Universidade de Trás-os-Montes e Alto Douro

Echocardiographic assessment of medetomidine-induced cardiovascular effects in cats

Dissertação de Mestrado

Mestrado Integrado em Medicina Veterinária

Sandra Isabel Ferreira Regada

Orientador:

Professor Doutor Luís Lima Lobo

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“As doutrinas apresentadas no presente trabalho são da exclusiva responsabilidade da autora”

To my parents

“All men dream but not equally.
Those who dream by night in the dusty recesses of their minds
wake up in the day to find it was vanity.
But the dreamers of the day...
The dreamers of the day are dangerous men,
for they may act their dreams with open eyes, to make it possible.”

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Abstract

Medetomidine is frequently used for induction of general anesthesia in cats. Its interference on cardiovascular function is known, but data is sparse in this specie. We postulate that medetomidine could have depressant effects on feline cardiac function.

To perform this study, ten healthy male cats presented at Hospital Veterinário do Porto were recruited. The procedure included measuring indirect blood pressure, assessment of femoral artery pulse by palpation and transthoracic echocardiographic examination previously to sedation and subsequently under the effect of medetomidine (0.08 mg/kg intramuscular).

Overall statistically significant changes were observed between basal and sedation values. Significant decrease of heart rate and increase of blood pressure occurred. Fractional shortening, ejection fraction and cardiac output decreased, whereas pre-ejection period, isovolumic contraction time and left ventricular ejection time increased, reflecting systolic dysfunction. Isovolumic relaxation time increased, implying an impairment of left ventricular relaxation. Mitral valve A wave peak velocity decreased and E/A ratio increased, which may suggest systolic dysfunction of the left atrium. Left atrium diameter increased significantly. Aortic and pulmonic valve peak velocities and the respective pressure gradients decreased significantly. Valvular insufficiencies (aortic, mitral and pulmonic) associated to sedation were also observed.

Our study shows that medetomidine has a significant depressant effect on feline cardiac function, being the reflex of altered loading conditions secondary to medetomidine increased systemic vascular resistance and bradycardia effects. In conclusion, medetomidine may be deleterious in cats with underlying heart disease. In these cases it should be avoided or used cautiously, as sudden changes in the loading conditions can be detrimental.

Keywords: Medetomidine; cats; cardiovascular effects; echocardiography.

Resumo

A medetomidina é frequentemente usada na indução de anestesia geral em gatos. A sua interferência na função cardiovascular é conhecida, contudo a informação nesta espécie é escassa. Nós postulamos que a medetomidina poderá ter efeitos depressores na função cardíaca em gatos.

Para a realização deste estudo, foram recrutados dez gatos saudáveis do sexo masculino apresentados no Hospital Veterinário do Porto. O procedimento incluiu a medição da pressão arterial indirecta, a avaliação do pulso pela palpação da artéria femoral e ecocardiografia transtorácica previamente à sedação e posteriormente sob o efeito de medetomidina (0.08 mg/kg intramuscular).

No geral foram observadas alterações estatisticamente significativas entre os valores basais e os da sedação. Ocorreu uma diminuição significativa da frequência cardíaca e um aumento da pressão arterial. A fração de encurtamento, a fração de ejecção e o débito cardíaco diminuíram, enquanto o período de pré-ejeção, o tempo de contração isovolumétrico e o tempo de ejeção do ventrículo esquerdo aumentaram significativamente, refletindo uma disfunção sistólica. O tempo de relaxamento isovolumétrico aumentou, indicando uma diminuição do relaxamento do ventrículo esquerdo. A velocidade do pico da onda A diminuiu e o rácio E/A aumentou, o que poderá sugerir uma disfunção sistólica do átrio esquerdo. O diâmetro do átrio esquerdo aumentou significativamente. A velocidade do pico da válvula aórtica e da válvula pulmonar e os respectivos gradientes de pressão diminuíram significativamente. Foram também verificadas insuficiências valvulares (aórtica, mitral e pulmonar) associadas à sedação.

O nosso estudo mostra que a medetomidina tem um efeito depressor significativo na função cardíaca felina, sendo o reflexo de condições de carga alteradas secundárias ao aumento da resistência vascular sistémica e à bradicardia induzidas pela medetomidina. Em conclusão, a medetomidina pode ser deletéria em gatos com doença cardíaca subjacente. Nestes casos, deve ser evitada ou utilizada com cautela, já que alterações súbitas nas condições de carga poderão ser prejudiciais.

Palavras-chave: Medetomidina; gatos; efeitos cardiovasculares; ecocardiografia.

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Abbreviations

µg/kg - microgram per kilogram
2D - two-dimensional
ADH - antidiuretic hormone
Ao - aortic diameter
ASA - American Society of Anesthesiologists
ASE - American Society of Echocardiography
AV - atrioventricular
AVpeak - aortic valve peak velocity
AVPG - aortic valve pressure gradient
cAMP - cyclic adenosine monophosphate
BW - body weight
CNS - central nervous system
CO - cardiac output
DEX - dexmedetomidine
DP - diastolic pressure
ECG - electrocardiogram
EF - ejection fraction
FS - fractional shortening
GABA - gamma aminobutyric acid
HDO - High Definition Oscillometry
HR - heart rate
IM - intramuscular
IV - intravenous
IVCT - isovolumic contraction time
IVRT - isovolumic relaxation time
IVSd - Interventricular septal thickness in diastole
IVSs - Interventricular septal thickness in systole
LA - left atrium diameter
LA/Ao - left atrium to aortic diameter ratio
LEV - levomedetomidine
LV - left ventricle
LVEDV - left ventricular end-diastolic volume
LVESV - left ventricular end-systolic volume

