuronidation of levomedetomidine and dexmedetomidine thus occur with different kinetics (Kaivosaari *et al*., 2008). In addition, an O-glucuronidation pathway has been reported for medetomidine (Salonen, 1992).

A phenotypic polymorphism of the cytochrome P450 (CYP)-catalyzed phase I hydroxylation of medetomidine, affecting the biotransformation rate of medetomidine has been reported in rabbits (Avsaroglu *et al*., 2008) However, this has not been demonstrated in dogs. In a report from Dutta *et al*. (2000), there is pharmacodynamic alteration of medetomidine clearance in humans with increasing dosage as a result of medetomidine-induced cardiac output decrease, and reduced hepatic blood flow decreasing hepatic clearance. However, it is likely that major species differences in medetomidine metabolism may exist (Kaivosaari *et al*., 2002).

In human adults with severe hepatic failure, Vss and $T_{½}$ were increased and clearance decreased (Cunningham *et al*., 1999). In adults with severe renal disease, there was no significant difference between renal disease and control patients for Vss and clearance. However, the $T_{½}$ was decreased with renal disease, while the perceived clinical sedation was prolonged.

In children, the pharmacokinetic profile appears similar to adults except in very young infants. The neonates have been reported to clear dexmedetomidine faster (Tobias, 2007). By contrast, in another study using population analysis techniques, clearance in

neonates was approximately one-third of that described in adults (Potts *et al*., 2008). In addition, two studies in paediatric patients showed either comparable pharmacokinetic data to adults (Diaz *et al*., 2007), or slightly different data with respect to larger weight-adjusted Vss in children younger than 2 years of age (Vilo *et al*., 2008), indicating a need for larger loading doses in younger infants.

2.0 CARDIOVASCULAR EFFECTS

Alpha-$_2$-adrenoceptor agonists have severe physiological cardiovascular side effects. They can produce a biphasic blood pressure response, a decrease in heart rate and cardiac index, and an increase in systemic vascular resistance index and central venous pressure. Myocardial contractility and perfusion are decreased and dysrhythmias can be present (Savola, 1989; Vainio, 1989A). Minimal changes in pulmonary arterial pressure or pulmonary capillary wedge pressure have been reported (Kuusela *et al*., 2000; Pypendop and Verstegen, 1998; Bloor *et al*., 1992).

Alpha-$_2$ agonists induce dose-dependent changes in cardiovascular function (Vainio and Palmu, 1989B). The effects of medetomidine on heart rate have been found to be, to a certain extent, dose dependent in dogs (Bergström, 1988; Pypendop and Verstegen, 1998). However, in a dose titration study, only the lowest dosages (1-2 µg/kg IV) induced less pronounced effects compared to higher doses. Even at a dosage as low as 5 µg/kg IV nearly maximal cardiovascular effects were observed. Dosages above this value minimally further influenced cardiovascular function, while the duration of these effects was prolonged (Pypendop and Verstegen, 1998).

Even though cardiovascular effects of medetomidine and dexmedetomidine are mainly seen as adverse effects to the patient, studies in animal models (Roekaerts *et al*., 1996; Okada *et al*., 2007) and studies on human patients support evidence of cardioprotective effect especially in patients who either have, or are at high risk of developing, cardiac disease (Aantaa and Jalonen, 2006). A meta-analysis of human trials demonstrated reduced mortality and myocardial infarction with the use of alpha-$_2$ agonists

in patients undergoing non-cardiac, vascular surgery (Wijeysundera *et al*., 2003). In addition, dexmedetomidine was associated with a trend toward improved cardiac outcomes during non-cardiac surgery which was shown by a decrease both in mortality and non-fatal myocardial infarction or myocardial ischemia (Biccard *et al*., 2008). In a canine experiment, dexmedetomidine had cardioprotective effects by optimizing coronary artery blood flow (Roekaerts *et al*., 1996). In an isolated rat heart model, dexmedetomidine had a cardioprotective effect on global ischemia, which was mediated by alpha-$_2$ adrenergic receptors (Okada *et al*., 2007). Since peri-operative hemodynamic responses are identified as major indicators of increased risk for post-operative cardiac complications in human patients, the hemodynamic stability induced by low-dose alpha-$_2$ agonist administration may reduce the risk of cardiac events (Aantaa and Jalonen, 2006).

2.1 Blood pressure

There is an initial transient rise in blood pressure (hypertensive phase) during the first few minutes following IV injection (due to peripheral vasoconstriction through stimulation of postsynaptic alpha-$_2$-adrenoceptors of vascular smooth muscle), followed by a baroreceptor-mediated decrease in heart rate leading to sinus bradycardia. After a transient rise, arterial blood pressure falls to normal or below normal levels (hypotensive phase) (Short, 1992; Hall and Clarke, 1991) as the central effects of alpha-$_2$ agonists appear to predominate (due to stimulation of presynaptic receptors located in the CNS).

In human patients, the hypotensive phase seems to predominate even during a loading dose administration. However, hypertension may be seen on rare occasions (Tobias, 2007). The actions on blood pressure in humans are dose- and dose regimen-dependant: systemic blood pressure increases when therapeutic concentrations are significantly exceeded, and transient hypertension may occur during rapid administration of a loading dose. With appropriate doses, alpha-$_2$ agonists reliably control heart rate and blood pressure, thus augmenting hemodynamic stability in human patients undergoing surgery (Aantaa and Jalonen, 2006).

2.2 Heart rate

Heart rate was shown to decrease significantly after alpha-$_2$ agonist administration. In a study in laboratory beagles, medetomidine given at 40 μg/kg IM decreased heart rate by 63% (Vainio, 1991). In another study, heart rate decreased by 63% at all dosages (40, 80, and 160 μg/kg) with both IM and IV administration, 2-4 minutes after injection in dogs (Vainio, 1989A). Decreased heart rate may be a form of sinus bradycardia. First and second degree atrioventricular (AV) blocks may also be observed (Short, 1992). Heart rate may decrease dramatically with higher doses; decreases can reach 75% of control values (Short, 1992). Heart rates with values of 35 bpm may be seen with elevated doses. The decrease in heart rate is partly a physiological vagally mediated baroreceptor reflex to the initial hypertension and increased afterload (Maze and Tranquilli, 1991), and partly a centrally-mediated decrease due to decreased sympathetic tone. However, lower dosages (0.5-5 μg/kg) of medetomidine are presently used in clinical practice because they are associated with milder effects on heart rate. Increasing interest exists to exploit the centrally-mediated sympatholytic properties of alpha-$_2$ agonists, since it may effectively blunt the potentially deleterious increases in heart rate and blood pressure (Aantaa and Jalonen, 2006), and thus increase hemodynamic stability. This may be especially important during emergence from anaesthesia, when heart rate often accelerates in response to increased sympathetic drive.

2.2.1 Decreased heart rate and oxygen consumption

Following medetomidine administration, bradycardia is accompanied by a proportional reduction in myocardial oxygen consumption, ensuring oxygen requirements of the heart (Short, 1992; Murrell and Hellebrekers, 2005). Dexmedetomidine was found to decrease myocardial energy requirements and oxygen consumption, in parallel with decreased myocardial blood flow and oxygen supply (Lawrence *et al*., 1996B). Lowering heart rate and thereby oxygen consumption provide beneficial effects in human patients with coronary artery disease by preventing deleterious tachycardia in response to stressful

situations (Tobias, 2007; Aantaa and Jalonen, 2006). These benefits of dexmedetomidine in cardiac patients provide cardioprotection by reducing risks of myocardial ischaemia (Aantaa and Jalonen, 2006).

2.3 Cardiac output

Cardiac output decreases and peripheral resistance increases following alpha-$_2$ agonist administration in dogs (Short, 1992). A precise mechanism accounting for the huge reduction in cardiac output remains unknown although several mechanisms have been suggested. These mechanisms include a direct myocardial depressant effect, drug-induced decrease of metabolic demands, and decrease in response to alpha-$_2$ agonist-mediated increase in afterload. Other mechanisms also include decrease in heart rate, myocardial hypoxia and dysfunction in response to coronary vasoconstriction, and decrease in plasma circulating catecholamines (Murrell and Hellebrekers, 2005; Bloor *et al*., 1992; Housmans, 1990). It is likely that several of these mechanisms are involved together to decrease cardiac output during alpha-$_2$ agonist administration. These mechanisms are briefly discussed below.

A study with medetomidine in autonomically (pharmacologically) blocked dogs showed that the cardiac depressor effect of medetomidine is most likely attributable to an increase in peripheral vascular resistance caused by postsynaptic activation of alpha-$_2$ receptors in the peripheral vasculature. In that study, medetomidine did not produce any direct myocardial negative inotropic effect (Autran de Morais *et al*., 1995). To support these findings, other studies have been published on dexmedetomidine. One of them showed that dexmedetomidine in isolated dog hearts (peripheral alpha-$_2$ receptors were ruled out) did not show depressant effects (Flacke *et al*., 1992). In addition, another study concluded that dexmedetomidine did not seem to produce direct negative inotropic or chronotropic myocardial effects (Housmans, 1990).

It has been suggested that cardiac output decreases in response to dexmedetomidine, as a result of the increased afterload provoked by increased systemic vascular resistance (Bloor *et al*., 1992). However, increased systemic vascular resistance alone could not

account for the degree of cardiac output depression recorded in dogs given dexmedetomidine, because the normal canine heart maintains cardiac output when afterload is increased even when the heart is denervated (Murrell and Hellebrekers, 2005; Flacke *et al*., 1992).

Drug-induced decrease in metabolic demands could account for some of the reduction in cardiac output. However, it is unlikely that it could account alone for the high degree of cardiac output depression.

Dexmedetomidine does not seem to cause myocardial hypoxia, despite the fact that dexmedetomidine induces vasoconstriction in coronary arteries (Coughlan *et al*., 1992). Dexmedetomidine induces coronary blood flow reduction in anaesthetized dogs. This reduction was associated to increased coronary vascular resistance and increased oxygen extraction from the coronary blood supply (Flacke *et al*., 1993). However, alpha-$_2$ agonists induce a reduction in myocardial oxygen demand in parallel with decreased oxygen supply (due to coronary vasoconstriction) in healthy dogs. Thus, the oxygen delivery is maintained above the level of oxygen demand of the myocardium.

The circulating plasma catecholamines are reduced to almost undetectable levels after dexmedetomidine administration (20 µg/kg IV). This causes a reduction in inotropic support which may thus decrease cardiac output. However, this reduction was shown to occur without sympathetic support in spinal sympathectomized dogs (Bloor *et al*., 1992) and therefore does not fully explain the cardiac output reduction due to alpha-$_2$ agonist administration in dogs.

Heart rate decrease seems to be an important factor in the cardiac output reduction by medetomidine and dexmedetomidine. Nevertheless, this factor alone does not seem to account for the degree of cardiac output depression, since anticholinergic pretreatment (glycopyrrolate), used to correct bradycardia, diminished the cardiac output reduction only by one-third (Bloor *et al*., 1992).

2.4 Heart rhythm

Earlier studies raised concerns that high levels of alpha-$_2$ agonists sensitized myocardium to epinephrine-induced arrhythmias in halothane or isoflurane anaesthetized dogs. Indeed, xylazine (1.1 mg/kg IV followed by infusion at 1.1 mg/kg/h) was found to increase the likelihood of dysrhythmias in halothane- and isoflurane-anaesthetized dogs (Tranquilli *et al*., 1988; Muir *et al*., 1975).

Subsequent studies in dogs showed that lower levels of alpha-$_2$ agonists, medetomidine (750 µg/m^2 IV or 15 µg/kg IM) or xylazine (1.1 mg/kg IV or IM), did not facilitate the development of re-entrant ventricular arrhythmias in isoflurane or halothane anaesthetized dogs (Tranquilli *et al*., 1988; Pettifer, *et al*., 1996; Dyson and Pettifer, 1997; Lemke and Tranquilli, 1994, Lemke *et al*., 1993A & B). In fact, when anaesthetic-induced arrhythmogenicity is a concern, selection of the inhalation agent may be a more important consideration than the selection of alpha-$_2$ agonists.

Furthermore, decreased sympathetic tone and increased parasympathetic tone induced by lower doses of alpha-$_2$ agonist dexmedetomidine (0.1, 0.2, and 0.5 µg/kg/min) appear to attenuate the development of epinephrine-induced arrhythmias in dogs. This action seems to be mediated, at least in part, by stimulation of the central alpha-$_2$ adrenoceptors (Hayashi *et al*., 1991).

The vagal activity plays a significant role in the antiarrhythmic action of dexmedetomidine. Indeed, this action seems to be mediated more by imidazoline receptors in the CNS than by alpha-$_2$ adrenoceptors (Kamibayashi *et al*., 1995A & B), and this sustains a major interest for the preferential use of medetomidine and dexmedetomidine.

2.5 Blood flow

There is some evidence that medetomidine produces a redistribution of blood flow to preserve blood supply to vital organs (*e.g*. brain, heart, kidneys and liver), and reduces blood flow in less vital organs like skin, intestine, and skeletal muscles. A study on the

effects of a combination of medetomidine with butorphanol and midazolam, before isoflurane anaesthesia on renal cortical, intestinal, and muscle microvascular blood flow, showed a decrease in intestinal and skeletal blood flow, suggesting that this combination produced a redistribution of blood flow (Pypendop and Verstegen, 2000).

In another study on the effects of dexmedetomidine on organ blood flow, results indicated preserved blood flow to the brain, heart, liver and kidneys, at the expense of less vital organs (Lawrence *et al*., 1996A). Renal blood flow was studied in a recent study in mice after radiocontrast-induced nephropathy, which demonstrated that alpha-$_2$ agonists (dexmedetomidine and clonidine) preserved outer-medullary renal blood flow, thus improving outcomes after iodinated radiocontrast exposure (Billings *et al*., in press).

A study was conducted to determine if medetomidine could be used to decrease intracranial pressure (by decreasing cerebral blood flow) prior to anaesthetic management of animals with intracranial lesions or increased intracranial pressure. It was concluded that medetomidine (30 µg/kg IV) did not change intracranial pressure despite its significant cardiovascular effects inducing cerebral blood flow decrease (Keegan *et al*., 1995).

However, earlier studies showed that dexmedetomidine (10 µg/kg) reduces cerebral blood flow up to 50% in dogs, during halothane or isoflurane anaesthesia (Karlsson *et al*., 1990; Zornow *et al*., 1990). It was found that dexmedetomidine had no effect on cerebral metabolic rate of oxygen. Furthermore, there was no evidence of global cerebral ischemia (Zornow *et al*., 1990). The cerebral vasoconstrictive effect, combined to the significant reduction of Minimal Alveolar Concentration (MAC) for halothane or isoflurane, indicates that dexmedetomidine might be useful if used as adjunct to inhalation anaesthetics during brain surgery, in situations where an increase in cerebral blood flow should be avoided (Karlsson *et al*., 1990).

In light of these studies, alpha-$_2$ agonists-induced blood flow reduction does not cause hypoperfusion of vital organs in healthy dogs (Murrell and Hellebrekers, 2005).

2.6 Oxygen delivery

Earlier studies implied that alpha-$_2$ stimulation plays an important role in myocardial ischemia induction. Further studies showed that myocardial energy requirement decreases at low concentrations of medetomidine, whereas moderate coronary vasoconstriction occurs with high concentrations (Flacke *et al*., 1993; Coughlan *et al*., 1992). Because lower doses of the alpha-$_2$ agonist are currently used, the myocardial energy sparing effects are most likely preserved (Lawrence *et al*., 1996B).

It seems likely that alpha-$_2$ adrenergic coronary vasoconstriction could be overcome by metabolite-induced vasodilatation (a common control pathway of coronary blood flow), which preserves endocardial blood flow (Roekaerts *et al*., 1996). This was confirmed in conscious dogs (less susceptible to myocardial hypoxia than anesthetized animals) receiving a low dose of medetomidine, either as bolus (Schmeling, 1991) or as CRI (Grimm *et al.*, 2005), giving evidence that the oxygen delivery still exceeds the oxygen consumption. In an isolated rat heart model, dexmedetomidine significantly decreased coronary blood flow and significantly decreased myocardial infarct size after ischemia/reperfusion (Okada *et al*., 2007).

Cardiac output is one of the major determinants of peripheral oxygen delivery. Alpha-$_2$ agonists reduce cardiac output thus decreasing tissue oxygen tension and, due to redistribution of blood flow the peripheral oxygen delivery particularly may decrease. This effect could theoretically result in more postoperative wound infections (Akça *et al*., 2002). Decreased peripheral blood flow and oxygen delivery have prompted studies on skin perfusion during flap implantations. A recent study showed that post-operative use of dexmedetomidine for deep sedation in a porcine model of musculocutaneous transplantation did not have deleterious effects on local perfusion or tissue metabolism in denervated musculocutaneous flaps (Nunes *et al*., 2007).

Cyanosis is a frequently noticed effect of medetomidine in dogs and is thought to demonstrate poor oxygen delivery. However, the arterial oxygen tensions are not significantly changed and arterial oxygen saturation is usually above 95%. Cyanosis, following alpha-$_2$ agonist administration, occurs due to increased oxygen extraction leading

to venous desaturation. Lower heart rate and slower blood flow through tissues allows more oxygen to be extracted (Paddleford and Harvey, 1999; England and Clarke, 1989; Lin *et al*., 2008; Uilenreef *et al*., 2008).

3.0 EFFECTS OF ANTICHOLINERGICS WITH ALPHA-$_2$ AGONISTS

The use of anticholinergics to prevent bradycardia and atrioventricular blockade induced by preoperative administration of selective alpha-$_2$ agonists is controversial (Dart, 1999). Antimuscarinic (anticholinergic) pre-medication has been used with alpha-$_2$ agonists to prevent bradyarrhythmias. However, the antimuscarinic-induced increase in heart rate does not ensure an improvement of the overall cardiac performance. It may actually potentiate alpha-$_2$-adrenoceptor-mediated hypertension, produce tachycardia, and increase myocardial work (Vainio and Palmu, 1989B; Alibhai *et al*., 1996; Ko *et al*., 2001A; Sinclair *et al*., 2003A).