LVET - left ventricular ejection time

LVFW - left ventricular free wall

LVOT - left ventricular outflow tract

m/s - meter per second

MAP - mean arterial pressure

MED - medetomidine

mg/kg - miligram per kilogram

mg/ml - miligram per mililiter

MHz - megahertz

mmHg - milimeter of mercury

MPI - myocardial performance index

ms - milisecond

MV A or **A peak** - mitral valve A wave peak velocity

MV E or **E peak** - mitral valve E wave peak velocity

MV E/A or **E/A ratio** - E wave peak velocity to A wave peak velocity ratio

PEP - pre-ejection period

PEP/LVET - left ventricular ejection time to pre-ejection time ratio

PPM - anterior and posterior papillary muscle,

PVpeak - pulmonic valve peak velocity

PVPG - pulmonic valve pressure gradient

PW - pulsed-Wave Doppler

SP - systolic pressure

STI - systolic time intervals

SVR - systemic vascular resistance

α - alpha

β - beta

Preface

Being Anesthesiology and Cardiology particularly appealing areas for me and once this study was proposed by two remarkable professionals in these same areas, this was undoubtedly the ideal study for my dissertation.

This study was performed as part of my curricular externship, which was held at Hospital Veterinário do Porto during the period from 3rd September 2012 to 24th February 2013.

In addition to the collaboration of Hospital Veterinário do Porto, which provided the means, this study relied on the collaboration of Clínica dos Gatos and an animal protection association, which provided most of the animals.

The cardiovascular effects of α_2-agonists have already been investigated, which therefore contributed for the limitations of its use in the clinical practice. Although research on these drugs and their clinical use are extensive, data about the effects of medetomidine and dexmedetomidine on feline cardiac function is still incomplete. This study is a continuation from a previous investigation about the cardiovascular effects of dexmedetomidine already done. Therefore, the ultimate goal of this study was the comparison of the echocardiographic changes caused by medetomidine with those caused by the sedation with dexmedetomidine.

Chapter 1 – Literature review

1.1 - Introduction

In the clinical practice of companion animals anesthesiology has always been one of the most complex and challenging procedures to put into practice, being however routinely performed (Novak, 2003). Anesthesia is defined as the total loss of sensibility in part or in the entire body, induced by a drug or combination of several drugs which depress the activity of the peripheral nervous system (local or regional anesthesia) or the central nervous system (general anesthesia). Anesthesia is a reversible process essential in the veterinary clinical practice, allowing secure and efficient immobilization of the patient, minimizing the stress, pain and facilitating a wide variety of procedures (Cornick-Seahorn 2001). Currently there is a wide variety of injectable agents available to supply the need for premedication, induction, maintenance and postoperative analgesia or to decrease anxiety and motor activity (chemical restraint). Although the choice of the anesthetic drug is important for achieving favorable results, this is only a small portion of the factors to consider for a successful anesthesia (Novak, 2003).
The maintenance of cardiovascular health in animals under anesthesia is an extremely important factor to consider, since changes at this level may jeopardize the animal's life. By interfering with cardiovascular function, sedation requires specific care, including a pre-anesthetic evaluation and monitoring during and after anesthesia, which include cardiovascular parameters. Work undertaken in small animal practice has documented moderately high risks of mortality in cats. This appears to be decreasing over time as anesthetic drugs and monitoring improve, however, cats show greater risk of death compared with dogs (Brodbelt 2010).
It is essential to know the effects medetomidine promotes to reduce potentially fatal complications, once it is often used with other drugs for induction of general anesthesia in cats, with potential cardiovascular complications.

The aims of the present study included:

- The acquisition of skills in anesthesiology practice and echocardiography;
- The observation and assessment of cardiovascular effects associated with the sedation with medetomidine, in order to maintain the integrity of the cardiovascular system;
- The analysis and comparison of the observed cardiovascular effects of medetomidine with those produced by dexmedetomidine;
- The contribution for preventing and reducing perioperative anesthetic complications associated with α_2-agonists use in small animal clinical practice.

1.2 - Alpha-2-adrenoceptor agonists

The interest for the use of α_2-agonists in veterinary anesthesia is due to its ability to produce sedation, analgesia, muscle relaxation and anxiolytic action. They are one of the most potent sedatives. The *locus coeruleus* is most likely the center of action of these agents. Muscle relaxation is an advantage to these agents, which is due to inhibition at interneural level in the spinal cord. Due to its analgesic action, these compounds may be as effective as opiates, in certain situations, but its short time of action when administered systemically limits its use as analgesics (Paddleford and Harvey 1999). The cardiovascular effects of α_2-agonists limited their use in the clinical practice. Research on these drugs use is extensive, but data in feline cardiac function effects is still sparse so studies in this area should be performed.

Medetomidine (MED) (± 4-[1-(2, 3-dimethylphenyl) ethyl]-1 H-imidazole) is a highly potent, selective, specific and lipophilic α_2-agonist (Savola, Ruskoaho et al. 1986). This drug is a racemic mixture of equal proportions of two optical enantiomers – the levo- and dextro-rotatory optical isomers with generic names levomedetomidine (LEV) and dexmedetomidine (DEX) respectively. Pharmacological activity of MED is stereospecific and is due predominantly to its dextro-rotatory isomer (Savola and Virtanen 1991).

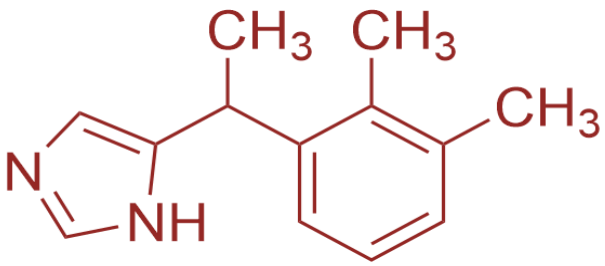


Figure 1: Medetomidine chemical structure (adapted from www.northerncheminc.com)

1.2.1 - Medetomidine action in the α_2-receptors

MED has very weak or no binding affinity for β_1, β_2, adrenergic, H_1, H_2, histamin, 5-$HT5_1$, 5-HT_2, muscarine, dopamine, tryptamine, GABA, opiate and benzodiazepine receptors (Virtanen, Savola et al. 1988). Nevertheless, the binding affinity of MED for the α_2-receptors is high. In binding studies with rat brain preparations, the α_2/α_1 selectivity ratio of MED was found to be 1620, which was 5-10 times higher than that for similar reference compounds like xylazine, brominidine, clonidine and detomidine (Virtanen, Savola et al. 1988). The α_2-receptors are connected to a transmembrane G-protein found pre-, post- and extra-synaptically in different tissues. There are three subtypes of receptors, α_{2a}, α_{2b} and α_{2c}, based on their affinity for different ligands (Murrell and Hellebrekers 2005).

The activation of α_2-receptors promotes the inhibition of adenylate cyclase, resulting in a decrease of cAMP formation, an important regulator of cellular function. Other effects include the activation of the G-protein linked to potassium channels, causing neuronal cell hyperpolarization, which contributes to a decrease in the excitability of the CNS neurons, which translates into sedation, associated with α_2-agonists (Aghajanian and VanderMaelen 1982).

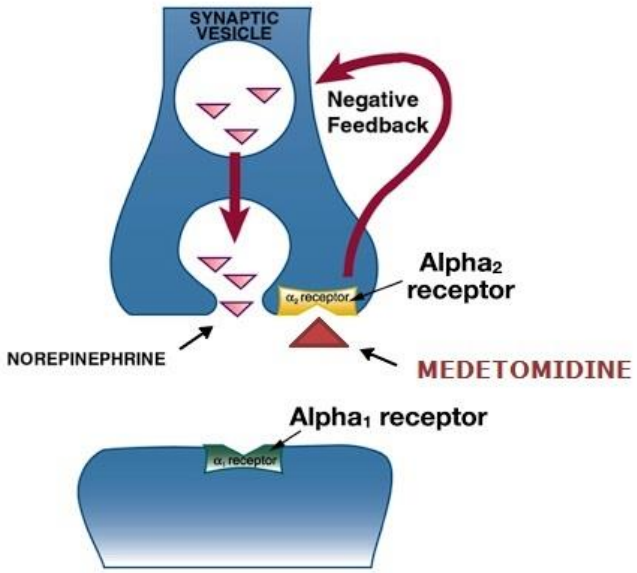


Figure 2: Medetomidine action in the α_2-receptors – The stimulation of the α_2-receptors, results in an inhibition of the opening of synaptic vesicle and the release of neurotransmitters such as norepinephrine.
(adapted from www.pharmacology2000.com)

The stimulation of the α_2-receptors, results in an inhibition of the release of neurotransmitter, which is mediated by a decrease in ion conductance calcium, involving a direct regulation of the influx of calcium through energy dependent channels (Lipscombe, Kongsamut et al. 1989). The post-synaptic α_2-receptors have distinct physiological function in many tissues including liver, kidney, pancreas, adipose tissue and eye. The pre-synaptic α_2-receptors are present on sympathetic nerve endings, and noradrenergic neurons of the central nervous system, which inhibit noradrenaline release when activated (Langer 1980). The *locus coeruleus* is a small neuronal nucleus located bilaterally in the upper base of the brain, and is the largest group of noradrenergic cells in the brain. This nucleus is an important modulator of alertness and may be the primary site of the sedative action of α_2-agonists, mediated by the α_2-receptor located there (Scheinin and Schwinn 1992). There are also a large number of α_2-receptors on the vagus nerve, in the intermediolateral cell column and in the gelatinous substance. The dorsal portion of the spinal cord has α_{2a} subtype adrenoceptors, while the primary sensory neurons have α_{2a} and α_{2c} subtype adrenoceptors. In the thalamus only α_{2a} subtype were found (MacDonald and Scheinin 1995), although these receptors, also present on vascular smooth muscle, are crucial in mediating the peripheral hypertension induced by α_2-agonists (Link, Desai et al. 1996).

1.2.2 - Pharmacokinetic

Following intramuscular (IM) administration (in dogs and cats), MED is rapidly absorbed into the blood stream and rapidly distributed into well-perfused tissues, including the brain, effectively penetrating these tissues and readily reaching its target receptors. Peak concentration after IM administration in the dog and in the cat is seen within 30 minutes (Salonen 1988).