Cardiovascular effects after alpha-$_2$-adrenergic agonist administration are advocated to be inseparable from sedative and analgesic effects. It has even been suggested that they can be beneficial for healthy animals and should not be prevented/treated. Bradycardia, after alpha-$_2$ agonist administration, is initially a physiological vagal response to increased blood pressure and vasoconstriction. After this initial response, a central origin response is seen (Maze and Tranquilli, 1991).

Anticholinergics used to increase heart rate when necessary in combination with sedative drugs, should not be used with alpha-$_2$ agonists. Even though they may prevent medetomidine-induced bradycardia, this inhibitory effect is transient (Vainio and Palmu, 1989B).

In a study with romifidine (another potent and selective alpha-$_2$ agonist) in dogs, concurrent use of anticholinergic (glycopyrrolate) was associated with a higher frequency of dysrhythmias. Its use was therefore not recommended. Prior or concurrent administration of glycopyrrolate produces increased myocardial workload and oxygen demand (Sinclair *et al*., 2002). Pre-treatment with glycopyrrolate actually appeared to be detrimental to

cardiovascular performance, and when used with romifidine, they produced additive adverse effects on myocardial function in conscious dogs (Sinclair *et al*., 2003A).

It has been suggested that when the heart is forced to beat more frequently with the use of anticholinergics, the myocardium may suffer from a failure to meet its oxygen demand (Lemke *et al*., 1993C; Paddleford and Harvey, 1999) which may lead to myocardial ischemia and promote arrhythmias. Furthermore, the bradycardia produced by alpha-$_2$ agonists may be nonresponsive to anticholinergic drugs. The use of anticholinergics in animals receiving alpha-$_2$-agonists may promote fatal ventricular arrhythmias (Short, 1991; Tranquilli and Benson, 1992; Klide, 1992).

In addition, dexmedetomidine has antiarrhythmic effects, presumably via imidazoline receptors. These effects are associated with vagal stimulation. This demonstrates another reason not to combine them to antimuscarinic drugs (also called vagolytic agents) which would inhibit the pro-vagal antiarrhythmic effects of certain alpha-$_2$ agonists (Murrell and Hellebrekers, 2005). A meta-analysis of human trials found that co-administration of an anticholinergic with dexmedetomidine did not significantly decrease the incidence of bradycardia. In fact, their use may decrease the potential vagally-mediated cardioprotective effects of dexmedetomidine (Biccard *et al*., 2008).

For the reasons listed above, it has been suggested that the safest remedy for life-threatening bradyarrhythmias is reversible with alpha-$_2$ antagonists (Short, 1991; Pypendop and Verstegen, 1998).

4.0 RESPIRATORY EFFECTS

Medetomidine produces a slight depression of respiratory rate. This reduction in respiratory frequency is probably centrally mediated (Vainio, 1990). Intravenous dexmedetomidine in dogs was shown to induce a potent dose-dependent suppression in the slope of the CO_2 response curve, a significant decrease in resting respiratory rate, but no change in resting end-tidal CO_2 (Sabbe *et al*., 1994).

Alpha-$_2$ agonists do not induce profound respiratory depression, a common side effect associated with opioids. Although respiratory rate and minute ventilation decrease with medetomidine, arterial blood gas values do not usually change significantly (Short, 1992; Pypendop *et al*., 1996). Arterial partial pressure of CO_2 usually remains at normal levels or slightly lower and pH usually stays within acceptable range.

In a study on the effects of medetomidine on ventilatory drive in dogs, it was found that medetomidine produces less depression on ventilatory drive than isoflurane (Bloor *et al*., 1989). In spite of similar receptor locations and functions with opioids, medetomidine does not affect ventilatory drive by the same mechanism. The effects of narcotics on the ventilatory drive are profound at drug levels required during anaesthesia. In comparison to the narcotic class, medetomidine has anaesthetic qualities with far less respiratory depression (Bloor *et al*., 1989).

However, in a more recent study, it was concluded that IV administration of medetomidine at dosages of 5 or 10 µg/kg IV decreases respiratory rate, minute volume, and respiratory drive in conscious dogs. Thus, medetomidine should be used cautiously in dogs with pre-existing respiratory dysfunction, especially when given concurrently with drugs known to depress respiration, a common procedure during perianaesthetic period (Lerche and Muir, 2004).

In addition to other ventilatory effects, IV administration of dexmedetomidine in dogs was shown to prevent histamine-induced bronchoconstriction (Groeben *et al*., 2004).

The arterial partial oxygen tension (PaO_2) may decrease during the peak effect of medetomidine, because of decreased ventilation associated with an increase in $PaCO_2$. However, this corresponds to the period of slowest heart rates with a resulting decrease in whole body oxygen demand and thus adequate oxygenation of the tissues is usually maintained (Pettifer and Dyson, 1993).

When used in combination with opioids and benzodiazepines to produce profound anaesthesia, medetomidine may increase the respiratory depression primarily caused by opioids, and will lead to hypoxia, hypoxaemia (Dart, 1999), as well as compromised tissue perfusion (Pypendop *et al*., 1996; Pypendop and Verstegen, 1999). Because of these additive or synergistic side effects, oxygen supplementation should be provided during

anaesthesia and is especially important for compromised patients. In addition, ventilatory support should be provided when using these combinations (Pypendop and Verstegen, 1999).

5.0 METABOLIC AND OTHER EFFECTS

5.1 Effects on blood glucose level

Medetomidine inhibits insulin release, and increases blood glucose levels (Short, 1992). While inhibition of insulin release is rapid and significant after medetomidine administration (10 or 20 µg/kg IV), lasting for about 2 hours, the increase in plasma glucose concentration has been found to be less dramatic, slow, and non-significant with medetomidine (because of its higher alpha-$_2$ selectivity), when compared to xylazine (Burton *et al*., 1997). Mean plasma glucose concentration tended to be higher after medetomidine treatment (10 or 20 µg/kg IV) than with placebo (0.9% sodium chloride), but no significant differences between treatments were demonstrated, and plasma concentrations remained within normal physiologic range for dogs.

Another study comparing metabolic and neurohormonal effects of medetomidine and xylazine (both drugs at several different dose levels, given IM) found that both drugs increased blood glucose levels, although medetomidine far less than xylazine. In addition, medetomidine did not show a dose-dependent increase in blood glucose levels, contrary to xylazine (Ambrisko and Hikasa, 2002). Moreover, it was found that plasma peak level following medetomidine administration shifted further in time as the dosage increased. Namely, glucose peaked 2 h after 20 µg/kg IM medetomidine, 3 h after 40 µg/kg, and 4 h after 80 µg/kg.

By contrast, in another study with dexmedetomidine (5 µg/kg IV), plasma glucose concentrations were substantially decreased 30 minutes after administration of dexmedetomidine (Raekallio *et al*., 2005). Such a finding had never been described in dogs

before. However, it has been described in children after clonidine treatment. In the canine study, plasma glucose levels returned to baseline values within 90 minutes, after dexmedetomidine administration. It was suggested that with a longer follow-up period, glucose peak concentrations may have been seen.

5.2 Effects on growth hormone level

Medetomidine increases growth hormone levels in plasma by potentiating its secretion (Short, 1992; Hayashi and Maze, 1993). However, at clinical doses, this effect is not likely to have serious consequences (Hayashi and Maze, 1993; Sinclair, 2003B).

5.3 Effects on urination

Medetomidine induces a diuretic effect that last up to 4 hours (with dosages of 10 or 20 µg/kg IV) in dogs. The most probable mechanism to cause this increased production of urine is the interference with ADH-mediated water permeability in the renal tubules and collecting ducts (Burton *et al*., 1998; Crighton, 1990). This mechanism has been reported after administration of other alpha-$_2$ agonists in rats.

It has been suggested that medetomidine, like xylazine, increases plasma and urine glucose levels, which then causes osmotic diuresis. However, other studies inferred that medetomidine has a very small effect on plasma glucose concentration (Burton *et al*., 1997) and a recent study showed that dexmedetomidine decreased plasma glucose concentrations (Raekallio *et al*., 2005). These findings suggest that hyperglycemia and glucosuria, causing osmotic diuresis, are probably not appreciable factors causing voluminous urination in dogs after medetomidine/dexmedetomidine administration.

5.4 Effects on intestine

Medetomidine reduced intestinal motility and gut sounds in small animals (Dart, 1999). In fasted dogs, medetomidine (30 μg/kg IV) disrupted the migrating myoelectric complex pattern of the small intestine for approximately 2 hours. The same dose inhibited colonic motility in fasted dogs, although medetomidine-induced inhibition was preceded by a short period of increased muscle tone. In fed dogs, medetomidine (30 μg/kg IV) induced a strong increase of the proximal colon tone, while the activity of the medium and distal colon was completely suppressed (Maugeri *et al*., 1994).

Administration of medetomidine (40 μg/kg IM) significantly inhibited the motility of the gastric antrum, duodenum, mid-jejunum, and ileum. The inhibition of motility was longer in the gastric antrum and the duodenum than in the mid-jejunum and ileum. Medetomidine also inhibited gastric contractions associated with gastrin secretion (Nakamura *et al*., 1997).

This inhibitory action on intestinal motility is believed to be mediated via peripheral alpha-$_2$ receptors rather than central receptors. In addition, this inhibitory action outlasts the duration of sedation (Hall and Clarke, 1991; Cullen, 1996; Maugeri *et al*., 1994). The effects of medetomidine on gastric emptying have been shown to be weaker and of shorter duration than those of morphine (Tobias, 2007).

5.5 Emetic effects

There is an emetic effect in dogs and cats particularly after IM administration. Vomiting occurs in 5-20 % of dogs and in most cats. In another study, vomiting occurred in 17 % of dogs regardless of dose studied; however, none of the dogs receiving optimal dosage (in that study 1000 μg/m^2 IM) vomited (Hamlin and Bernarski, 1989). Normally vomiting is not a problem, but the potential for development of aspiration pneumonia exists. Moreover, vomiting also increases intracranial and intraocular pressure, which may be a problem for some patients with cerebral or ocular injury or disease (Lemke, 2004A).

5.6 Hypothermia

A decrease in body temperature has been associated with alpha-$_2$ agonist administration. The temperature reduction may be centrally mediated, with specific CNS depression, and/or in combination with non-specific depression of general metabolism and reduction in muscular activity (Virtanen, 1989; Verstegen and Petcho, 1993). In addition, it has been postulated that a direct action on noradrenergic receptors in the hypothalamus by alpha-$_2$ agonists may cause hypothermia in a dose-dependent manner (Cullen, 1996). After IV, and to a lesser extent, epidural dexmedetomidine administration, a dose dependent reduction in core body temperature was observed (Sabbe *et al*., 1994). However, in some studies with medetomidine only slight reductions of rectal temperature were observed (Pypendop and Verstegen, 1998; Pettifer and Dyson, 1993; Verstegen and Petcho, 1993).

In contrast, alpha-$_2$ agonists may allow for better maintenance of body temperature due to the peripheral vasoconstriction and central redistribution of blood, with a consequent reduction in cutaneous heat losses compared to other sedatives and anaesthetic agents that induce vasodilatation (Lemke, 2004A).

5.7 Effects on the uterus

Alpha-$_2$ agonists were found to increase the contractility of the pregnant and nonpregnant uterus in some studies. In a canine study, it was found that the effect of medetomidine depends to a higher degree on the level of steroid hormones. A rise in oestrogen levels increases the sensitivity of alpha-$_2$-adrenoceptors, while a high level of progesterone during pregnancy stimulates the sensitivity of beta-adrenoceptors and decreases the contractility of the uterus. Medetomidine does not appear to promote abortion in pregnant dogs (Jedruch *et al*., 1989).

5.8 Neuroprotection

A possible neuroprotective effect of alpha-$_2$ agonists has been suggested. The neurologic outcome after several types of cerebral ischemia may be improved with the use of alpha-$_2$ agonists (Iida *et al*., 2006) yet the underlying mechanisms still remain unclear. It was suggested that the alpha-$_2$ agonist-induced sympathetic blockade and/or decreased release of excitatory neurotransmitters (such as glutamate) may account for the neuroprotective effects during and after ischemia. It has also been postulated that neuroprotection may be mediated by a reduction in caspase-3 expression (a pro-apoptotic factor) and an increased expression of active (autophosphorylated) focal adhesion kinase, a non-receptor tyrosine kinase that plays a role in cellular plasticity and survival (Dahmani *et al*., 2005; Tobias, 2007). In addition, the cerebrovascular and cerebral metabolic effects of of alpha-$_2$ agonists may contribute, in part, to the neuroprotective action. Conflicting evidence exists for this action, since some rodent studies have demonstrated it (Kuhmonen *et al*., 1997; Jolkkonen *et al*., 1999), whereas studies in dogs (Iida *et al*., 2006) and humans lack this evidence (Sulemanji *et al*., 2007).

5.9 Effects on adrenocortical function, inflammatory response, and neuromuscular blockade

Compounds that contain an imidazoline ring (etomidate, medetomidine, dexmedetomidine) can inhibit hydroxylase enzymes involved in the production of adrenocorticosteroids (Tobias, 2007). There was no evidence of depressed adrenocortical function with dexmedetomidine concentrations used clinically in human patients, to the extent that occurs, for example, with etomidate. However, higher doses can inhibit steroidogenesis.

Dexmedetomidine decreased interleukin-6 levels from baseline (Nishina *et al*., 1999). It also blunts the systemic inflammatory response during endotoxaemia (Taniguchi *et al*., 2004).

Effects of dexmedetomidine on neuromuscular blockade function have been studied. There was no change when vecuronium was used. It induced a significant decrease in the height of the first twitch of train-of-four and an increase in neuromuscular blocking agent (rocuronium) plasma concentration. There was no evidence of direct effects on the neuromuscular junction, and these effects seemed related to alterations of pharmacokinetics of rocuronium (Talke *et al*., 1999).

6.0 ANALGESIA

Pain is defined as a subjective experience consisting of two components: perception of pain (which includes unpleasant sensory and emotional experiences) and reaction to pain, which usually results in a reaction to avoid further pain sensation.

In sedated animals the sensory message of a painful event relayed to the CNS may be unchanged, but due to the sedative effect, the emotional experience of pain feeling may be suppressed and the animal may therefore not react as vigorously as an unsedated animal.

When analgesic effects of a sedative drug are studied, it is very difficult to distinguish between true sedative and true analgesic effect (Vainio *et al*., 1989C). However, there is clear evidence (based on analgiometric measurement techniques) that medetomidine and other alpha-$_2$ agonists are highly potent analgesic agents.

Some observations from the use of medetomidine in humans at sedative doses are accompanied by the attenuation of the emotional experience of pain, although not its intensity. However, this may further complicate pain studies since the investigational models of pain may not fully reflect the patients complete clinical experience. Moreover, amelioration of pain experience is a valid goal, whether it is attributed to direct analgesic effects, sedation, or other processes (Aantaa and Jalonen, 2006).

6.1 Pain mediating alpha-$_2$ receptors

Sedative and anxiolytic effects of alpha-$_2$ agonists are mediated by activation of supraspinal receptors located in the pons (locus ceruleus). Analgesic effects are mediated by activation of receptors located in the dorsal horn of the spinal cord. However, there is also evidence that the supraspinal receptors located in the pons also play a prominent role in descending modulation of nociceptive pathway (Lemke, 2004B; Cullen, 1996; Ossipov *et al*., 1990; Stenberg, 1989). Previous animal studies have demonstrated a powerful antinociceptive effect following spinal administration of alpha-$_2$ agonists. This effect, mediated at the spinal level is present after systemic, epidural, and intrathecal administration. However, the time

to reach the peak effect and the duration of the action depend on dose and route of administration (Sabbe *et al*., 1994). Recent evidence from an animal model suggests that dexmedetomidine hyperpolarizes the membrane potential of substantia gelatinosa (superficial dorsal horn, especially lamina II) neurons by G-protein-mediated activation of potassium channels through postsynaptic alpha-$_{2A}$ and alpha-$_{2C}$-adrenoceptors. This action may contribute to its antinociceptive action in the spinal cord (Ishii *et al*., 2008).

6.2 Similarities between alpha-$_2$ receptor and opioid receptor mediated analgesia

In pain modulation, there are interactions between opioid and alpha-$_2$ receptors in the brain and spinal cord. Alpha-$_2$ receptor stimulation produces analgesic and sedative effects similar to those of opioid receptor stimulation in the CNS (Paddleford and Harvey, 1999).

First, alpha-$_2$ and opioid receptors are found in similar regions of the brain and on some of the same neurons. Both receptors are found in *locus ceruleus* (LC) and in the dorsal horn of the spinal cord (Paddleford and Harvey, 1999).

Second, these receptors have similar physiological influences. They suppress nociceptive signals with a multifactorial action on pain pathways: 1) by inhibiting neurotransmitter release from primary afferent fibers to second order neurons; 2) by affecting pre- and post-synaptic modulation of nociceptive signals in dorsal horn; 3) by influencing descending modulatory systems from the brainstem; 4) or by altering ascending modulation of nociceptive signals in the diencephalon and limbic areas (Murrell and Hellebrekers, 2005).

Third, these receptors share common molecular machinery: both receptor types are activated *via* stimulation of the pertussis toxin-sensitive G-proteins (G_i and/or G_o) on the cell membrane. Adenylate cyclase is inhibited, resulting in the reduction of the intracellular cAMP content. This leads to the opening of potassium channels, causing the cell to loose potassium and inhibition of the voltage-gated calcium channels. Calcium is blocked and noradrenaline release is inhibited. The cell becomes hyperpolarized (more negatively charged), making the cell unresponsive to excitatory input; thus, the transmission pathway

is blocked (Fukuda, 2005; Paddleford and Harvey, 1999; Maze and Tranquilli, 1991; Ossipov *et al*., 1990).