A relatively low proportion (approximately 15%) of MED exists as a free unbound fraction in circulation, while most of it circulates in its inactive protein-bound form. Elimination occurs mainly by biotransformation in the liver and excretion via the urine as inactive metabolites, being that only traces of the drug are excreted unchanged (Salonen 1988). MED's therapeutic effects terminate by removal from its target tissue, which parallels the elimination of the drug from blood plasma (Salonen 1988). Both DEX and LEV inhibit human cytochrome P450 catalytic activity equally (Kharasch, Herrmann et al. 1992), and it has also been demonstrated that both inhibit microsomal drug metabolism in rat and human livers (Pelkonen, Puurunen et al. 1991).

Several studies have been conducted regarding the use of MED as premedication in cats, followed by reversal with atipamezole at the end of anesthesia for recovery, confirming that MED is a potent sedative and may be administered prior to numerous anesthetic agents such as propofol, ketamine and isoflurane. Recovery with atipamezole is usually fast and of good quality (Verstegen, Fargetton et al. 1990; Young, Brearley et al. 1990; Hellebrekers and Sap 1997; Hellebrekers, Van Herpen et al. 1998), and although there has been extensive cardiovascular monitoring performed in all cases, these studies have found that MED is a safe pre-anesthetic agent in healthy cats in combination with common use anesthetics.

The advantages of incorporating α_2-agonists for anesthesia include: potent sedation, reducing the amount of other anesthetics necessary to allow surgery (Young, Brearley et al. 1990; Ewing, Mohammed et al. 1993; Hammond and England 1994), analgesia (Pypendop and Verstegen 1994) and the reversal of its effects (Bartram, Diamond et al. 1994).

1.2.3 - Effects

1.2.3.1 - Sedative effect

The sedative effect induced by α_2-agonists result from the action on the *locus coeruleus* (the predominant noradrenergic nucleus of the brain associated with the anxiolytic effect similar to that produced by benzodiazepines). As a result, patients can be awakened and stay alert while being stimulated (Cortopassi and Fantoni 2002). MED sedation is profound and dose-related.

However, a plateau effect is reached and beyond this point further increases in dose prolong the duration of effect rather than increase the intensity of sedation (Seymour, *et al*., 2008).

1.2.3.2 - Analgesic effect

Medetomidine is licensed in cats and dogs as a sedative. However, it also has analgesic properties that are primarily mediated via α_2-adrenergic receptors at various sites in the pain pathway within the brain and spinal cord (Sinclair 2003). These receptors modulate the release of neurotransmitters responsible for transmission of nociceptive signals to higher centers. Alpha-2 receptors located in the periphery may also play a role in the mediation of nociception (Seymour, *et al*., 2008).

1.2.3.3 - Muscle relaxation

It has been recognized that α_2-agonists provide muscle relaxation and analgesia (Paddleford and Harvey 1999). The muscle relaxant effect that accompanies sedation is due to inhibition at α_2-adrenoreceptors at the interneuron level of the spinal cord and is a beneficial property of the α_2-agonists in clinical practice (Cullen 1996)

1.2.4 - Other pharmacological effects

1.2.4.1 - Cardiovascular effects

Administration of α_2-agonists may induce a biphasic blood pressure response in humans and animals, which is characterized by an initial transient hypertensive phase which is accompanied by a hypertension-induced-baroreceptor-reflex decrease in HR and followed by a hypotensive phase and stabilization of heart rate to below baseline values. The bradycardia induced by the α_2-agonists may be associated with vagal-induced bradyarrhythmias, such as 1st and 2nd degree atrioventricular heart block. Typically, these arrhythmias are not life threatening and are attributed to a baroreceptor mediated reflex to the peripheral vasoconstriction and a diminished sympathetic outflow (Savola, 1989).

Heart rate: Changes in heart rate (HR) result from the stimulation of α_2-adrenoreceptors located around peripheral blood vessels and in the CNS and can be divided temporally into two phases.

Phase 1: The immediate response of the cardiovascular system to MED is an increase in blood pressure, caused by peripheral vasoconstriction via activation of α_2-receptors located in the peripheral vasculature. This increase, however, causes a reflex reduction in HR, mediated by the baroreceptor reflex.

Phase 2: The peripheral vasoconstriction induced by MED lasts for approximately 20 minutes and in phase 2 blood pressure returns to normal or slightly below normal. Despite the reduction in blood pressure back to approximately normal values, HR remains low throughout the period of MED administration. Phase 2 bradycardia is mediated centrally as a result of the reduced norepinephrine outflow within the CNS, and consequent inhibition of central sympathetic tone. This beneficially results in sedation, but the reduced sympathetic tone also promotes a prolonged reduction in HR (Sinclair 2003).

Cardiac output: Alpha-2 agonists cause a reduction in cardiac output (CO), which was demonstrated, by several research articles, not to be due to a direct negative action of the α_2-agonist on myocardial contractility, but secondary to the increased systemic vascular resistance (SVR) and reduced HR (Autran de Morais and Muir 1995; Schmeling, Kampine, et al. 1991; Muir and Piper 1977). The increase in afterload resulting from peripheral vasoconstriction is thought to be a contributing factor. In animals with a healthy, normally functioning cardiovascular system, the reduction in CO is not associated with reduced oxygen delivery to central organs, namely the CNS, heart, kidney and liver. However, in animals with limited cardiovascular reserve, the reduction in CO following MED may have detrimental consequences for organ function due to reduced oxygen delivery (Seymour, *et al*., 2008).