Consequently, the alpha-$_2$ agonists and mu-opioids produce analgesia by similar mechanisms.

6.3 Clinical implications in pain management

Alpha-$_2$ agonists are highly effective to treat short-term pain in humans. They are used intraoperatively and postoperatively. Using alpha-$_2$ agonists instead of opioids allows avoiding problems like respiratory depression, pruritus, urinary retention, and abuse liability. Using alpha-$_2$ agonists together with opioids reduces opioid requirements (Kamibayashi *et al*., 2000). When using a combination of alpha-$_2$ agonist and opioid, the doses may be reduced and consequently the side effects of both drugs are reduced. Decreased doses of opioids induce less respiratory depression, while alpha-$_2$ agonists induce less cardiovascular depression (Ossipov *et al*., 1990).

In studies with rats, alpha-$_2$ agonists also have some advantages against neuropathic pain. Alpha-$_2$ agonists may attenuate or even reverse the allodynia that occurs in neuropathic pain. Neuropathic pain is highly difficult to manage with other modalities such as opioids therefore alpha-$_2$ agonists may have a potential to treat opioid-resistant pain (Murrell and Hellebrekers, 2005).

Increasing evidence from human medicine, with the use of dexmedetomidine infusion, seems to imply that analgesic efficacy for postoperative pain may only be moderate, with currently recommended doses (Gomez-Vasquez *et al*., 2007). However this moderate analgesic effect in conjunction with the anxiolytic and sedative effects may attenuate the unpleasantness of pain (Aantaa and Jalonen, 2006).

6.4 Alpha-2 agonists induce analgesia dose-dependently

Medetomidine and dexmedetomidine in dogs showed that the degree of analgesia was significantly dose-dependent (Kuusela *et al*., 2001). The analgesic effect of medetomidine in the dog was suggested to begin at plasma levels of 1-5 ng/ml (Salonen, 1992). By contrast, in a study where analgesia was assessed by limb withdrawal to toe pinching, analgesia was already considered practically nonexistent with a medetomidine plasma level as high as 9.5 ng/ml (Kuusela *et al*., 2000). In addition, analgesia with pure dexmedetomidine lasted longer than with the corresponding level of racemic medetomidine, suggesting greater potency of dexmedetomidine in dogs (Kuusela *et al*., 2000).

Assessment of the analgesic effect based on the pinprick and pedal reflex tests showed that analgesia observed in dogs was dose-dependent in strength at dosages of 10-80 µg/kg IM. Slight analgesia was observed at 10-30 µg/kg IM and was most prominent between 40 and 80 µg/kg IM. Good analgesia lasted 1 hour at 40 µg/kg IM (Vainio *et al*., 1986). Using analgesiometric technique, after a single dose of dexmedetomidine (20 µg/kg), analgesia was suggested to last for about one hour (Murrell and Hellebrekers, 2005). Time to reach maximal effect and duration of analgesia (evaluated by skin twitch) were dependent of the dose and the route of administration in dogs following IV, epidural, and intrathecal administration of dexmedetomidine (Sabbe *et al*., 1994). After IV administration of 10 µg/kg dexmedetomidine, the analgesic effect began within 3 minutes and lasted 90 minutes. Analgesic effect appears to be more potent and to last longer after epidural administration, with less systemic redistribution providing less systemic (hemodynamic and neurobehavioral) effects.

Alpha-$_2$ agonists were shown to produce excellent sedation, lasting longer than with the effective analgesia (Short, 1992). This was important when medetomidine was used for premedication and the analgesic effect was needed for the entire duration of the procedure. Thus readministration of the drug might be needed to prolong the analgesic effect (Murrell and Hellebrekers, 2005).

Based on human studies, there are conflicting results on analgesic efficacy of dexmedetomidine. While some have reported good peri-operative analgesia and reduction of the opioid consumption (Tufanogullari *et al*., 2008), others have reported only moderate analgesic effects in the early postoperative period (Gomez-Vazquez *et al*., 2007). This discrepancy may be related to dose regimen given as well as invasiveness of the surgery. Healthy adults for elective orthopaedic surgery appear to benefit less from the analgesic effect of dexmedetomidine. In addition, the induced sedation in this context may not be desirable.

7.0 SEDATION, ANAESTHETIC SPARING, AND SYNERGISTIC OR ADDITIVE EFFECTS WITH OTHER DRUGS

The pharmacological sedation induced by medetomidine or dexmedetomidine *via* their action on the *locus coeruleus* of the brain stem has been demonstrated to closely resemble physiological non-REM sleep (Huupponen *et al*., 2008). Endogenous sleep pathways may be involved in dexmedetomidine-induced sedation (Nelson *et al*., 2003).

When medetomidine or detomidine were used as premedication, there was a major reduction in any subsequent anaesthetic requirements (Ewing *et al*., 1993, Vainio, 1991, Young *et al*., 1990). This supports the evidence of the sedative and analgesic properties of medetomidine and detomidine (Short, 1992). This anesthetic sparing effect was found to be significantly dependent of medetomidine dose level (Kuusela *et al*., 2001).

Synergistic or additive effects may be observed when medetomidine or dexmedetomidine is combined with other agents (tranquilizers, opioids, injectable anaesthetics, and inhalant anaesthetics) (Verstegen and Petcho, 1993; Hammond and England, 1994).

7.1 Synergistic and/or additive effects in combinations

Combinations of opioids and alpha-$_2$ agonists can result in profound sedation and analgesia in dogs (Short, 1992). Evidence of synergistic effects of alpha-$_2$ agonists with opioids was found in studies with mice and rats, and more recently in studies in dogs and cats.

In a study from Ossipov et al. (1990), evidence was found for synergy of medetomidine with opioids (fentanyl, morphine, and meperidine) after intrathecal administration of these combinations and additive effects of these combinations after IV administration in rats (Ossipov *et al*., 1990). Another study using an alpha-$_2$ agonist, moxonidine, demonstrated spinal antinociception and synergy with opioids in the mouse spinal cord (Fairbanks *et al*., 2002).

In addition, a study in cats has shown the ability of subanalgesic doses of the alpha-$_2$ agonist, clonidine, to have an additive or synergistic effect on analgesia produced by opiates, when both drugs were administered epidurally or intrathecally (Omote *et al*., 1991).

In a study on epidurally administered morphine (0.11 mg/kg) and medetomidine (5 µg/kg) in dogs, a simultaneous administration of these drugs suggested an additive and even synergistic interaction between these two agents when administered epidurally (Branson *et al*., 1993). The synergistic effects in dogs seem to be restricted to epidural or intrathecal administration (Ossipov *et al*., 1990; Branson *et al*., 1993).

This synergy between alpha-$_2$ and opiate agonists was suggested to be caused by the activation of alpha-$_2$ adrenoceptors on opiate-containing interneurons. This would result in increased release of opiate peptides (Omote *et al*., 1991; Branson *et al*., 1993). The therapeutic advantages of opioids and medetomidine combinations are envisioned as increased analgesia with reduced respiratory and cardiovascular involvement by decreasing dose requirements of both drugs.

Studies with combinations of medetomidine and opioids such as hydromorphone or butorphanol have suggested 1) improved analgesia (Grimm *et al*., 2000) and 2) the sedation prior to induction, may facilitate orotracheal intubation, improve quality of anesthesia, and have similar cardiovascular effects when compared to medetomidine alone (Kuo and

Keegan, 2004; Muir *et al*., 1999). Contrary to these findings a study using a combination of medetomidine (10 µg/kg) and butorphanol (0.2 µg/kg) failed to demonstrate any advantages when compared to 40 µg/kg of medetomidine given alone (Ko *et al*., 1996). However, in a more recent study, the same author concluded that a combination of medetomidine (30 µg/kg) with butorphanol (0.2 mg/kg) or ketamine (3 mg/kg) resulted in a more reliable and uniform sedation in dogs, when compared to medetomidine (30 µg/kg) alone (Ko *et al*., 2000B).

There is also evidence that medetomidine prevents or blunts stress-related neurohormonal changes produced by opioids or ketamine administration in dogs. This supports the use of medetomidine in combination for sedation or anaesthesia of healthy dogs (Ambrisko *et al*., 2005).

Combining low doses of alpha-$_{2}$-, opioid-, and benzodiazepine-agonists in dogs, resulted in a synergistic CNS depressant response, while minimizing the undesirable side effects of these three classes of drugs (Verstegen and Petcho, 1993; Paddleford and Harvey, 1999).

7.2 Anaesthetic sparing effects

Alpha-2 agonists have highly potent anaesthetic sparing effects. Medetomidine can reduce propofol dosage requirements by 75 % in dogs (Short, 1992; Vainio, 1991). Medetomidine also produced a dose-dependent reduction of dose requirements of propofol for induction. With a dose 5 µg/kg IM of medetomidine, the mean induction dose of propofol was decreased by more than 50% from 6.0 to 2.86 mg/kg. With medetomidine doses of 10, 20, and 40 µg/kg IM the mean induction dose of propofol was decreased to 1.44, 1.12, and 0.77 mg/kg, respectively (Hammond and England, 1994).

Medetomidine extends the duration of propofol anaesthesia and provides post-anaesthetic sedation and analgesia (Bulafari *et al*., 1996). In addition, propofol infusion in medetomidine premedicated dogs was suggested to alleviate medetomidine-induced vasoconstriction (Thurmon *et al*., 1994). In a previous study by Vainio (1991), propofol

also had a positive chronotropic effect after medetomidine premedication, alleviating the medetomidine-induced negative chronotropic effect.

In a human study, dexmedetomidine reaching plasma concentrations approximately 0.66 ng/ml, reduced propofol concentrations required for sedation and for suppression of motor response to electrical stimulation by approximately 65-80%, and 40% respectively (Dutta *et al*., 2001).

Medetomidine markedly reduced thiopentone dose required for intubation in a dose-dependent manner (Young *et al*., 1990, Cullen, 1999, Ko *et al*., 2000A). In a study by Young *et al*., (1990) the barbiturate sparing effect of medetomidine was significant at all three dose rates examined. The mean doses of 1.25% thiopentone required for intubation were 6.9, 4.5, and 2.4 mg/kg with medetomidine at dose levels 10, 20, and 40 µg/kg IM, respectively. At high medetomidine dosages (40 µg/kg), some dogs can even be intubated with medetomidine alone (Young *et al*., 1990). In another study, after 40 µg/kg medetomidine, the thiopental induction dose was 4.4 mg/kg compared with 14.8 mg/kg without medetomidine (Ko *et al*., 2000A).

Medetomidine, given at 40 µg/kg IM, reduced halothane dose requirements by at least 30 %, compared to a dose level of 20 µg/kg IM in a canine study (Räihä *et al*., 1989B). In a study with halothane, the dosage of medetomidine 10 µg/kg IM had a halothane sparing effect comparable to other sedatives (acepromazine and meperidine) while a dose level of 40 µg/kg IM of medetomidine showed a clear decrease in halothane consumption (Räihä *et al*., 1989A).

In a study with rats, dexmedetomidine decreased dramatically the MAC of halothane in a dose dependent manner (doses of 10, 30, and 100 µg/kg IP) such that at 100 µg/kg, halothane could even be discontinued for up to 30 minutes without eliciting a purposeful response to tail-clamping (Segal *et al*., 1989).

In a study with dogs using three dosages of medetomidine (1, 3, and 10 µg/kg administration *via* right atrial port over 15 minutes) the MAC for halothane significantly decreased in a dose-dependent manner. Following medetomidine administration, the MAC for halothane decreased progressively and at the highest dosage (10 µg/kg), the anaesthetic requirement decreased by 90 % (Vickery and Maze, 1989).

In addition, medetomidine at 30 µg/kg IV reduced isoflurane maintenance requirements by 47 % (Ewing *et al*., 1993). Moreover, dexmedetomidine at 20 µg/kg IV reduced isoflurane MAC maximally (89 %) 30 minutes after the injection (Bloor *et al*., 1992). In a recent study using three dosages (0.1, 0.5, and 3.0 µg/kg/h) of continuous infusion of dexmedetomidine in dogs, the MAC reduction was found to increase dose-dependently (Pascoe *et al*., 2006). Significant decreases in MAC were found with 0.5 and 3.0 µg/kg/h doses (decreases of 18 % and 59 %, respectively).

Medetomidine premedication is also often used prior to ketamine administration, an injectable dissociative anaesthetic. This combination characterized by fewer bradycardic effects, induces more adverse effects as well as an inferior overall quality of anaesthesia and recovery than the medetomidine-propofol combination (Hellebrekers, 1998). In addition, respiratory depression is usually more profound when dogs are given ketamine (Ko *et al*., 2001B).

When alpha-$_2$ agonists are used as premedication, it is necessary to remember that due to their cardiovascular effects (decreased blood flow), the distribution of other anaesthetic drugs is slower than expected and it is thus important to wait before re-administration of other anaesthetic drugs (propofol, barbiturates, etc.). The uptake of inhaled anaesthetics is also delayed, meaning that an adequate time should be allowed to permit stabilization. Failure to recognize these factors may lead to overdosing of other anaesthetic agents (Manners, 1990; Short, 1992; Hellebrekers *et al*., 1998; Lemke, 2004A).

Because all general anaesthetics (thiopental, propofol, halothane, isoflurane, etc.) have dramatic effects on myocardial function and a very narrow therapeutic range, the dose reduction achieved by administering alpha-$_2$ agonists preoperatively reduces the adverse cardiovascular effects associated with administration of most general anaesthetics. For example, preoperative medetomidine administration counteracts the cardiovascular effects of isoflurane, first, by reducing the amount of isoflurane needed and, then, by restoring vascular tone (vasoconstriction effect of alpha-$_2$ agonists) (Lemke, 2004A).

8.0 CLINICAL USE

Alpha-$_2$ agonists have been used alone for minor procedures. They are not regarded as anaesthetics; therefore, additional agents (local or general anaesthetics) are needed for surgery. Medetomidine is a highly potent sedative and analgesic agent for clinical use. Relatively high doses of medetomidine alone suffice for examination, clinical procedures, and simple surgical operations in dogs (Vähä-Vahe 1989B). However, low doses and combination with other analgesic and anaesthetic agents to produce balanced anaesthesia and analgesia are preferred.

8.1 Chemical restraint and sedation

Alpha-$_2$ agonists are useful for chemical restraint alone or in combination with opioids and benzodiazepines, and are reversible with alpha-$_2$ antagonist (Short, 1992). Because medetomidine and dexmedetomidine provide rapid and completely reversible sedation with analgesia, along with almost no respiratory depression, these agents may provide increased patient safety in certain situations (Talke, 1998).

Administration of a moderate dosage of medetomidine (5 µg/kg IV) provided a useful adjunct to diazepam-ketamine induced anaesthesia in dogs. It improves the quality of anaesthetic induction, ease of endotracheal intubation, and extends the duration of analgesia and lateral recumbency in anaesthetized dogs (Ko *et al*., 1998).

8.2 Premedication

Medetomidine used as premedication (at dosage levels of 1000 or 1500 µg/m^2, equivalent to 40 µg/kg or 60 µg/kg for a 25-kg dog, respectively), provided a good basis for anaesthesia (in terms of sedation and hypnosis) and satisfactory analgesia for surgical intervention. Premedication was achieved reliably with medetomidine, and provided an

uneventful and stress-free preparation for surgery and anaesthesia induction. (Hellebrekers and Sap, 1997).

Several studies have found that medetomidine is a good premedication to be used before induction (and maintenance) of anaesthesia by propofol (Hellebrekers and Sap, 1997; Thurmon *et al*., 1994; Vainio, 1991).

8.3 Analgesic and anaesthetic adjuvant to reduce perioperative stress and increase patient safety

Medetomidine and dexmedetomidine have been shown to control the stress response induced by anaesthesia and surgery during the perioperative period. They reduced perioperative levels of stress-related hormones (Väisänen *et al*., 2002).

In humans dexmedetomidine attenuated increases in heart rate and plasma norepinephrine concentrations during emergence from anaesthesia (Talke *et al*., 2000); Moreover, dexmedetomidine seemed to conceal stress effects of anaesthesia during recovery (Kuusela *et al*., 2003) in dogs. These findings have increased interest in use of alpha-$_2$ agonists as preanaesthetic to promote balanced anaesthesia and minimize overall stress response (Ambrisko *et al*., 2005, Väisänen *et al*., 2002, Benson *et al*., 2000).

Medetomidine premedication in combination provides safer anaesthesia by lowering the dose of other sedative, analgesic and anaesthetic agents. Furthermore, when used in combination the dose requirement of medetomidine itself is decreased, adding to the safety of the anaesthesia.

As adjuncts to general anaesthetics, alpha-$_2$ agonists have a nearly ideal pharmacodynamic profile in dogs. In addition to providing sedation, analgesia, and muscle relaxation, they produce substantial reduction in the amount of injectable and inhalational anaesthetic requirements and also attenuate the sympathetic activity and stress response to surgical trauma by reducing catecholamine and cortisol levels postoperatively (Benson *et al.*, 2000, Ko *et al.*, 2000A, Väisänen *et al*., 2002, Talke *et al*., 1997).

Alpha$_{-2}$ agonists have their place in controlling the emergence from anaesthesia. During this phase, patients may benefit from the sedative, anxiolytic, and analgesic effects

and attenuation of the hemodynamic disturbances due to increased sympathetic drive. In addition, dexmedetomidine is used to control and treat opioid withdrawal after prolonged use of opioids and benzodiazepines (Tobias, 2006). A significant reduction in the incidence of delirium with dexmedetomidine after surgery in humans has been documented. Prevention of shivering, which has deleterious influences including increased oxygen consumption and potentially increased demand on myocardial capacity was also reported (Aantaa and Jalonen, 2006).

8.4 Side effects

Side effects (other than cardiovascular) reported after medetomidine use were almost exclusively limited to vomiting and muscle jerking in dogs (Vähä-Vahe, 1989A). However, vomiting may sometimes be an advantage before surgery if owners have failed to fast their dogs prior to sedation.

Other side effects following medetomidine administration include cyanotic or pale mucous membranes, irregular breathing pattern, squalling at injection, diarrhea, panting, restlessness, and collapse.

8.5 Failures

Stress, excitement or pain may increase endogenic catecholamine levels interfering with smooth sedation. When possible, a calm and gentle handling of the animal during administration of drug is desirable. Sedation is more effective in quiet areas without environmental stimulation (Short, 1992).

Cardiac or respiratory disorders, obesity or cachexia, may influence levels of sedation. Very young and very old animals usually need a lower dose of drug to achieve sedation than what would be predicted from their bodyweight alone. Small dogs seem to need higher doses of medetomidine per kilo bodyweight to obtain an equal effect, compared to large dogs (Vähä-Vahe, 1989A).

If the route of administration is IM or SC, sometimes the final site of injection may occur between fascias or within connective tissue or fat. Absorption of the drug may be delayed, resulting in poor sedation.

8.6 Safety

Alpha-$_2$ agonists have minimal toxicity and a remarkably wide safety margin (Kamibayashi *et al*., 2000). Alpha-$_2$-compounds are excreted via the kidneys after elimination by biotransformation by the hepatic system (Salonen, 1989).

Because alpha-$_2$ agonists are mainly metabolized by the liver, it is implied that hepatic blood flow, and therefore cardiac output (reduced by alpha-$_2$ agonists), might influence its pharmacokinetics and further, its clearance. However, in a study by Dutta *et al*., (2000) no clinically significant decrease in dexmedetomidine clearance was found in humans receiving the therapeutic dose range. In another report in human adults with severe hepatic failure, there was an increase of Vss and elimination $T_{½}$ and a decrease in clearance (Cunningham *et al*., 1999).

In a pharmacokinetics study on dexmedetomidine in humans severe renal impairment minimally affected pharmacological effects. The sedative effects were prolonged (probably because of lower plasma protein binding and therefore more effective and free molecules in the plasma) in patients with renal disease although the drug half-life was shorter (De Wolf *et al*., 2001).

8.7 Constant rate infusion

A low dose medetomidine CRI may provide more constant levels of analgesia by maintaining constant plasma levels of alpha-$_2$ agonists (Murrell and Hellebrekers, 2005). Intermittent administration of a drug may fail to provide its effects continuously. This problem can be overcome by administering analgesic by continuous infusion to maintain effective plasma level of analgesic (Flecknell, 2000).

In humans dexmedetomidine infusion at a dosage of 1 µg/kg over 10 minutes followed by 0.2-0.7 µg/kg/h for less than 24 hours, is approved in many countries for use in the intensive care setting as a sedative in adults, initially intubated and mechanically ventilated patients, before, during, and after extubation (http://precedex.hospira.com/_docs/PrecedexPI.pdf).

A study with dexmedetomidine CRI in dogs showed that at infusion levels of 0.5 and 3.0 µg/kg/h (with loading dose of 0.5 or 3.0 µg/kg over 6 min, respectively) could be used to manage dogs undergoing surgery, where the provision of analgesia and limitation of stress is desirable (Pascoe *et al.*, 2006). Dexmedetomidine is the active enantiomer in the racemate medetomidine and was found to produce approximately similar effects, when administered at half the dose, compared to medetomidine (Virtanen, 1989).

A study using a high fentanyl bolus dose (15 µg/kg IV) during an 11-hour medetomidine CRI at 1.5 µg/kg/h showed that even with this small dose level of medetomidine there were marked hemodynamic changes. Decreased heart rate and cardiac index occurred in most dogs within 15-30 minutes of the beginning of the infusion without a loading dose. After one hour, all dogs had reduced heart rates. However, stroke volume index was not decreased, suggesting the change in cardiac index was related to lower heart rate. Profound cardiorespiratory effects were seen during co-administration of fentanyl bolus and medetomidine (Grimm *et al*., 2005).

Although medetomidine will always be associated with some cardiovascular changes, these effects may be diminished by lowering the dose and using CRI to maintain adequate plasma concentrations (plasma levels slightly lower than those obtained with 2

μg/kg IV). This alternative decreases the cardiovascular changes and controls the duration of sedation (Pypendop and Verstegen, 1998).

Two recent studies with dexmedetomidine CRIs in dogs have demonstrated the usefulness of low-dose CRI administration in this species as a reliable and valuable adjunct during and after general anaesthesia (Lin *et al*., 2008; Uilenreef *et al*., 2008). Plasma concentrations were maintained, as well as sedative and anxiolytic effects, whilst hemodynamic effects were decreased and overall tissue perfusion remained adequate.

9.0 ALPHA-$_2$ ANTAGONISTS

A highly potent and selective antagonist of centrally and peripherally located alpha-$_2$-adrenoceptors, atipamezole, has been created for its use as a reversal agent for medetomidine (Virtanen, 1989). Atipamezole is able to antagonize the behavioural, cardiovascular, gastrointestinal, neurochemical, analgesic, and hypothermic effects of medetomidine (Virtanen, 1989; Savola, 1989; Vainio, 1990).

In a study by Vainio (1990), the medetomidine-depressed heart rate was significantly increased by atipamezole, although not to the initial level. Simultaneously, the bradyarrhythmic features observed in ECG, were abolished (Vainio, 1990).

The arousal time after IM atipamezole administration (dose approximately 5 times the dose of medetomidine) is more or less 5 minutes (Vähä-Vahe, 1990). Administration of the antagonist will also reverse analgesia produced by alpha-$_2$ agonist (Short, 1992).

Atipamezole can be given to reverse medetomidine in emergency situations. Atipamezole can reverse the cardiopulmonary effects of medetomidine in sick dogs, before any complications might be expected (Vainio, 1990). Usually, atipamezole is given to reverse the effects of medetomidine after non-painful diagnostic or therapeutic procedures, and is not usually given perioperatively.

Complete reversal of the sedative and analgesic effects of medetomidine is achieved when atipamezole is given IM to dogs at 4-6 times the dose of medetomidine (Vähä-Vahe, 1990). Atipamezole and anticholinergics can both cause dramatic heart rate increases. Concurrent use of these drugs should therefore be avoided.

Recently, there has been increasing interest to find clinically useful alpha-$_2$ antagonists that specifically antagonise the peripheral cardiovascular effects whilst maintaining the centrally mediated sedative, analgesic and anxiolytic effects of dexmedetomidine and medetomidine (Enouri *et al*., 2008, Honkavaara *et al*., 2008). This may further increase the safety of these drugs, if clinically available selective peripheral antagonists become available.

10.0 RESEARCH HYPOTHESIS

This literature review brings forward the hypotheses for the study. We first hypothesised that the cardiovascular effects of alpha-$_2$ agonist medetomidine, as CRI, depend on the dose and that a dose level could be found with minimized cardiovascular changes. The second hypothesis is that this dose level of medetomidine CRI would represent a protocol for perioperative sedation and provision of analgesia, which could be demonstrated by measured adequate analgesic plasma concentrations.

SECOND CHAPTER – ARTICLE

Hemodynamic response to an intravenous infusion of medetomidine at six different dose regimens in isoflurane-anesthetized dogs

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Clinical Relevance

This study investigated the dose-dependency of hemodynamic effects of IV medetomidine (MED) constant rate infusions (CRI) during isoflurane (ISO) anesthesia. Twenty-four healthy beagles randomly received one of six MED CRI regimens. A loading MED infusion was administered at 0.2, 0.5, 1.0, 1.7, 4.0 or 12.0 $\mu g \cdot kg^{-1}$ for 10 min, followed by a maintenance CRI providing identical dose amounts over 60 min. Heart rate (HR) and mean arterial blood pressure (MAP) were recorded, blood gases analyzed and cardiac index (CI) determined. Statistical analysis involved a repeated measures linear model. Baseline CI decreased dose-dependently as MED dose increased by: 14.9 (12.7), 21.7 (17.9), 27.1 (13.2), 44.2 (9.7), 47.9 (8.1), and 61.2 (14.1) % respectively. The four lowest doses induced limited and transient changes in HR, MAP, and CI. Further investigation into potential perioperative uses of MED CRI is warranted.

1. Introduction

Medetomidine (MED) is a highly potent and selective alpha-$_2$ agonist which has sedative, anxiolytic, muscle relaxant, and analgesic properties. It reduces requirements for other anesthetic agents and is widely used for sedation and pre-medication before general anesthesia in small animals[1]. It is supplied in a 50:50 racemic mixture of two optical enantiomers (dexmedetomidine and levomedetomidine), of which dexmedetomidine (DMED) is the active enantiomer[2,3]. Medetomidine has a very high affinity for alpha-$_2$ adrenoceptors where it acts as a full agonist and possesses a selectivity ratio of 1620/1 (α_2/α_1) which is 5-10 times higher than for xylazine (α_2/α_1 ratio 160/1) or detomidine (260/1)[2].

Medetomidine is licensed in North America to be administered intramuscularly (IM) or intravenously (IV). After IM administration, absorption of the drug is rapid as peak serum levels are reached within 30 min[4]. When given IV, the onset of action is rapid and the peripheral cardiovascular effects are more pronounced than by IM administration[5]. Low MED doses are adequate for perioperative use when given with other anesthetic/analgesic drugs, due to its significant sedative, analgesic, and anesthetic sparing effects[6].

In spite of the analgesic and perioperative stress response reducing effects[7] MED has not been used to its full potential in veterinary medicine. Unfortunately, alpha-$_2$-adrenoceptor agonist administration, particularly IV, is associated with major side-effects on the cardiovascular system. These include a biphasic blood pressure response (hypertension, followed by normo- or hypotension) with reflex bradycardia and decreased cardiac index (CI), increased systemic vascular resistance (SVR) index and central venous pressure (CVP), and bradydysrhythmias[8,9]. Hence, these hemodynamic effects have popularized the use of low rate MED or DMED IV infusions in an attempt to improve the risk/benefit ratio. Several reports in the literature describe the clinical potential of this administration strategy[10-13], however, to the authors' knowledge, no previous study has quantified the dose-dependency of MED constant rate infusion (CRI) hemodynamic effects to determine a dose rate, which optimizes cardiovascular safety.

It has been reported that the cardiovascular effects of MED following IV bolus administration in conscious dogs do not follow a clear dose-response relationship based on evaluation of, time-effect data[5]. It is possible that failure to reveal such a dose-response relationship could be related to inter-individual variation in the disposition pharmacokinetics of the drug. The aim of this study was to quantify the dose-dependency

of the cardiovascular/ hemodynamic effects when MED is administered as a CRI in isoflurane (ISO)-anesthetized dogs. To our knowledge, despite the recent quantification of the minimum alveolar concentration (MAC) sparing effect of DMED CRI[11], the dose-response effects of MED or DMED on the degree of cardiovascular depression are yet to be determined, and this information is necessary to establish an optimal dose rate. Two studies have been recently published investigating DMED CRIs in dogs. In one, a clinical study, 3 doses (1, 2 and 3 $\mu g \cdot kg^{-1} \cdot h^{-1}$) of DMED resulted in acceptable mean arterial blood pressure (MAP) and adequate tissue perfusion[13]. A second, experimental study, using a single dose (25 $\mu g \cdot m^{-2} \cdot h^{-1}$) of DMED CRI compared cardiovascular and respiratory effects between propofol and isoflurane anesthetic groups[12]. They reported adequate oxygen delivery and a significant effect of general anesthetic on heart rate (HR), vasoconstriction and CI. In order to test the hypothesis that the intensity and duration of the hemodynamic changes associated with MED exposure vary as a function of dose rate, we administered MED at six different CRI dose rates. Furthermore, identification of a CRI dose rate associated with minimal hemodynamic effects that still maintains what has previously been proposed[14] as an analgesic plasma concentration of MED would be of great interest.

2. Materials and Methods

2.1. Animals

Clinically healthy purpose-bred laboratory beagles (n=24; 13 spayed females and 11 castrated males) were used in this study. Dogs were between 1 and 3.5 years old and weighed between 8.6 and 16 kg. They were housed in groups of 6-7 dogs in large pens. Commercial dog food was given once daily and water was freely available. The care and

use of the dogs complied with Canadian Council for Animal Care[15]. The Animal care committee of the institution approved the study protocol (05-Rech-1298). All procedures were performed during the day, with two experiments completed during each study day. Dogs were brought to single cages the night before each study day, where water was given and food was withheld. Dogs were fed following full recovery from the experiment. All dogs were accustomed to handling and instrumentation.

2.2. Treatments

Each dog randomly received one of 6 treatments (6 groups, n=4 per group), in a prospective, controlled, blinded design. Medetomidine hydrochloride (Domitor; Orion Pharma, Espoo, Finland / Pfizer Animal Health, Kirkland, QC, Canada) was administered over 10 min as a manual loading infusion rate of 1.2, 3.0, 6.0, 10.2, 24.0 or 72.0 $\mu g \cdot kg^{-1} \cdot h^{-1}$, followed by a 60 min maintenance CRI at automated rates of 0.2, 0.5, 1.0, 1.7, 4.0 or 12.0 $\mu g \cdot kg^{-1} \cdot h^{-1}$ respectively. Isoflurane (AErrane; Baxter Corp, Mississauga, ON, Canada) was administered during the whole duration of the experiment, including the time required for instrumentation and stabilization, a resting time where baseline values were recorded before MED administration, the 70 min-long exposure to MED combined with ISO, and again a 60 min follow-up (ISO alone) after the end of MED CRI.

2.3. Study procedure

Each treatment was initiated by mask induction with ISO in oxygen. Dogs were intubated and general anesthesia was continued with the use of a Bain non-rebreathing system (Moduflex coaxial; Dispomed, QC, Canada) by maintaining the end-tidal ISO

concentration (ET-ISO) at a constant level of approximately 1.0 MAC (*i.e.* 1.3-1.4% in dogs[16]), and the ET-CO_2 at 35-45 mmHg by controlled intermittent positive pressure ventilation (IPPV) (Hallowell EMC Model 2000 ventilator; Hallowell Engineering & Manufacturing Corp, Pittsfield, MA, USA). During the experiment, body temperature was monitored and stabilized at 37.0 C^o with warm-water circulating heating mats (Micro-Temp II 747; Cincinnati Sub-zero Products Inc, OH, USA). Following initiation of IPPV, a 22 SWG cannula (BD Insyte-W^{TM} catheter; Becton Dickenson Infusion Therapy Systems Inc, UT, USA) was placed in the dorsal pedal artery of a pelvic limb, to monitor directly the systemic blood pressures, cardiac output (CO), and to collect arterial blood samples. Two 20 SWG cannulas (BD Angiocath I.V. catheter; Becton Dickenson Infusion Therapy Systems Inc., UT, USA) were placed in each cephalic vein: one for MED infusion, and the other to allow administration of fluid (0.9% Sodium Chloride Injection USP; Baxter Corporation, Mississauga, ON, Canada) at a rate of 10 $mL \cdot kg^{-1} \cdot h^{-1}$, and lithium chloride (LiCl inj; LiDCO Ltd, London, UK). A 20 SWG cannula was placed in a jugular vein for venous blood sampling. Dogs were placed in lateral recumbency and arterial cannulas were connected to a transducer (Pressure Monitoring Kit with Truwave disposable Pressure Transducer; Edwards Lifesciences, Irvine, CA, USA) that was connected to a multiparametric vital signs monitor (Life window LW-6000 Multi-Parameter Vital Signs Monitor; Digicare Biomedical, FA, USA). The pressure transducer was adjusted to heart level. Heart rate, lead II electrocardiogram, direct systolic, diastolic, and mean systemic arterial pressures (SAP, DAP and MAP, respectively), pulse oximetry, capnography, ET-ISO, and rectal temperature were recorded at 5-min intervals with the vital signs monitor from baseline until the end of the 130 min follow-up period. Systemic blood pressures and

HR were allowed to stabilize (three consecutive measurements with minimal variation: HR±5 bpm, MAP=60 mmHg±15 mmHg) before baseline values were recorded. Respiratory rate (RR) and tidal volume (TV) were also monitored and stabilized during the study.

The lithium dilution method (LiDCO Ltd, London, UK) was used to measure CO and calculate CI, once at baseline and then every 10 min during the 130 min anesthesia. The LiDCO values were determined by use of a commercial LiDCO computer (LiDCO plus hemodynamic monitor HM 71-02, LiDCO Ltd, London, UK); measurements were performed according to manufacturer's instructions, and reports for small animals use[17,18]. Lithium chloride (5 $\mu mol \cdot kg^{-1}$) was administered for each CO measurement through the cannulated cephalic vein[17]. The SVR was calculated with the formula SVR=80 x (MAP-CVP)/CO, where an average value of 4 mmHg was used for CVP.

The MED loading doses were diluted with isotonic saline to a final 2 mL volume. Doses were hand-injected with 3 mL syringes over 10 min. All maintenance infusion doses were diluted with isotonic saline to a final 30 mL volume, and were administered through a cephalic venous cannula with an infusion pump (Harvard Apparatus 22, model 55-2222, MA, USA) over 60 min.