Atropine administration to treat bradycardia induced by MED should be avoided. It's safer to use a small dose of atipamezole instead (partial reversal). Fatal arrhythmias and cardiac arrest may occur after atropine administration, possibly because massive hypertension and tachycardia are induced, but the high afterload remains, increasing cardiac workload. Tachycardias also reduce diastolic filling time (and coronary perfusion), so CO can be further reduced, and myocardial oxygen supply compromised in the face of increased demand (Sinclair 2003).

1.2.4.2 - Respiratory effects

Sedation with α_2-agonists results in a reduction in respiratory rate for varying periods, which occurs secondary to the CNS depression produced by α_2-adrenoreceptor stimulation. However the effects on the respiratory system seen in healthy animals are minimal and arterial oxygen and carbon dioxide tensions remain within normal limits (Sinclair 2003).

1.2.4.3 - Endocrine effects

Alpha2-agonists, typically xylazine, have been reported to induce an increase in serum glucose by suppressing insulin release, stimulating glucagon release, or both, in β and α cells of the pancreas, respectively (Angel and Langer 1988). However, MED given at doses of 10 and 20 µg/kg, IV, decreased insulin values significantly but was not found to alter plasma glucose concentrations in normal beagles (Burton, Lemke, et al. 1997). Differences in plasma glucose concentrations are likely associated with the greater specificity of MED, compared with that of xylazine, at the α_2-adrenoreceptors. Despite this, the use of MED in animals with diabetes mellitus cannot be recommended until more information is available.

It is well recognized that animals recovering from α_2-agonist sedation typically have large volumes of urine with low specific gravity (Crighton 1990). Reasons for the diuresis involve the actions of α_2-agonists on antidiuretic hormone (ADH) and the renin-angiotensin system. This diuretic effect negates the use of these agents in animals with a urinary tract obstruction (Sinclair 2003).

1.2.4.4 - Body temperature

Temperatures may decrease in animals sedated with α_2-agonists. However, in dogs, only slight reductions in rectal temperature were observed with MED. In fact, although MED has a direct depressant effect on the thermoregulatory center, it may allow for better maintenance of body temperature. Consequently to the peripheral vasoconstriction and central redistribution of blood, it reduces cutaneous heat losses, in contrast to the consistent reductions in body temperature reported with the use of other anesthetic agents that induce vasodilation. However, body temperature should still be monitored in small animals and appropriate conservation of body heat to prevent dramatic reductions in temperature (Sinclair 2003).

1.2.4.5 - Vomiting

By stimulating the chemoreceptor trigger zone, which is in close proximity to the *locus coeruleus* in the brain, α_2-agonists typically induce vomiting in small animals. With MED sedation, vomiting was observed in up to 90% of cats (Vainio, Palmu, et al. 1986; Vaha-Vahe 1989).

1.2.4.6 - Intraocular pressure

After α_2-agonist administration, mydriasis was reported to be observed in animals. This effect is postulated to occur from central inhibition of parasympathetic tone to the iris, a direct sympathetic stimulation of the α_2-adrenoreceptors located in the iris, CNS, or both. Topical administration of MED in the eye of rabbits and cats readily induces mydriasis and decreases intraocular pressure by suppressing sympathetic neuronal function and decreasing aqueous flow (Potter and Ogidigben 1991). Nevertheless, the IV administration of MED to dogs induced miosis and did not lower intraocular pressure (Verbruggen and Akkerdaas 2000). Despite these contradictory results, the detrimental effects of vomiting and lowered head posture on the intraocular pressure induced with MED sedation would contraindicate the use of α_2-agonists in small animal patients with ocular problems in which an increase in intraocular pressure would be damaging (Sinclair 2003).

1.2.5 - Reversal of alpha-2 agonists with atipamezole

By the administration of a specific α_2-adrenoreceptor antagonist such as atipamezole, α_2-agonist sedation and analgesia are rapidly reversed. Recoveries following IM administration of atipamezole are generally smooth and of good quality. Intravenous administration of atipamezole is not recommended because it usually produces a very rapid, excitable recovery from anesthesia or sedation. It is essential to ensure that analgesia is supplemented, if necessary, with different classes of drugs (such as opioids and non-steroidal anti-inflammatory drugs) before reversal by atipamezole. Shortening the length of the recovery period using atipamezole can contribute to improved patient safety during the perioperative period. Yohimbine and tolazoline are commercially available (in some countries) α_2-antagonists that may also be used as reversal agents after MED or other α_2-agonists sedation. However, compared with atipamezole, these drugs have a lower α_2:α_1 receptor selectivity (Sinclair 2003).

1.3 – Echocardiography

Echocardiography has become the most important diagnostic technique for the diagnosis of canine and feline heart disease. Through the interaction between ultrahigh-frequency sound waves and the heart, echocardiography has revolutionized the non-invasive assessment of cardiac morphology, assessment of myocardium and valves movement, and blood flow within the heart (Tilley 2008).

1.3.1 - Types of Imaging

Two-Dimensional Echocardiography consists in a sector-shaped beam of ultrasound waves reflected by the interfaces of cardiac tissue to provide a two-dimensional (2D) cross-sectional image. This type of imaging allows the demonstration of cardiac morphology and is increasingly important in quantification of chamber dimensions (Tilley 2008).