Arterial and venous blood samples were taken from the pedal artery and jugular vein cannulas with syringes connected to 3-way stopcocks. The first 1 mL of blood diluted with the heparinized saline lock was discarded, the sample collected, and the cannula flushed with isotonic heparinized saline solution. Arterial and venous samples were drawn simultaneously for blood gas analysis at baseline (for control values) and at 15 and 45 min after starting the loading dose, using 1 mL heparinized (Hepalean, heparin sodium injection

USP 10000 UI·mL^{-1}; Organon, Toronto, ON, Canada) syringes that were placed on ice immediately after sampling, and analyzed within 15-30 min (StatProfile M; Nova Biomedical, Waltham, MA, USA). Blood-gas values were corrected to body temperature. In addition to arterial and venous pH, oxygen and carbon dioxide tensions, plasma glucose, lactate and HCO_3^- concentrations were analyzed. Venous blood samples (5 mL) were collected into 10 mL dry vacuum tubes for drug concentration analysis before the beginning of the MED loading dose, and 5, 15, and 45 min after initiating the CRI. Additional venous samples were drawn at 30 and 60 min after the end of the maintenance CRI. Samples were allowed to clot at room temperature for 30 to 60 min, centrifuged for 15 min at 1000×*g* at room temperature, and serum was harvested and stored at -80 C^o pending analysis with liquid chromatography-electrospray ionization-tandem mass spectrometry (LC-ESI/MS/MS) techniques (LC-MS/MS system *PE*Sciex API 3+; *Applied Biosystem/MDS Sciex*, Concord, ON, Canada). The lower limit of detection for this method was 50 pg·mL^{-1}, the coefficient of variation for the analysis was ≤ 11.1% and percentage bias ≤ 6%.

2.4. Statistical analyses

All numerical variables were analyzed by use of repeated-measures linear mixed-effect models. All models were built with dose, time and the time × dose interaction as fixed-effect variables, and the animal nested into treatment as a random-effect variable. The variance-covariance matrix of the data was modeled according to a strategy described by Littell *et al*.[19]. Briefly, a mixed-effect model containing no interaction was estimated with a free covariance structure. The model was then re-estimated with more parsimonious

covariance matrices (*e.g.*, variance components, compound symmetry, and first-order autoregressive), of which structures resembled that of the unstructured covariance matrix. The final covariance model was selected according to the value of the Schwarz Bayesian Criterion[19]. A number of *a priori* contrasts were performed to explore differences between pairs of means: a) differences between mean values at each time during the MED phase and the overall pretreatment mean for each treatment, and b) a comparison between mean values of each treatment at each time period. Critical level of significance for all comparisons was $\alpha = 0.05$. Data are expressed as mean (SD) unless indicated otherwise.

3. Results

There was an even distribution of gender (2 males and 2 females per group) for all doses except with the 1.7 $\mu g \cdot kg^{-1} \cdot h^{-1}$ dose where there were 3 females and 1 male. Body weight did not significantly differ across dosing groups.

3.1. Hemodynamic effects

During MED administration, MAP and SVR initially increased and CI and HR decreased in a dose-dependent manner (Figure 1 and Table 1). From mean baseline values, MAP transiently increased for durations positively related to dose (Figure 1). Their maximal increase was 8.1 (22.9) (not statistically significant), 20.6 (16.5), 25.7 (39.3), 18.2 (8.3), 35.6 (20.5), and 64.8 (17.7) % with increasing dose. The effect on SVR was undetected for the 0.2 $\mu g \cdot kg^{-1} \cdot h^{-1}$ dose, and significant only at 10 min for the 0.5 and 1.0 $\mu g \cdot kg^{-1} \cdot h^{-1}$ doses (Table 1). The SVR maximally increased by 1.5 (23.8), 75.8 (19.7), 32.0

(27.4), 133.5 (35.4), 163.6 (67.8), and 328.5 (116.3) % with increasing dose. Compared with baseline value recorded before starting MED administration, CI decreased as MED dose increased for a maximal change of 14.9 (12.7), 21.7 (17.9), 27.1 (13.2), 44.2 (9.7), 47.9 (8.1), and 61.2 (14.1) % respectively. The differences between certain group mean baseline values of CI were significant ($p<0.0322$, Table 1). More precisely, the effect of the three lowest MED infusion rates on CI was not significantly different from baseline ($p>0.11$). A significant decrease in HR was observed at all doses and returned to baseline in a dose-dependent fashion, except for the 4.0 $\mu g \cdot kg^{-1} \cdot h^{-1}$ dose, which returned to baseline before the 1.7 $\mu g \cdot kg^{-1} \cdot h^{-1}$ dose, and 10 min after finishing MED CRI (Table 1). HR maximally decreased by 15.1 (15.7), 30.8 (9.6), 17.5 (6.8), 35.9 (11.9), 44.8 (10.2), and 53.3 (15.6) % with increasing dose.

When the different doses were compared, the three lowest dose regimens showed small and short-lived changes in HR, CI, MAP and SVR which disappeared before the end of each maintenance CRI. Minimal changes were induced by the 0.2 $\mu g \cdot kg^{-1} \cdot h^{-1}$ dose. The maximal effect on SVR and HR (10 min after MED administration commenced; Table 1) with the 0.5 $\mu g \cdot kg^{-1} \cdot h^{-1}$ dose was greater than that of the 1.0 $\mu g \cdot kg^{-1} \cdot h^{-1}$ dose. The 1.7 $\mu g \cdot kg^{-1} \cdot h^{-1}$ dose resulted in greater effects on hemodynamic variables, in magnitude and duration, than the three lowest doses. The exception was for MAP in the 1.0 $\mu g \cdot kg^{-1} \cdot h^{-1}$ dose group where a higher MAP was present from 60 minutes onwards. The two largest doses showed physiologically and statistically greater effects on each cardiovascular parameter and the duration of these effects was longer when compared to the three lowest doses (Figure 1).

3.2. Medetomidine serum concentrations

Statistical comparison of the serum MED concentrations normalized to the unit dose (1.0 $\mu g \cdot kg^{-1} \cdot h^{-1}$) revealed significant effects of dose and time ($p<0.0001$ in both cases), as well as the time × dose interaction ($p=0.0001$). Visual inspection of Figure 2 shows higher dose-normalized concentration curves for the 0.2 and 0.5 $\mu g \cdot kg^{-1} \cdot h^{-1}$ groups, as compared to the four higher dosage groups. Of note, the dose-normalized serum MED concentrations during the maintenance CRI continued to increase in the 0.2 and 0.5 $\mu g \cdot kg^{-1} \cdot h^{-1}$ groups, but slightly decreased in the four higher dosage groups. The dose-normalized concentrations in the 0.2 $\mu g \cdot kg^{-1} \cdot h^{-1}$ group significantly differed with all other groups ($p<0.0001$ for all pair-wise comparisons). The 0.5 $\mu g \cdot kg^{-1} \cdot h^{-1}$ group significantly differed from the 1.0, 1.7 and 12.0 $\mu g \cdot kg^{-1} \cdot h^{-1}$ groups ($p<0.0485$). Differences between the four highest dosage groups were not statistically significant ($p>0.12$).

3.3. Other effects

The arterial pH of some dogs receiving the two highest MED infusions decreased below the physiologic limit (7.35), a difference that reached statistical significance in the 12.0 $\mu g \cdot kg^{-1} \cdot h^{-1}$ group (Table 2). The values of the other measured respiratory, metabolic, and tissue perfusion variables (glucose, HCO_3^-, $PaCO_2$, or lactate) stayed within a physiologically acceptable range during MED administration for both arterial and venous samples. Arterial oxygen tension (PaO_2) was maintained in all dose regimens. However, venous oxygen tension decreased significantly with the three highest doses, with a tendency to be dose-dependent (Table 2).

4. Discussion

The dose-dependency of MED effects on MAP, SVR, CI, and HR was documented quantitatively. The typical alpha-$_2$ agonist-related increases in SVR and MAP associated with decreases in HR and CI were observed, and both the intensity and duration of these effects depended on CRI dose rate. Therefore, the results strongly suggest that a sigmoid concentration-response relationship exists. The hemodynamic effects were of a lesser intensity and shorter duration with the three lowest doses. They were greater and longer in duration with the middle dose (1.7 $\mu g \cdot kg^{-1} \cdot h^{-1}$) and most pronounced with both higher doses. The 0.2 $\mu g \cdot kg^{-1} \cdot h^{-1}$ group showed minimal effects in the intensity and duration of hemodynamic changes, and the 0.5 and 1.0 $\mu g \cdot kg^{-1} \cdot h^{-1}$ groups were similar. Of note, the intensity of effects was greater for the 0.5 $\mu g \cdot kg^{-1} \cdot h^{-1}$ group than 1.0 $\mu g \cdot kg^{-1} \cdot h^{-1}$ group for SVR and HR, but the magnitude of CI depression was as expected for each group. Also, the duration of these changes became longer with increasing dose. The maximal effects were seen shortly after loading dose administration with each dose regimen. These results with MED CRI in ISO-anesthetized dogs are comparable to those induced by a bolus IV administration of MED in conscious dogs[5] but, by comparison, our dogs anesthetized with ISO had lower baseline values for MAP, HR, and CI. As a result, the initial hypertensive effects of MED administration were more evident in ISO-anesthetized dogs, allowing better differentiation of their dose-response relationships. No hypotension was subsequently observed. The maximal increase in SVR recorded for our 4.0 $\mu g \cdot kg^{-1} \cdot h^{-1}$ and 12.0 $\mu g \cdot kg^{-1} \cdot h^{-1}$ groups were 163.6% and 328.5%, respectively, which is comparable to values recorded in conscious dogs dosed with 5 and 10 $\mu g \cdot kg^{-1}$ MED[5]. After the administration of 1 $\mu g \cdot kg^{-1}$

MED, the increase in SVR was approximately 210% in conscious dogs, which was markedly higher than that observed in the 1.0 $\mu g \cdot kg^{-1} \cdot h^{-1}$ group, a difference that may be attributed to the use of bolus administration in conscious dogs (given IV over 5 sec; B. Pypendop, personal communication, 2009) instead of an infusion over 10 min. The magnitude of the decreases in HR and CI documented in our 1.7 $\mu g \cdot kg^{-1} \cdot h^{-1}$ group was comparable with previous results reported with 1.5 $\mu g \cdot kg^{-1} \cdot h^{-1}$ MED where HR decreased by 41.7% and CI decreased by 41.2%[10]. Data in this study are also consistent with previously reported results with corresponding doses of DMED[12,20].

The cardiovascular effects of DMED have been suggested to depend on the initial status of blood vessel tone[12]. It has also been suggested that the central sympatholytic effects may predominate at small doses, which stimulate the alpha-$_{2A}$ adrenoceptor subtype preferentially and produce the characteristic sedation and analgesia, while the peripheral effects predominate when higher doses or rapidly injected loading doses are administered due to stimulation of the alpha-$_{2B}$ adrenoceptor subtype[21]. This has been recently confirmed by the IV combination of a peripheral alpha-2 adrenoceptor antagonist (L-659'066) with a dose (10 $\mu g \cdot kg^{-1}$) of DMED which attenuated the cardiovascular effects typically associated with DMED alone while still producing the expected level of sedation[22]. In spite of this, our study demonstrated a dose-dependency in intensity and duration of cardiovascular effects. The persistent increase in MAP for the 1.0 $\mu g \cdot kg^{-1} \cdot h^{-1}$ dose (Figure 1) was related to the individual response of two out of four tested dogs (note the high variability [SD] of results after MED administration for this dose in Table 1), which did not show such a response in subsequent evaluations (data not shown) when receiving the same MED dose under ISO-anesthesia. Technical difficulties with the arterial line, or an insufficient level of anesthesia

could explain the result for these two dogs. Of note, at low doses, the hemodynamic effects were small and transient, even disappearing before the end of CRI administration period. The peripheral vasoconstriction resulting from an alpha-$_{2B}$-induced increase in SVR was very limited in intensity and duration at the three lowest dosages (0.2, 0.5 and 1.0 $\mu g \cdot kg^{-1} \cdot h^{-1}$). This pharmacological action governs the increase in MAP and contributes to the bradycardic response, leading to reduced CI. Particularly evident at these low doses, HR was reduced for a longer time in comparison to other hemodynamic parameters. This persistent bradycardia has also been reported previously even at low serum concentrations (< 3.9 $ng \cdot mL^{-1}$) in dogs[3] and it has been theorized that this could be related to stimulation of central alpha-$_{2A}$ adrenoceptors[23]. Taken together, these results suggest that low doses of MED CRI during ISO anesthesia in dogs are associated with minimal hemodynamic changes. Whether these low doses also induce efficacious analgesia, muscle relaxation, and sedation remains to be determined.

The infusion rates (0.2, 1.0, 4.0 and 12.0 $\mu g \cdot kg^{-1} \cdot h^{-1}$) of MED for this study were extrapolated from DMED infusion rates and published pharmacokinetic and pharmacodynamic data[3,4,11,24]. Two intermediate doses (0.5 and 1.7 $\mu g \cdot kg^{-1} \cdot h^{-1}$) were added to accurately quantify the dose-dependent nature of the hemodynamic effects. The aim of the highest dose level was to provide a positive control, producing clinically significant cardiovascular effects. Within each group, the total doses of MED given during the loading and maintenance CRI periods were equal, and it appears clear that the loading doses were responsible for the dose-dependent effects on cardiovascular function that were noted. In the present study, in contrast to the conclusions derived from data in conscious dogs[5], increasing the dose not only prolonged the duration of drug effects, but also influenced the

magnitude of the cardiovascular effects in ISO-anesthetized dogs. While the four higher CRI rate (12.0, 4.0, 1.7 and 1.0 $\mu g \cdot kg^{-1} \cdot h^{-1}$) groups demonstrated homogenous pharmacokinetics, the two lowest dosage (0.5 and 0.2 $\mu g \cdot kg^{-1} \cdot h^{-1}$) groups demonstrated a different pharmacokinetic pattern. Specifically, the lower the rate below 1.0 $\mu g \cdot kg^{-1} \cdot h^{-1}$, the greater was the dose-normalized plasma concentration. This is further evidenced by the difference in decay slopes upon completion of the initial loading dose between the four highest and the two lowest dosage groups, with a plateau never being achieved during CRI administration in the lowest dosage groups. The difference in dose-normalized MED concentrations strongly suggests that MED systemic clearance increased with dose and reached a plateau. MED is mainly (80-90%) metabolized by hepatic hydroxylation followed by glucuronidation in dogs involving several biotransformation pathways[14].

While an evaluation of the metabolite kinetics of MED was beyond the scope of this study, recent publications provide indirect support for this hypothesis. The phase II glucuronidation of MED is actually accomplished by different UDP-glucuronosyltransferases with different affinity, regio-and stereo-selectivity in human and canine liver microsomes leading to N-glucuronidation of levomedetomidine (LMED) and DMED with different kinetics[25]. In addition, an O-glucuronidation pathway has been reported for MED[14]. Hence it is conceivable that at dose rates below 1.0 $\mu g \cdot kg^{-1} \cdot h^{-1}$, MED is metabolized by one pathway only, while the activity of other metabolic pathways becomes significant at increased dosages. Alternatively, DMED may require chiral conversion to LMED in order to be N-glucuronidated at low doses. But with increasing racemic dose, DMED may be involved in direct N-glucuronidation, which would hasten the elimination of MED. This is supported by an earlier report stating that clearance of LMED

is more rapid than DMED or racemic MED in dogs[3]. Another hypothesis is grounded on the phenotypic polymorphism of the cytochrome P450 (CYP)-catalyzed phase I hydroxylation of MED, a feature reported in rabbits[26]. If such polymorphism does exist in dogs, it would induce more rapid biotransformation of MED and different systemic exposure to the drug.

In contrast to a report from Dutta *et al*.[24] in human beings, we did not observe the pharmacodynamic alteration of MED clearance with increasing dose. In the above-cited study, the authors showed with pharmacokinetic / pharmacodynamic modeling that cardiac output and hepatic blood flow depression induced by MED decreased its own hepatic clearance. This could be explained by the major species differences in MED metabolism[27] and the possible interference of ISO-anesthesia on MED-induced hemodynamic effects.

A metabolic acidosis has been reported in earlier studies with MED and DMED[13,28], and was sporadically found at the highest dosage rates used in the current study. Since lactate-free fluids were administered in our study and in the study from Uilenreef *et al*.[13], the possibility of hyperchloremic acidosis was verified and changes in arterial or venous concentrations of chloride were not demonstrated (data not shown). Furthermore, in our study, this effect was apparent only with higher doses, which also argues against fluid induced acidosis. In this study, blood gas measurements did not extend beyond MED administration. However, based on previous reports, the magnitude of this acidosis is not clinically relevant[28]. This study demonstrated a dose-dependent effect on pH which has not been shown in earlier studies. This indicates a further advantage of decreasing the MED CRI dose below the level of potential metabolic acidosis induction.

Arterial oxygen tension (PaO_2) during 100 % oxygen administration was high, as expected, at all dose regimens. Venous oxygen tension (PvO_2) decreased significantly during the administration period of the three highest doses and this decrease had a dose-dependent tendency even though there were no statistically significant differences between these doses. This implies increased oxygen extraction during higher MED doses, which is consistent with a prior report with DMED[12]. The underlying cause may be due to a decreased CI and peripheral blood flow. Our study was a minimally invasive study and the dogs were instrumented with peripheral cannulas only. Thus, central mixed venous blood samples were not available and oxygen consumption and extraction could not have been calculated accurately. However, based on the results available, the extraction of oxygen appears to increase dose-dependently, which has not been reported previously with MED or DMED. Even though the oxygen balance would remain positive with increasing doses while its extraction is increased[12], these results indicate a further advantage of the use of low dose MED CRI when compared with higher doses.

Arterial and venous values of pH, PCO_2, HCO_3^-, glucose, and lactate remained within clinically acceptable ranges during each dose of MED CRI, and were consistent with previous findings[11,12]. Venous values of pH, $PvCO_2$, HCO_3^-, glucose, and lactate showed comparable results to arterial values with normal arterio-venous differences and thus only arterial values were reported here. However, plasma glucose levels are expected to increase with MED administration due to its ability to inhibit insulin release from the pancreas[29]. This was not demonstrated in our study, probably because samples were not taken beyond the end of infusion. Medetomidine has been found to produce slow (i.e. peaks in 2 to 4 hours post-administration) and non-significant changes in plasma glucose

concentrations[30,31]. Arterial lactate concentrations remained within normal physiologic range (below 2.5 $mmol \cdot L^{-1}$) with all dose regimens. This was consistent with findings from recent reports[11,13] with DMED during anesthesia, implying that the overall tissue perfusion was maintained during our study. Again, in our study, lactate measurement did not continue after MED CRI, and thus potential lactate retention during CRI may have occurred. Based on a previous study, some lactate retention may occur when increasing the dose of DMED CRI to 3 $\mu g \cdot kg^{-1} \cdot h^{-1}$ [13] but it was not demonstrated with lower doses. Thus, it may be speculated that lactate retention should not occur with low doses of MED CRI either.