M-Mode Echocardiography uses a single narrow beam of ultrasound, but displays the resulting echoes as a distance-time graph, being therefore used for time-dependent measurements (chamber dimensions, wall motion). It provides quantitative information in systole and diastole, and allows performing calculations of myocardial function. (Tilley 2008).

Doppler Echocardiography provides information about the direction and velocity of blood flow, based in the *Doppler principle* whereby the frequency of a reflected sound wave depends on the direction and velocity of the reflector and the transmitted frequency (producing a *Doppler shift*). On this basis, if the transmitted ultrasound frequency and the velocity of sound in soft tissue and blood are known, then the velocity of red blood cells can be calculated. In this type of imaging, the angle of the incident ultrasound beam is critical: *the ultrasound beam must be parallel with flow* (or less than 20° from the direction of flow) or the velocity will be underestimated (Tilley 2008; Boon 2011).

Doppler echocardiography includes several modes such as: *Spectral Doppler*, in which the velocity of blood flow is calculated in a region of interest selected by moving a cursor; *Color flow Doppler*, where the blood flow is coded in red or blue and superimposed on the black-and-white 2D image; and *Tissue Doppler imaging*, where the velocity of myocardial motion is displayed (Boon 2011). Doppler echocardiography applications include the characterization of abnormal direction (in conditions such as valvular insufficiency) or velocity of blood flow, and the assessment of the origin of turbulent blood flow. It may also be used to estimate flow volumes (combining Doppler with 2D) and abnormal blood flow velocities, turbulent blood flow profiles, to assess systolic and diastolic function, and to obtain information about intracardiac pressures (assessment of pressure gradients) (Tilley 2008).

1.3.2 - Echocardiographic Views

The most frequently used imaging planes are obtained with the transducer on the right side of the chest (right parasternal views). Views obtained from the left apical windows (caudal and cranial left parasternal views) are mainly used for Doppler echocardiography applications, being also helpful to confirm lesions in several views. Most Doppler Imaging recordings can be made from the left parasternal views, with the subcostal view preferred for aortic velocities. Color Doppler used in the right parasternal views can be used for screening mitral and aortic insufficiency (Tilley 2008).

1.3.3 - Echocardiographic Measurements

1.3.3.1 - Measurement and assessment of M-mode images

1.3.3.1.1 - Left Ventricle (LV)

When a two-dimensional transverse image is used to create left ventricular M-modes, it is required to fan the transducer between the level of the papillary muscles and the mitral valve until there is a good image of the chordae within a symmetrical circular left ventricular chamber. The M-mode cursor should bisect the left ventricular chamber into equal and symmetrical halves and be perpendicular to a line that connects the chordae tendinae (Boon 2011).
While the American Society of Echocardiography (ASE) recommends measuring diastolic chamber dimensions at the beginning of the QRS complex, the recommendation for measurement of systolic chamber size is at the peak downward point of septal motion. Diastolic and systolic left ventricular chamber measurements are made from the top of the endocardial surface of the left ventricular side of the septum to the top of the left ventricular free wall (“leading edge to leading edge” measurement method) (Boon 2011). Regarding left ventricular assessment, diastolic dimension is used to determine the presence or absence of left ventricular volume overload. This measurement reflects maximum ventricular filling when the heart is relaxed. Systolic dimensions are a reflection of systolic function in the heart and should not be used to assess the presence or absence of dilation neither of hypertrophy (Boon 2011).