With regard to the multitude of possible clinical uses of low dose DMED CRI in human patients[21,32] and the increasing volume of promising studies being published, the full application of these drugs may soon be realized in the veterinary domain. Potential indications for MED or DMED CRI in veterinary patients may include use as an adjunct to balanced anesthesia to enhance perioperative hemodynamic stability, as an adjunct to perioperative multimodal analgesia, and as a sedative-analgesic for use in intensive care units.

5. Conclusion

In conclusion, these results demonstrate the dose-dependency of the hemodynamic effects of MED CRI when used as an anesthetic adjunct to ISO-anesthetized dogs. The low dose MED CRI rates (0.2-1.7 $\mu g \cdot kg^{-1} \cdot h^{-1}$) induced limited and transient hemodynamic effects and showed fewer changes in pH and oxygen extraction when compared to higher doses. Thus, low dose MED CRI rates may prove clinically useful in the perioperative

management of canine patients. Further studies are warranted to demonstrate and quantify the efficacy of such CRI doses as analgesic and anesthetic adjuncts. This is particularly important as the correlation between the pharmacodynamic effects and serum MED concentrations may not be linear at all dose rates as suggested by the data presented here.

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Tables

Table 1 – Hemodynamic parameters [mean (SD)] measured at baseline (-5 minutes), and medetomidine constant rate infusion effect's characteristics during isoflurane anesthesia.

Parameter (units)	Dose ($\mu g \cdot kg^{-1} \cdot h^{-1}$)	Baseline value at -5 minutes	Duration of statistically significant effect (min)	Peak effect value	
				Zenith	Nadir
MAP (mmHg)	0.2	59 (8)	Not present	Not present[a,c]	
	0.5	62 (7)	10	70 (10)[a]	
	1.0	59 (2)	10	74 (23)[b]	
	1.7	73 (20)	10	85 (6)[c]	
	4.0	69 (14)	70	94 (14)[a]	
	12.0	70 (10)	85	116 (12)[a,b,c]	
SVR (Dynes·second·cm^{-5})	0.2	4782 (1203)	Not present	Not present[a,b,c]	
	0.5	5222 (1407)	10	9178 (1031)[a,d]	
	1.0	4062 (1246)	10	5357 (890)[d,e,f]	
	1.7	3797 (336)	20	8867 (1344)[b,e]	
	4.0	3486 (295)	70	9190 (2365)[c,f]	
	12.0	3780 (493)	130	16197 (4396)[a,b,c,e,f]	
CI ($L \cdot min^{-1} \cdot m^{-2}$)	0.2	2.3 (0.4)[a,b]	Not present		Not present[a]
	0.5	2.2 (0.5)[c,d,e]	Not present		Not present[b]
	1.0	2.4 (0.4)	Not present		Not present[c]
	1.7	3.3 (0.7)[a,c]	70		1.9 (0.3)
	4.0	3.3 (0.7)[b,d]	80		1.7 (0.3)
	12.0	3.1 (0.7)[e]	130		1.2 (0.4)[a,b,c]
HR (Beats·min^{-1})	0.2	96 (22)	5		82 (15)[a,b,c]
	0.5	85 (9)[a]	40		59 (8)[a,d]
	1.0	93 (7)	60		77 (6)[d,e,f]
	1.7	115 (26)	130		74 (14)
	4.0	96 (13)	70		55 (11)[b,e]
	12.0	109 (20)[a]	130		55 (16)[c,f]

Table 2 – Parameters [mean (SD)] measured in arterial and peripheral venous samples prior to (-10 minutes) and during medetomidine constant rate infusion with isoflurane anesthesia in dogs.

Blood parameter	Dose ($\mu g \cdot kg^{-1} \cdot h^{-1}$)	Baseline -10 minutes	Medetomidine constant rate infusion with isoflurane anesthesia	
			25 minutes	55 minutes
pH (arterial)	0.2	7.38 (0.04)	7.39 (0.04)[a]	7.37 (0.04)[a]
	0.5	7.44 (0.05)[a,b]	7.44 (0.06)[b,c,d]	7.42 (0.06)[b,c]
	1.0	7.39 (0.02)	7.39 (0.02)[e]	7.39 (0.03)[d]
	1.7	7.37 (0.03)[a]	7.36 (0.03)[b]	7.37 (0.03)[b]
	4.0	7.40 (0.03)	7.37 (0.05)*[,c]	7.38 (0.03)*[,e]
	12.0	7.37 (0.07)[b]	7.33(0.04)*[,a,d,e]	7.32 (0.04)*[,a,c,d,e]
PaO_2 (arterial) MmHg	0.2	501.0 (39.8)	502.2 (59.6)	512.3 (42.7)
	0.5	491.3 (73.2)	514.1 (51.6)	490.4 (39.0)
	1.0	554.7 (4.7)	546.4 (26.4)	550.5 (13.6)
	1.7	448.8 (220.3)	445.8 (218.9)	535.9 (38.8)
	4.0	519.6 (33.6)	547.4 (22.6)	551.7 (26.5)
	12.0	555.1 (26.0)	538.4 (54.0)	536.0 (56.9)
PvO_2 (peripheral jugular vein) MmHg	0.2	155.4 (66.6)	162.2 (94.0)	201.8 (95.3)[a]
	0.5	136.0 (51.0)	93.5 (19.7)	130.1 (45.7)
	1.0	192.5 (94.4)	168.2 (119.5)	157.3 (115.6)
	1.7	210.6 (139.6)	103.3 (18.2)*	104.7 (42.0)*
	4.0	216.7 (56.7)	87.4 (20.4)*	89.5 (18.7)*
	12.0	198 (110.4)	67.1 (12.5)*	78.2 (9.9)*[,a]
$PaCO_2$ (arterial) MmHg	0.2	39.0 (5.1)	40.8 (4.8)	46.4 (3.4)*[,a]
	0.5	39.7 (5.8)	34.5 (1.1)*[,a]	33.9 (4.2)*[,a,b,c,d]
	1.0	38.3 (5.4)	39.0 (6.4)[b]	41.5 (6.0)[c]
	1.7	40.5 (1.8)	45.8 (2.6)*[,a,b,c]	42.8 (3.2)[b,e]
	4.0	35.6 (6.2)[a]	40.7 (4.1)*	42.8 (3.1)*[,d]
	12.0	42.5 (4.2)[a]	45.7 (4.7)[c]	45.7 (6.9)[e]
Glucose (arterial) $mmol \cdot L^{-1}$	0.2	5.95 (1.24)	6.18 (0.56)	5.93 (0.51)
	0.5	5.73 (0.91)	6.10 (0.71)	5.67 (0.55)
	1.0	5.43 (1.17)	5.45 (1.10)	5.38 (0.43)
	1.7	5.43 (1.35)	6.33 (0.55)	6.57 (0.47)*
	4.0	5.88 (0.68)	6.33 (0.54)	5.98 (0.77)
	12.0	5.87 (0.95)	5.53 (1.08)	5.48 (0.60)
Lactate (arterial) $mmol \cdot L^{-1}$	0.2	N/A	N/A	N/A
	0.5	N/A	N/A	N/A
	1.0	1.55 (0.62)	1.58 (0.69)	1.33 (0.60)
	1.7	1.33 (0.19)	1.08 (0.25)	1.05 (0.33)
	4.0	1.30 (0.69)	1.20 (0.41)	0.85 (0.42)*
	12.0	1.63 (0.61)	1.47 (0.67)*	1.47 (0.93)*
HCO_3^- (arterial) $mmol \cdot L^{-1}$	0.2	25.1 (3.4)	25.6 (4.3)	28.8 (4.5)*
	0.5	27.0 (2.7)[a]	23.6 (3.4)*	22.2 (0.6)*
	1.0	23.2 (2.3)	23.4 (3.1)	25.1 (2.8)
	1.7	23.7 (1.6)	26.0 (3.4)	25.0 (3.7)
	4.0	22.6 (3.1)[a]	23.5 (2.8)	25.4 (3.2)*
	12.0	24.7 (2.3)	24.2 (0.6)	23.7 (1.5)

Legends

Figure 1 – Changes in mean systemic arterial blood pressure (MAP), systemic vascular resistance (SVR), cardiac index (CI), and heart rate (HR) during administration of isoflurane and six doses of medetomidine (MED) CRI, shown as percentages change(SD) from each group mean baseline values. Time 0 (min) = beginning of MED loading dose administration. Time 10 (min) = beginning of MED CRI. Time 70 (min) = MED CRI administration completed.

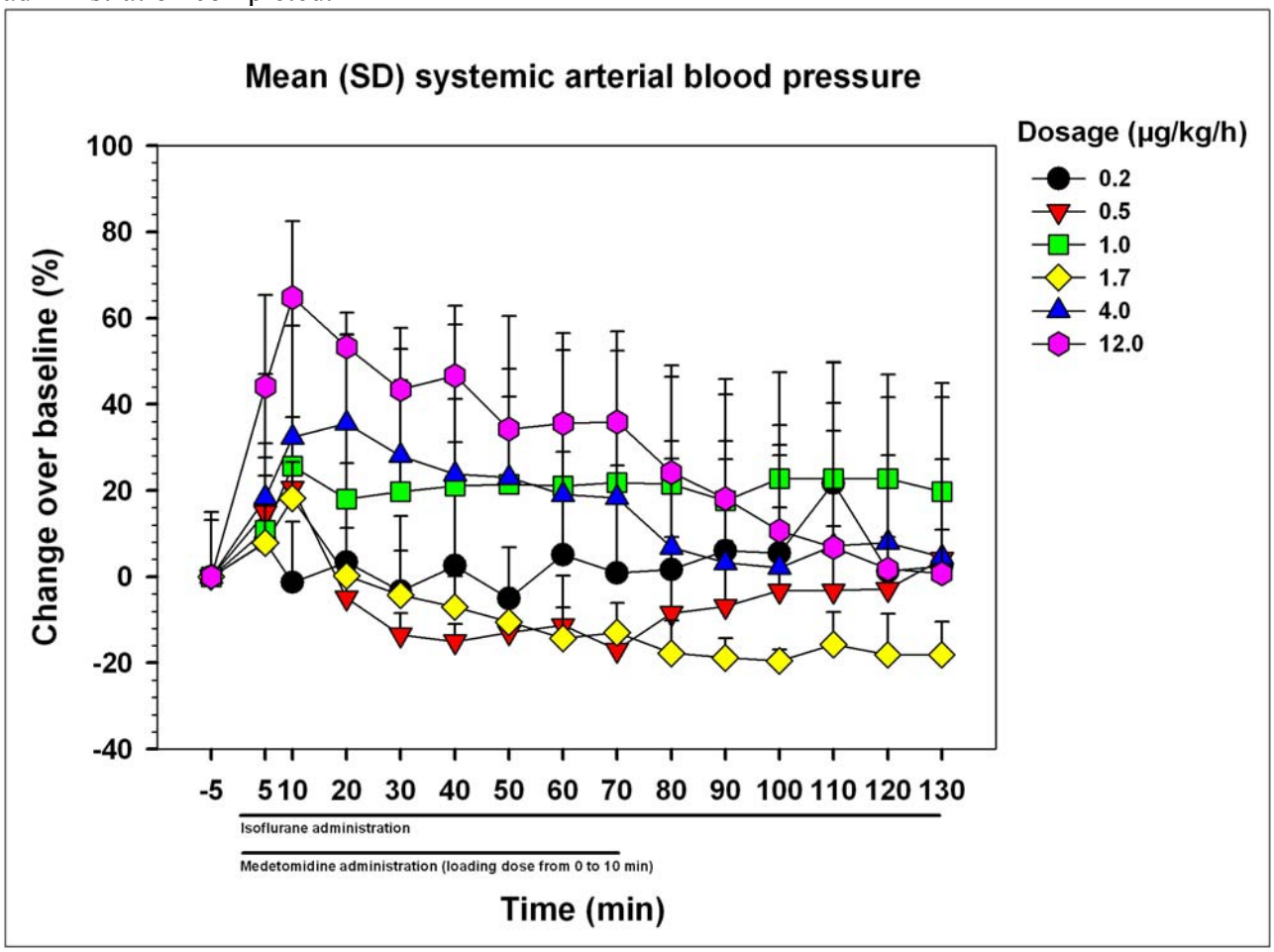
Figure 2 – Mean serum medetomidine (MED) concentrations (with 95% confidence intervals) for the six different groups, normalized to 1.0 $\mu g \cdot kg^{-1} \cdot h^{-1}$ infusion rate. Blood sampling were taken at Time 15, 25, 55, 100, and 140 min. Time 0 (min) = beginning of MED loading dose administration. Time 10 (min) = beginning of MED CRI. Time 70 (min) = MED CRI administration completed. A semi-logarithmic scale was used for presenting the data and artefactually all concentrations started from zero as baseline value.

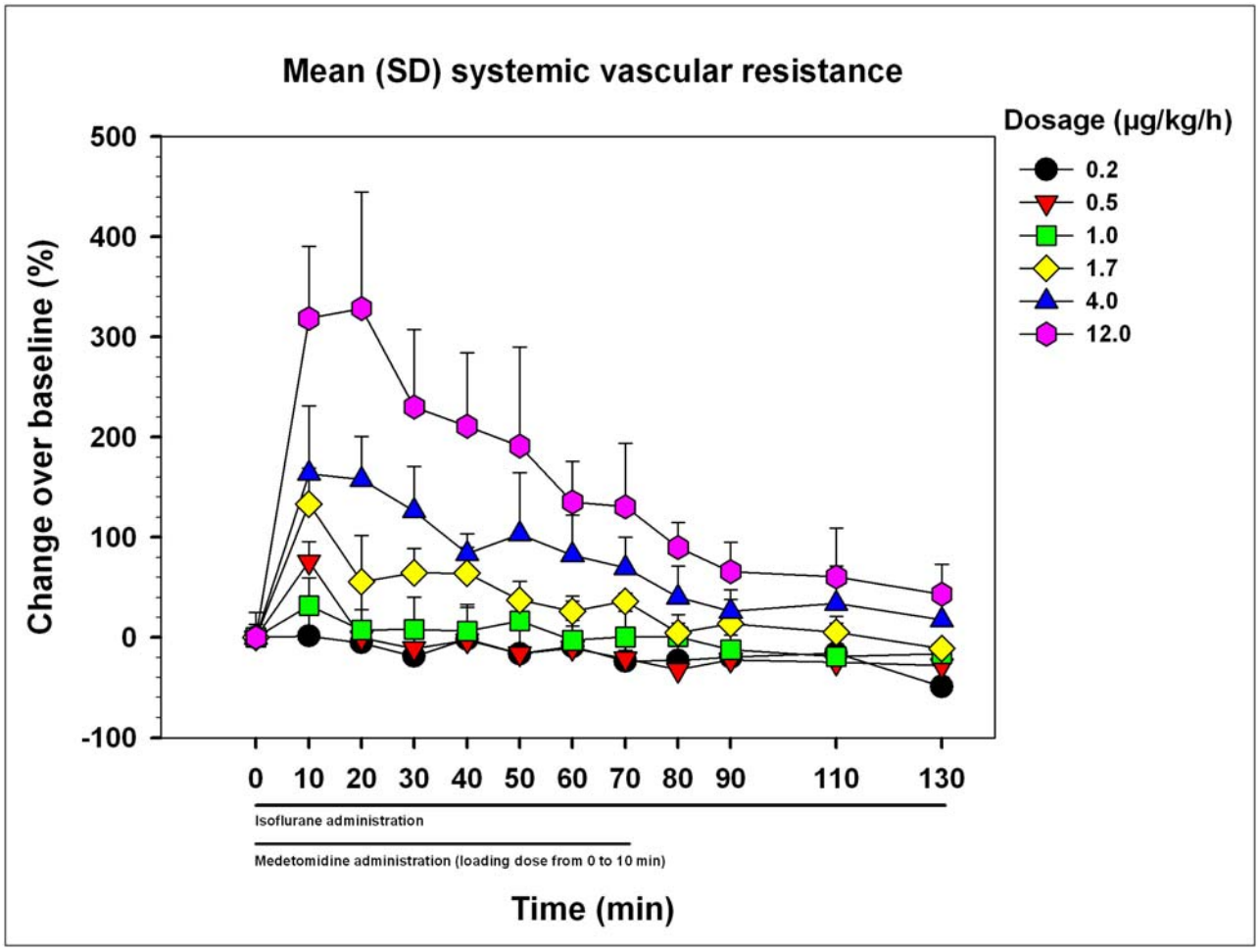
Table 1 – Hemodynamic parameters [mean (SD)] measured at baseline (-5 minutes) and medetomidine constant rate infusion effect's characteristics during isoflurane anesthesia.
MAP, mean systemic arterial blood pressure; SVR, systemic vascular resistance (see text for calculation); CI, cardiac index; HR, heart rate. Values of a given hemodynamic parameters with same superscript letter significantly differ ($p < 0.05$).

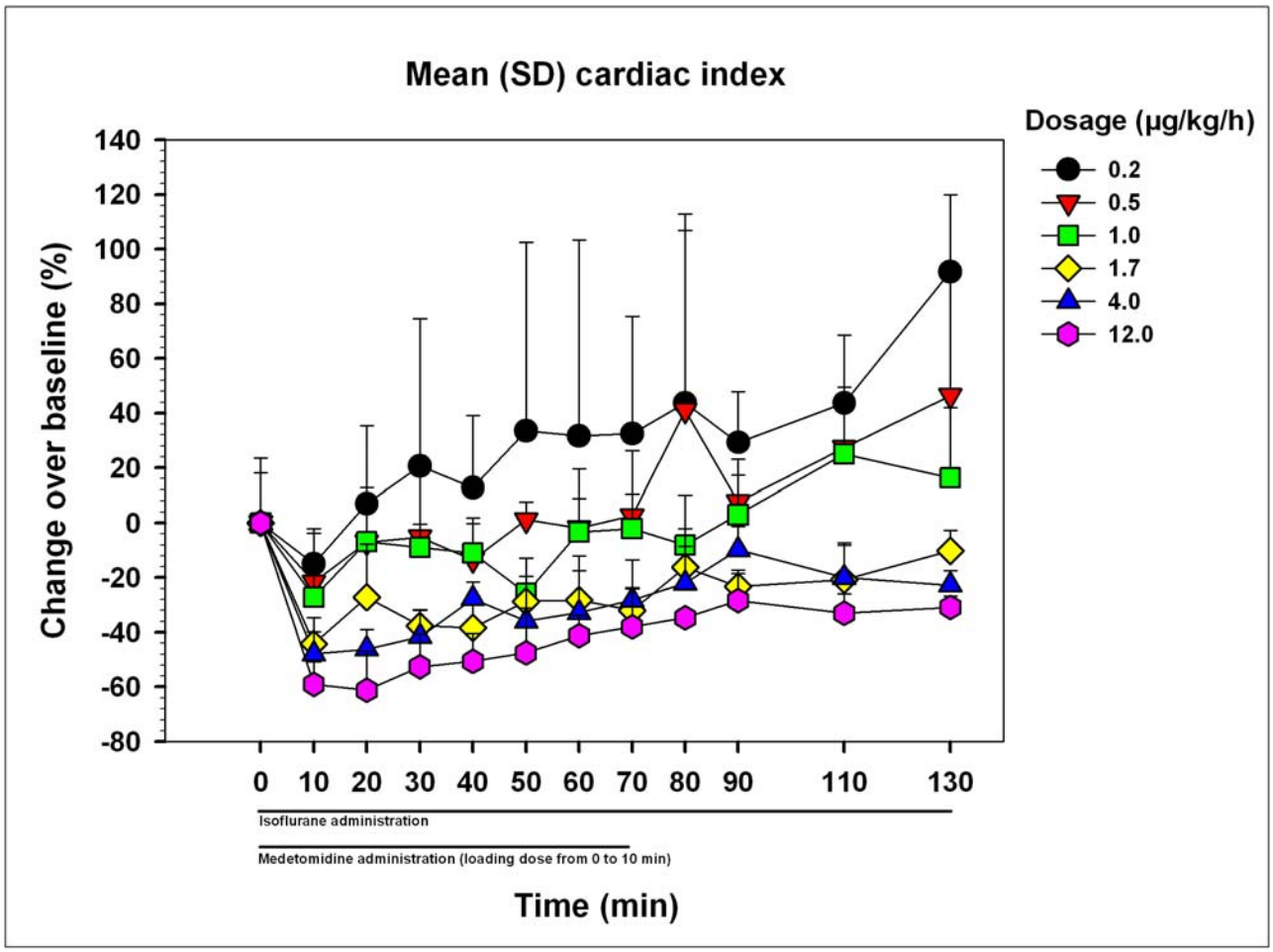
Table 2 – Parameters [mean (SD)] measured in arterial and peripheral venous samples prior to (-10 minutes) and during medetomidine constant rate infusion with isoflurane anesthesia in dogs.
***** Within a row, mean value differs from baseline ($p < 0.05$). Within a column, values with same superscript letter significantly differ; differences between doses ($p < 0.05$).
N/A = value not available.

Figures

Figure 1 – Changes in mean systemic arterial blood pressure (MAP), systemic vascular resistance (SVR), cardiac index (CI), and heart rate (HR) during administration of isoflurane and six doses of medetomidine (MED) CRI, shown as percentages change(SD) from each group mean baseline values. Time 0 (min) = beginning of MED loading dose administration. Time 10 (min) = beginning of MED CRI. Time 70 (min) = MED CRI administration completed.




Mean (SD) systemic vascular resistance
Dosage (µg/kg/h)
0.2
0.5
1.0
1.7
4.0
12.0
Change over baseline (%)
500
400
300
200
100
0
-100
0 10 20 30 40 50 60 70 80 90 110 130
Isoflurane administration
Medetomidine administration (loading dose from 0 to 10 min)
Time (min)


Mean (SD) cardiac index
Dosage (µg/kg/h)
0.2
0.5
1.0
1.7
4.0
12.0
Change over baseline (%)
140
120
100
80
60
40
20
0
-20
-40
-60
-80
0
10
20
30
40
50
60
70
80
90
110
130
Isoflurane administration
Medetomidine administration (loading dose from 0 to 10 min)
Time (min)

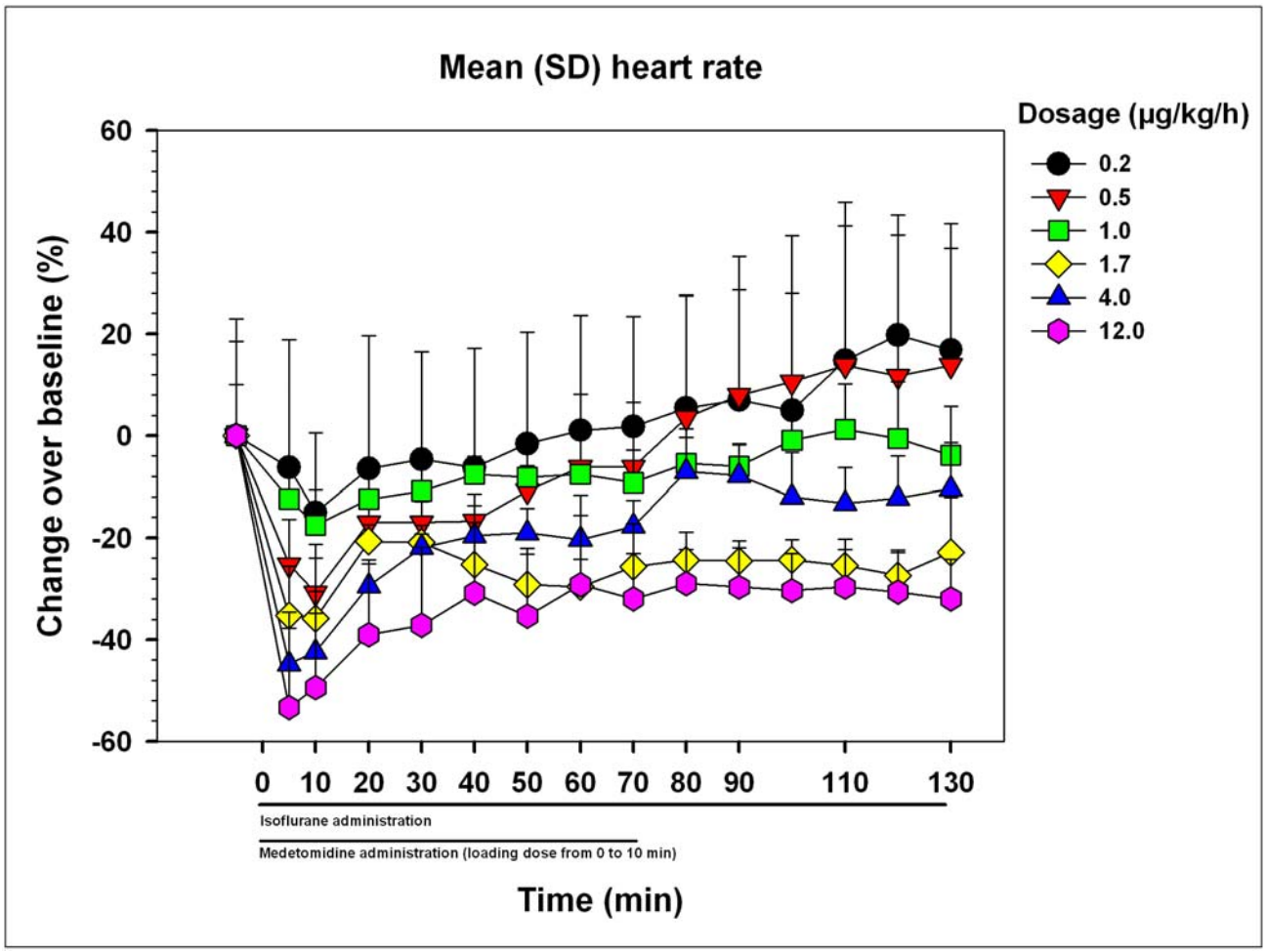
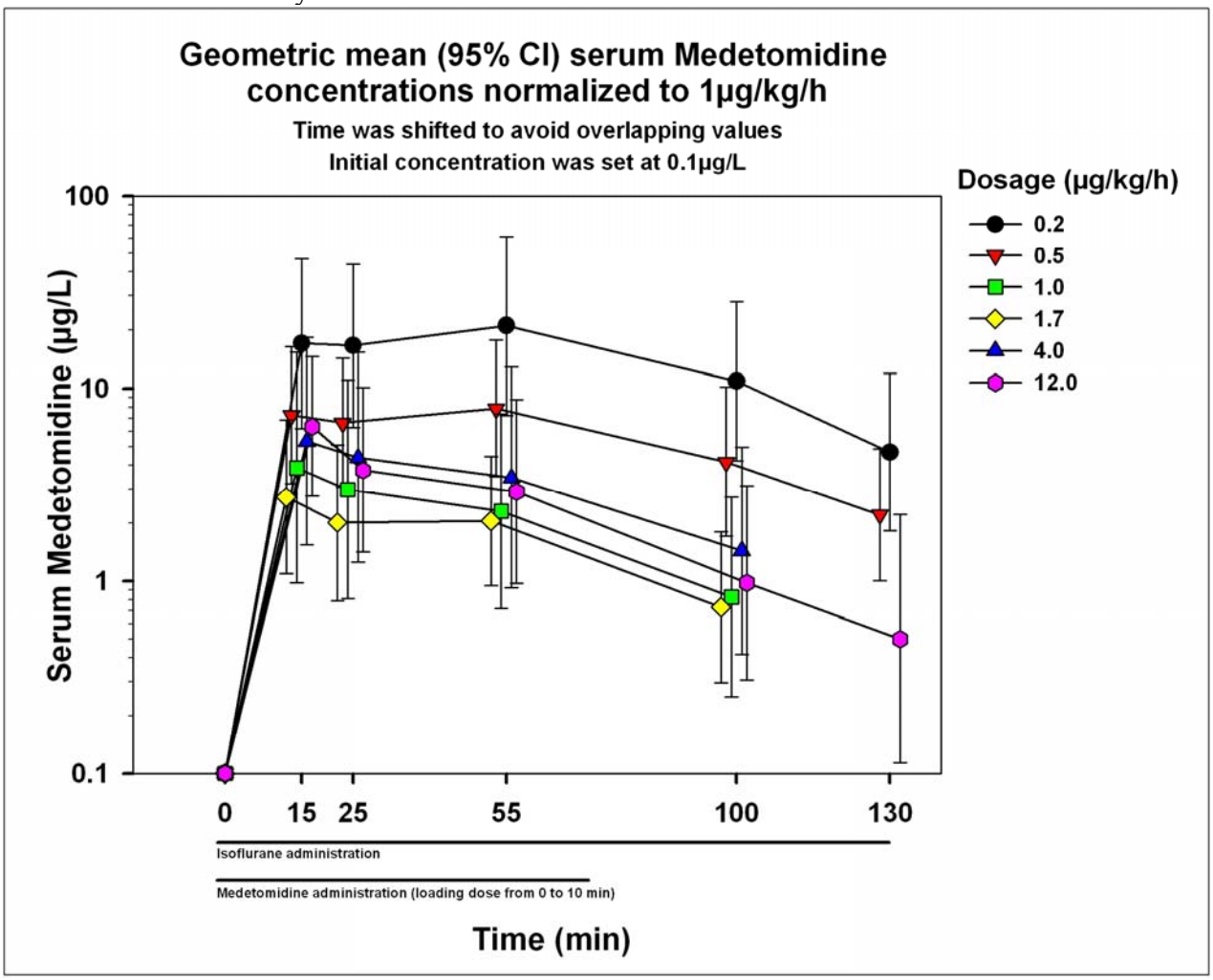

Mean (SD) heart rate
Dosage (µg/kg/h)
0.2
0.5
1.0
1.7
4.0
12.0
Change over baseline (%)
60
40
20
0
-20
-40
-60
0 10 20 30 40 50 60 70 80 90 110 130
Isoflurane administration
Medetomidine administration (loading dose from 0 to 10 min)
Time (min)

Figure 2 – Mean serum medetomidine (MED) concentrations (with 95% confidence intervals) for the six different groups, normalized to 1.0 $\mu g \cdot kg^{-1} \cdot h^{-1}$ infusion rate. Blood sampling were taken at Time 15, 25, 55, 100, and 140 min. Time 0 (min) = beginning of MED loading dose administration. Time 10 (min) = beginning of MED CRI. Time 70 (min) = MED CRI administration completed. A semi-logarithmic scale was used for presenting the data and artefactually all concentrations started from zero as baseline value.



THIRD CHAPTER – DISCUSSION AND CONCLUSION

Discussion

The dose-dependency of the hemodynamic effects of MED CRI on MAP, SVR, CI, and HR was quantified. The typical changes after alpha-$_2$ agonist administration were observed; increases in SVR and MAP associated with decreases in HR and CI were observed. These effects were small to moderate in intensity and short in duration with the three smallest doses. They were greater and longer in duration with the middle dose (1.7 $\mu g \cdot kg^{-1} \cdot h^{-1}$) and most pronounced with both higher doses. The 0.2 $\mu g \cdot kg^{-1} \cdot h^{-1}$ group showed minimal effects in the intensity and duration of hemodynamic changes, and the 0.5 and 1.0 $\mu g \cdot kg^{-1} \cdot h^{-1}$ groups were similar. Of note, the intensity of effects was greater for the 0.5 $\mu g \cdot kg^{-1} \cdot h^{-1}$ group than 1.0 $\mu g \cdot kg^{-1} \cdot h^{-1}$ group for SVR and HR, but the magnitude of CI depression was as expected for each group. Also, the duration of these changes became longer by increasing the dose. The maximal effects were observed shortly following loading dose administration with each dose regimen.

These results with MED CRI in ISO-anesthetized dogs are comparable to those induced by a bolus IV administration of MED in conscious dogs (Pypendop and Verstegen, 1998) but, by comparison, the presence of ISO had a significant effect on baseline values: MAP (approximately 60-75 mmHg in our study, *versus* 120-140 mmHg in conscious dogs), HR (90-110 beats$\cdot min^{-1}$ *versus* 120-130 beats$\cdot min^{-1}$), and CI (2-3.5 $L \cdot min^{-1} \cdot m^{-2}$ *versus* 5-7 $L \cdot min^{-1} \cdot m^{-2}$). As a result, the initial hypertensive effect of MED administration was more evident in ISO-anesthetized dogs, allowing better differentiation of their dose-response relationships. No hypotension was subsequently observed. The maximal increase in SVR recorded for our 4.0 $\mu g \cdot kg^{-1} \cdot h^{-1}$ and 12.0 $\mu g \cdot kg^{-1} \cdot h^{-1}$ groups were 163.6% and 328.5%, respectively, which is comparable to values recorded in conscious dogs dosed with 5 and 10 $\mu g \cdot kg^{-1}$ MED (Pypendop and Verstegen, 1998). After the administration of 1 $\mu g \cdot kg^{-1}$ MED, the increase in SVR was approximately 210% in conscious dogs, which was

markedly higher than that observed in the 1.0 $\mu g \cdot kg^{-1} \cdot h^{-1}$ group, a difference that may be attributed to the use of bolus administration in conscious dogs (given IV over 5 sec; B. Pypendop, personal communication, 2009) instead of an infusion over 10 min. The loading dose infusion could partially explain the apparent discrepancy observed between the 0.5 $\mu g \cdot kg^{-1} \cdot h^{-1}$ and 1.0 $\mu g \cdot kg^{-1} \cdot h^{-1}$ groups, because the loading dose administration was not automated. It is possible that, in some dog(s), the administration rate was faster in the 0.5 $\mu g \cdot kg^{-1} \cdot h^{-1}$ group than 1.0 $\mu g \cdot kg^{-1} \cdot h^{-1}$ group. The magnitude of change in group 1.7 $\mu g \cdot kg^{-1} \cdot h^{-1}$ in HR was comparable with results associated to a CRI of 1.5 $\mu g \cdot kg^{-1} \cdot h^{-1}$ MED leading to decrease in HR (-41.7%) and CI (-41.2%) (Grimm *et al*., 2005). Data in this study are consistent with previously reported results with corresponding doses of DMED (Flacke *et al*., 1993; Lin *et al*., 2008).

The cardiovascular effects of DMED have been suggested to depend on the initial status of the blood vessel tone (Lin *et al*., 2008). It was additionally suggested that the central sympatholytic effects may predominate at small doses, which stimulate the alpha-$_{2A}$ adrenergic receptor subtype (source of sedation and analgesia), while at higher or rapidly injected loading doses, greater peripheral effects arise, which result from stimulation of the alpha-$_{2B}$ adrenoceptors (Aantaa and Jalonen, 2006). This has been recently confirmed by the IV combination of a peripheral alpha-2 adrenoceptor antagonist (L-659'066, 250 $\mu g \cdot kg^{-1}$) with a dose (10 $\mu g \cdot kg^{-1}$) of DMED, attenuating the cardiovascular effect apparent with DMED alone, but leading to similar sedation (Honkavaara *et al*., 2008). In our study, there was an initial increase in MAP followed by maintained blood pressures with the 1.0, $\mu g \cdot kg^{-1} \cdot h^{-1}$ dose, while with the 1.7, $\mu g \cdot kg^{-1} \cdot h^{-1}$ dose there was a more typical biphasic effect with initial increase followed by decrease of MAP. The baseline values of HR, CI, and MAP with dose 1.7 were slightly different from the smaller doses. This initial difference may indicate a disparity in blood vessel tone in the individuals and may help to explain, at least in part, the difference of effect demonstrated on MAP between doses 1.0 and 1.7.