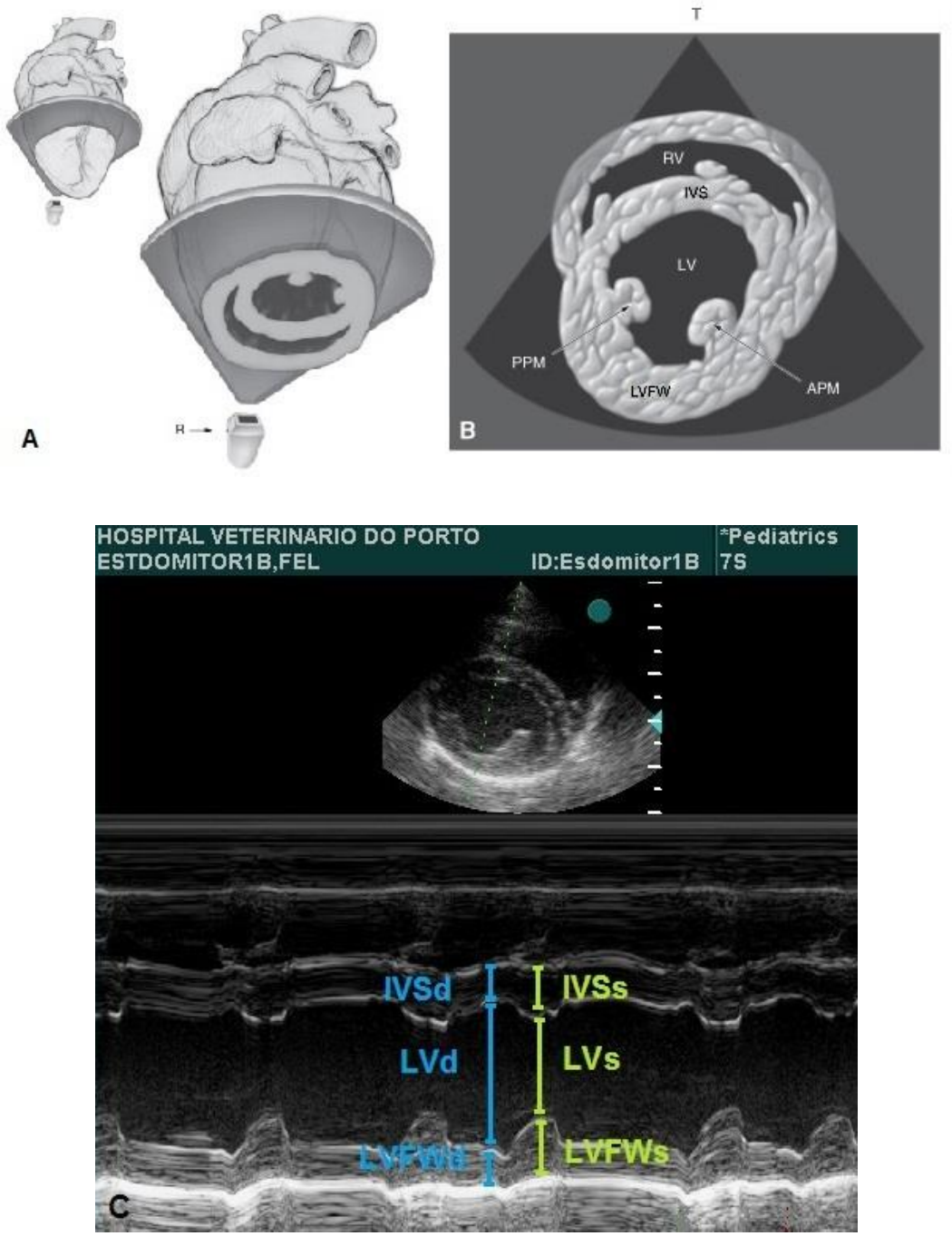


Figure 3: (A) Spatial orientation of the sound plane within the heart for the right parasternal short-axis left ventricle with papillary muscles view. **(B)** Illustration of the resulting 2D image and the relative positions of the cardiac structures. The top of the sector corresponds to the skin surface and transducer location. (Boon 2011) **(C)** 2D image of this plane through the heart and corresponding M-mode image below with diastolic and systolic measurements (note the “leading edge to leading edge” method of measurement);

R = reference mark, T = transducer, RV = right ventricle, IVS = interventricular septum, LV = left ventricle, APM and PPM = anterior and posterior papillary muscle, IVSd = Interventricular septal thickness in diastole, IVSs = Interventricular septal thickness in systole, LVd = left ventricular diastolic dimension, LVs = left ventricular systolic dimension, LVFW = Left ventricular free wall, LVFWd = Left ventricular free wall in diastole, LVFWs = left ventricular free wall in systole.

1.3.3.1.2 - Left Atrium and Aorta

The most common method of measuring the left atrium (LA) is on M-mode images at the largest left atrial dimension at end systole, from the top of the posterior aortic wall to the top of the pericardium. Left atrial wall thickness is generally not recorded well, and the pericardium provides a consistent easily visualized atrial boundary **(Fig. 4)**. The aorta (Ao) is measured from the top of the anterior aortic wall to the top of the posterior wall, at end diastole **(Fig. 4)**. Ideally two aortic valve cusps should be seen in the 2D image in order to minimize angle problems (Boon 2011). Regarding atrial dimension assessment, a ratio of left atrium to aortic root size (LA/Ao) may be used as an indicator of atrial dilation severity. This is generally a reliable value since the Ao usually maintains a fixed relationship with the chambers (Brown, Harrison et al. 1974). Left atrial size is very similar to aortic root size in dogs (range LA/Ao=0.83-1.13), while in cats the left atrium may be much larger than the aorta (range LA/Ao=0.88-1.79) (Boon 2011).

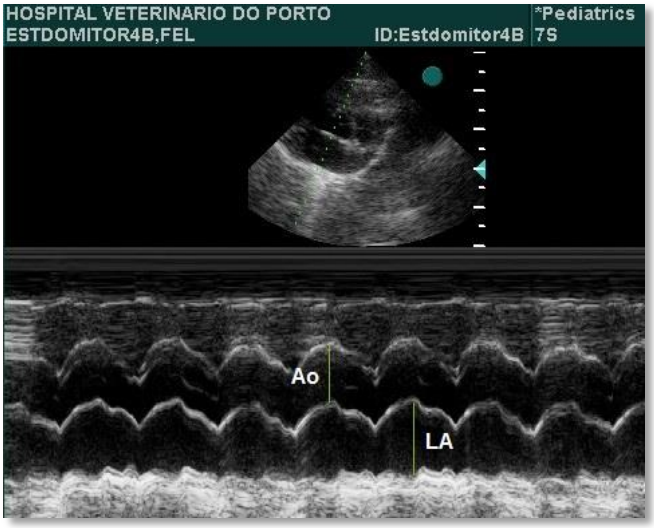


Figure 4: Right parasternal short-axis at aortic valve level; Two dimensional and corresponding M-mode image below (note the “leading edge to leading edge” method of measurement); LA = left atrium, Ao = aorta