In addition, an important factor influencing our results was the variability in the rate of the loading dose injection because it was hand-injected instead of using a constant rate infusion pump. This may increase the interindividual variance to some extent. In spite of these influencing factors, this study demonstrated a dose-dependency in intensity and

duration of cardiovascular effects. The persistent increase in MAP for the 1.0 $\mu g \cdot kg^{-1} \cdot h^{-1}$ dose was related to the individual response of two out of four tested dogs, which did not show such response in subsequent evaluations (data not reported) when receiving the same MED dose under ISO-anesthesia. Technical difficulties with the arterial line or an insufficient level of anesthesia may explain the result for these two dogs.

It is interesting to note that at lowest doses the hemodynamic effects were small and transient, disappearing before the end of CRI administration. The peripheral vasoconstriction resulting from alpha-$_{2B}$-induced increase in SVR was very limited in intensity and duration at the three lowest dosages (0.2, 0.5, and 1.0 $\mu g \cdot kg^{-1} \cdot h^{-1}$). This pharmacological action governs the increase in MAP and contributes to the bradycardic response, leading to reduced CI. Particularly evident at these low doses, HR was reduced for a longer time in comparison to other hemodynamic criteria, as demonstrated in an earlier report, where HR decrease also persisted at low serum concentrations (< 3.9 $ng \cdot mL^{-1}$) in dogs (Kuusela *et al*., 2000). This could be related to bradycardic and potentially hypotensive stimulation of central alpha-$_{2A}$ adrenoceptors (Maze and Fujinaga, 2000). This suggests that low doses of MED CRI may be used during ISO anesthesia in dogs with minimal hemodynamic changes. The question remaining is whether such low doses of MED CRI could induce efficacious analgesia, muscle relaxation, and sedation.

Four infusion rates (0.2, 1.0, 4.0, and 12 $\mu g\ kg^{-1}\ h^{-1}$) of MED for this study were extrapolated from DMED infusion rates and published pharmacokinetic and pharmacodynamic data (Salonen, 1989; Dutta *et al*., 2000; Kuusela *et al.,* 2000; Pascoe *et al*., 2006) and two intermediate doses (0.5 and 1.7 $\mu g\ kg^{-1}\ h^{-1}$) were added to accurately quantify the dose-dependency of hemodynamic effects. The aim of the highest dose level was to provide a positive control, producing clinically significant cardiovascular effects. Loading doses were given at a numeric dose identical to the following infusion rate. Obviously, these loading doses were responsible for the dose-dependency on intensity, and that in contrast to the conclusions derived from conscious dog data (Pypendop and Verstegen, 1998), as increasing the dose above 5 $\mu g \cdot kg^{-1}$ not only prolongs drug effects, but also influences cardiovascular function in ISO-anesthetized dogs. The higher serum concentrations of MED immediately after loading dose administration correlated with the

more pronounced effects on hemodynamic data. Thus, lowering the loading dose may be indicated when intending to further decrease hemodynamic effects while maintaining analgesia and anxiolysis.

A difference in pharmacokinetics between higher and lower CRI dose rates was apparent in this study: Whilst the four higher CRI rates (12.0, 4.0, 1.7 and 1.0 $\mu g \cdot kg^{-1} \cdot h^{-1}$) demonstrated homogenous pharmacokinetics, the two lowest rates (0.5 and 0.2 $\mu g \cdot kg^{-1} \cdot h^{-1}$) groups presented a different pharmacokinetic pattern. One hypothesis is that, the lower the rate below 1.0 $\mu g \cdot kg^{-1} \cdot h^{-1}$, the greater could be the degree of accumulation of the drug in the central compartment. This might explain the apparent absence of a statistically significant difference in the MED serum concentration observed for the four lower dosage groups. It has been previously reported that MED in the circulation is present in its inactive protein bound form (Salonen, 1989). Being a weak organic base, MED at high dose (80 $\mu g \cdot kg^{-1}$) presented a low free fraction (f_u) estimated at 15% in dogs, cats and rats, binding of the drug to α-proteins (globulins, lipoproteins, glycoproteins) is suspected. It may be suggested from the results of this study that f_u may be lower at doses below 1.0 $\mu g \cdot kg^{-1} \cdot h^{-1}$. This could explain the apparent higher accumulation at low doses and the associated lower f_u leading to fewer pharmacodynamic effects. This phenomenon requires further pharmacokinetic / pharmacodynamic exploration.

Another possible hypothesis to explain the differences in pharmacokinetics is that, the lower the rate below 1.0 $\mu g \cdot kg^{-1} \cdot h^{-1}$, the greater appears to be the dose-normalized plasma concentration. This is further evidenced with the difference in decay slopes upon completion of the initial, fast-rate infusion between the four highest and the two lowest dosage groups, resulting in an absence of plateau during CRI administration for the latter. This difference in dose-normalized MED concentrations strongly suggests that MED systemic clearance increased with dose and reached a plateau. Medetomidine is mainly (80-90%) metabolized by hepatic hydroxylation followed by glucuronidation in dogs involving several biotransformation pathways (Salonen, 1992). This phase I reaction proceeds with a rate sufficient for the rapid removal of the drugs from the animal body and is mainly regulated by the hepatic blood flow.

The difference in clearance between doses is suggestive that at a dose rate below 1.0 $\mu g \cdot kg^{-1} \cdot h^{-1}$, MED is metabolized through a high-affinity, limited-capacity pathway, and with higher dose rates, the drug is going through a second pathway presenting lower-affinity and bigger capacity. The study of metabolite kinetics of MED was outside the scope of this study, but some recent publications provide indirect support for this hypothesis. The phase II glucuronidation of MED with glucuronic acid is accomplished by different UDP-glucuronosyltransferases with different affinity, regio-and stereo-selectivity in human and canine liver microsomes leading to N-glucuronidation of levomedetomidine (LMED) and DMED with different kinetics (Kaivosaari *et al*., 2008). In addition, an O-glucuronidation pathway has been reported for MED (Salonen, 1992). Hence it is conceivable that at dose rates below 1.0 $\mu g \cdot kg^{-1} \cdot h^{-1}$, MED is metabolized by one pathway only, and the activity of other metabolic pathways becomes significant at increased dosages. Alternatively, DMED may require chiral conversion to LMED in order to be N-glucuronidated at low doses. But with increasing racemic dose, DMED may be involved in direct N-glucuronidation, which would fasten the elimination of MED. This is supported by an earlier report about clearance of LMED being more rapid than DMED or racemic MED in dogs (Kuusela *et al*., 2000). In addition, LMED has been shown to interfere with the metabolism of other anesthetic drugs in the liver, such as slowing ketamine metabolism (Kharasch *et al*., 1992). Another hypothesis is grounded on the phenotypic polymorphism of the cytochrome P450 (CYP)-catalyzed phase I hydroxylation of MED, that affects the biotransformation rate of MED, a feature reported in rabbits (Avsaroglu *et al*., 2008). If such polymorphism would exist in dogs, it would induce biotransformation rate of MED and different systemic exposure to the drug. In contrast with a report from Dutta *et al*. (2000) in humans, we did not record the pharmacodynamic alteration of MED clearance with increasing dose. In the above-cited study, the authors shown with pharmacokinetic / pharmacodynamic modeling that cardiac output and hepatic blood flow depression induced by MED decreased its own hepatic clearance. This could be explained by the major species differences in MED metabolism (Kaivosaari *et al*., 2002) and the possible interference of ISO-anesthesia on MED-induced hemodynamic effects.

There was a physiologically significant decrease in pH during MED administration with the two largest doses only. A metabolic acidosis has been reported in earlier studies with MED and DMED (Kuusela *et al*., 2001; Uilenreef *et al*., 2008). Since lactate-free fluids were administered in this study and in the study reported by Uilenreef *et al*. (2008) the possibility of hyperchloremic acidosis was verified and changes in arterial or venous concentrations of chloride were not demonstrated (data not shown). Furthermore, in our study this effect was apparent only with higher doses, which also argues against fluid induced acidosis. In this study, blood gas measurements did not extend beyond MED administration. However, based on a previous report, the magnitude of this acidosis is not clinically relevant (Kuusela *et al*., 2001). This study demonstrated the dose-dependent effect on pH, which has not been shown in earlier studies. This indicates a further advantage of decreasing the MED CRI dose below the level of potential metabolic acidosis induction.

Arterial oxygen tensions (paO_2) during 100 % oxygen administration were expectedly high during each dose regimen. Venous oxygen tensions (pvO_2) decreased significantly during administration of the three highest doses and this decrease had a dose-dependent tendency even though there were no statistically significant differences between these doses. This implies increased oxygen extraction during higher MED doses, which is consistent with a prior report with DMED (Lin *et al*., 2008). The underlying cause may be due to decreased CI and peripheral blood flow. This study was minimally invasive and dogs were instrumented only with peripheral catheters. Thus, central mixed venous blood samples were not obtainable and oxygen consumption and extraction could not have been calculated accurately. However, based on the results of peripheral oxygen tensions available, the extraction of oxygen appears to increase dose-dependently, which has not been reported previously with MED or DMED. Even though the oxygen balance would remain positive with increasing doses while its extraction is increased (Lin *et al*., 2008), these results indicate a further advantage of the use of low dose MED CRI when compared with higher doses.

Arterial and venous values of pH, pCO_2, HCO_3^-, glucose, and lactate remained at clinically acceptable range during each dose of MED CRI, and were consistent with

previous findings (Pascoe *et al*., 2006; Lin *et al*. 2008). Venous values of pH, pCO_2, HCO_3^-, glucose, and lactate showed comparable results to arterial values with normal arterio-venous differences and thus only arterial values were reported here. However, plasma glucose level is expected to increase with MED administration due to its insulin release inhibiting effect on pancreas that increases blood glucose levels (Short, 1992). This was not demonstrated in our study, probably because samples were not taken after the end of infusion. Medetomidine has been found to produce slow (peak in 2-4 hours post-administration) and non-significant change in plasma glucose concentrations (Burton *et al*., 1997; Ambrisko and Hikasa, 2002). Arterial lactate concentrations remained within normal physiologic range (below 2.5 $mmol \cdot L^{-1}$) with all dose regimens. This was consistent with findings from recent reports (Pascoe *et al*. 2006; Uilenreef *et al*. 2008) with DMED during anesthesia, implying that the overall tissue perfusion was maintained during this study. Again, in our study lactate measurements did not continue after MED CRI, and thus a potential of lactate retention during CRI may have occurred. Based on a previous study, some lactate retention may occur when increasing the dose of DMED CRI to 3 $\mu g\ kg^{-1}\ h^{-1}$ (Uilenreef *et al*., 2006) but it was not demonstrated with lower doses. Thus, it may be speculated that lactate retention should not occur with low dose MED CRI either.

Conclusion

With regards to the multitude of possible clinical uses of low dose DMED CRI in human patients (Aantaa and Jalonen, 2006; Tobias, 2007) with increasing amount of promising studies being published, the full advantage of these drugs may potentially follow in veterinary use. Such indications of MED or DMED CRI in veterinary patients could include the use as an adjunct to balanced anesthesia and enhance perioperative hemodynamic stability, as an adjunct to perioperative multimodal analgesia, and as a sedative-analgesic for intensive care use.

In conclusion, these results demonstrated the dose-dependency of the hemodynamic responses of MED CRI, when used as an anesthetic adjunct to ISO anesthesia in dogs. The low doses MED CRI (0.2-1.7 μg kg^{-1} h^{-1}) induced limited and transient hemodynamic changes correlated to pharmacokinetics, promising enhanced hemodynamic stability, and showed fewer changes in pH and oxygen extraction when compared to higher doses. Thus, these low doses of MED CRI could be implicated to the perioperative care of canine patients with minimized hemodynamic changes.

Limitations of this presented study where the low number of dogs used and the lack of some laboratory measurements such as insulin measurements, due to the finantial limitations during this study. Subsequent studies have been proceeded on the effects of medetomidine CRI on 24 hour echocardiogram (Appendix 1) and on the clinical efficacy during and after orthopaedic surgery (Appendix 2). However, further studies are warranted to fully demonstrate and quantify the clinical efficacy of these CRI doses as analgesic and anesthetic adjuncts.

"There are only two mistakes
one can make along the road to truth;
not going all the way,
and *not* starting."
Buddha

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APPENDIX 1

ABSTRACT presented in IVAPM congress in Montréal 2008.

TITLE: Variable anti-arrhythmic effect of different dose levels of medetomidine constant rate infusion in isoflurane-anaesthetized dogs.

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In this prospective, blinded study, 16 healthy beagles (1-3.5 years old, weighing 8.6-16.0 kg) randomly received one of 4 medetomidine infusion regimens (4 dogs per regimen at 1.0, 1.7, 4.0 or 12 μg/kg/h for 1h). One supplemental control group (n=3) received solely isoflurane. 24-hour ambulatory electrocardiography was performed. Recording was initiated at a minimum of 4 hours prior to induction of anaesthesia with isoflurane in oxygen. Prior to each infusion, a similar loading dose was given over 10 min. Each medetomidine dosing regimen was randomly administered twice for all dogs (protocols A and B). Isoflurane was administered alone for 1h before (Protocol A) or after (protocol B) a 1h10 min administration of isoflurane combined with medetomidine CRI (2 week intervals between experiments). In the 12 μg/kg/h group only, the imidazoline-receptor antagonist efaroxan was administered intramuscularly 1h after the end of general anaesthesia. To control the effects of efaroxan, two additional dogs were anaesthetized with 12 μg/kg/h using protocol B without efaroxan administration. Electrocardiographic recordings were examined on hourly sessions to determine the indices of heart rate variability (HRV), heart rate, and cardiac conduction disturbances (ventricular premature complexes and atrioventricular blocks). Statistical analyses were conducted with a repeated measures linear model ($P<0.05$).

Isoflurane decreased HRV indices and cardiac vagal activity (decreased RR interval and SDNN), an effect that was counteracted by each dose of medetomidine CRI in both A and B protocols. Indeed, dogs in protocol B demonstrated basal vagal activity during the one hour isoflurane anaesthesia after medetomidine CRI was finished. In the recovery phase, HRV decreased significantly in the first 3h for the 3 lower doses before increasing back to basal level. But in the 12 μg/kg/h group with efaroxan, HRV was normal in the initial 1h post-anaesthesia, and was significantly decreased for the following 5h for both protocols. No cardiac conduction disturbances were noted in any dog.

An anti-arrhythmic effect of medetomidine CRI was evident at all doses during anaesthesia, but was apparently present only at the highest dose tested in this study during the post-anaesthetic period. This potentially cardioprotective effect seems to be mediated by binding of medetomidine to the imidazoline receptor.

APPENDIX 2

ABSTRACT presented in AVA/ECVAA spring congress in Helsinki 2009.

TITLE: Comparison of clinical analgesia induced by medetomidine constant rate infusion and/or loco-regional anaesthesia in canine orthopaedic surgery.

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This study investigated analgesic effects of a low dose medetomidine (MED) constant rate infusion (CRI) in dogs undergoing cranial cruciate ligament repair surgery compared to a loco-regional anaesthesia (LRA) technique.

In this prospective, blinded, controlled study, 32 client-owned dogs were randomly assigned to receive one of 4 treatments (n=8): 1–MED-CRI with placebo-LRA; 2–MED-CRI with bupivacaine-LRA; 3–placebo-CRI with bupivacaine-LRA; and 4–placebo-CRI with placebo-LRA. Standardized anaesthesia included intramuscular pre-medication with butorphanol (0.3 $mg \cdot kg^{-1}$) and acepromazine (0.03 $mg \cdot kg^{-1}$), intravenous (IV) propofol induction, constant 1.4% end-tidal isoflurane, controlled ventilation and continuous multiparametric monitoring. Femoral and sciatic nerve blocks were performed using bupivacaine (1 $mg \cdot kg^{-1}$) or saline. Medetomidine (or saline) IV CRI was initiated before surgery with loading dose (0.8 $mcg \cdot kg^{-1}$) and infusion (1.7 $mcg \cdot kg^{-1} \cdot h^{-1}$). Post-operative pain was scored for 24h using the composite 4A-VET scale[a]. Rescue analgesia was based on intra-operative SAP increase and post-operative pain; and consisted of additive levels: hydromorphone (0.05 $mg \cdot kg^{-1}$ IV) and/or MED-CRI, and carprofen. Linear model for repeated measures and Cochran-Mantel-Haenszel tests were used for statistics.

During surgery, all dogs of Gr.4 and Gr.3 required rescue analgesia, 7/8 in Gr.1 and 5/8 in Gr.2. During recovery, Gr.1 showed significantly more pain than Gr.2. After surgery, Gr.3 needed significantly lower doses of rescue analgesia compared to Gr.4 or Gr.1. None of the dogs with LRA needed the highest level of post-operative rescue analgesia. Neither

surgeon, nor surgery technique (TPLO, FLO, TTA) had a significant effect on the post-operative pain score.

Neither MED-CRI, at this dosage, nor femoral/sciatic LRA were efficient analgesics in this study. However, their combination demonstrated a synergistic effect, both pre-emptively (Gr.2) and after surgical pain occurrence (Gr.3 + rescue analgesia). Pre-medication with butorphanol alone for orthopaedic surgery (Gr.4) demonstrated not only insufficient analgesia but also a more difficult subsequent pain management.

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