1.3.3.2 - Measurement and assessment of Spectral Doppler Flow

Normal peak flow velocities in systole in the outflow tract regions and great vessels in dogs and cats are usually around 1m/s, with some patients having velocities approaching 2 m/s. Flow velocities in diastole are generally lower than systolic velocities. Normal intracardiac blood flow is laminar, although aliasing may occur in normal individuals. Most valves are best interrogated using left-side views because they give the best parallel alignment to flow (Kittleson 1998).The pulmonary valve is best interrogated from the left cranial position, or in some cases the right parasternal short-axis view. The aortic valve and left ventricular outflow tract (LVOT) are best

imaged in the left apical views or from a subcostal approach, which usually allows the best alignment with the flow (Yuill and O'Grady 1991; Kirberger, Berg et al. 1992). The semilunar valves (aortic and pulmonic) Doppler profile shows a single systolic wave signal away from the transducer and below the baseline, in the views described. The spectral signal across the aortic valve is different from that of the pulmonary valve, showing slightly higher peak velocities and a faster early acceleration, while pulmonary valve signal has a very symmetrical shape with very similar acceleration and deceleration rates (Brown, Knight et al. 1991). Aortic flow profile should have peak velocities < 1.7 m/s (left caudal parasternal view) or < 2.0 m/s (subcostal), while pulmonary flow profile should have peak velocities < 1.5 m/s (Tilley 2008).

Systolic time intervals measurement is one of the non-invasive techniques for the quantitative assessment of cardiac performance and can be measured from aortic and pulmonary flow profiles. Left and right ventricular ejection times (LVET and RVET) are measured from the onset of flow to the end of flow, at the baseline. Pre-ejection periods (PEP) are measured from the onset of the QRS complex to the onset of systolic flow **(Fig.6)** (Brown, Knight et al. 1991; Kirberger, Berg et al. 1992). Being LVET affected by HR, PEP to LVET ratio (PEP/LVET) is usually calculated in order to reduce this effect. This is considered to be a more accurate indicator of the LV function (Boon 2011).

While mitral inflow is more accurately recorded from the left apical long-axis views, the tricuspid inflow may be examined from both left apical and left cranial views. Flow across the atrioventricular valves show both passive and active components, resulting in two waves of diastolic flow both directed toward the transducer and above the baseline. The early diastolic wave, or E wave, corresponds to passive filling and the late diastolic A wave is associated with atrial systole. The E wave is normally higher and longer in duration than the A wave, and the ratio of the peak E wave to peak A wave (E/A) should be greater than 1.0 (Boon 2011).

Rapid HR, shorten diastole, causing merging of the A wave and E wave into a single diastolic wave. Atrial fibrillation eliminates atrial contraction and the Doppler A wave. In fact, many factors, including ventricular compliance and rate of diastolic relaxation, can affect the E/A ratio, since changes in relaxation affect early filling of the left ventricular chamber (E wave), and changes in compliance affect late diastolic filling of the ventricle (A wave). Peak velocities across the atrioventricular valves are usually less than 1 m/s and are almost always somewhat less than the velocities across the semilunar valves in the same patient (Kittleson 1998).

Although, the tricuspid valve signal usually looks qualitatively similar to the mitral valve signal, there is greater variation in the tricuspid valve signal because of the influence of respiration and because peak velocities tend to be slightly lower. Physiologic tricuspid valve regurgitation is relatively common (50%), whereas physiologic regurgitation of the mitral valve is not very common (Kittleson 1998).

Diastolic time intervals, which include the isovolumic relaxation time (IVRT), that corresponds to the time interval from cessation of aortic flow to the beginning of mitral inflow, are measured by placing the pulsed-wave Doppler (PW) signal in the LVOT near the mitral valve and recording part of both the aortic and the transmitral flow profile (Boon 2011). Ventricular relaxation is indirectly measured form IVRT, and subsequently delayed relaxation is reflected in longer IVRT. This parameter is affected by increased systolic aortic pressure and decreased left atrial pressure, both of which will prolong the IVRT and may not truly reflect impaired relaxation (Thomas, Flachskampf et al. 1992; Santilli and Bussadori 1998; Boon 2011).

The determination of pressure gradients is another common application of Doppler echocardiography in veterinary medicine. The physical principle of Conservation of Energy is the root of the Bernoulli equation, which is used to calculate the pressure gradient between two areas of the heart (Nishimura and Tajik 1994). The principle states that when a constant volume of blood flows through a narrowed area, its velocity must increase by an amount equal to the pressure drop. When a constant volume of blood is moved through an orifice or vessel, the pressure increase proximal to the obstruction creates a proportional increase in blood velocity through the obstruction. The simplified Bernoulli equation is as follows:

Pressure gradient (PG) = 4 (maximum velocity)^2 (Boon 2011).

1.3.3.3 - Evaluation of color-flow Doppler

Color-flow Doppler provides qualitative and semi-quantitative flow information. Spectral Doppler is often required in order to determine if flow velocity is truly high, turbulent, or reversed (Boon 2011). Pathological regurgitation can be semi-quantitatively assessed by measuring the size of the color-flow jet within the atria in the case of AV valvular insufficiency or within the outflow tract or ventricle in the case of aortic or pulmonic insufficiency (Cooper, Nanda et al. 1988).

1.3.4 - Evaluation of Ventricular Function

1.3.4.1 - Systolic Function

Concerning left ventricular function, an adequate amount of blood must be pumped out of the heart with every beat in order to perfuse the peripheral tissues and meet the metabolic needs of the body. The pumping ability or systolic function of the heart is dependent upon several factors including preload, afterload, contractility, distensibility, coordinated contraction and heart rate (Otto 2012). Systolic dysfunction is characterized by impaired pumping ability and reduced ejection fraction (Boon 2011). Preload is the force stretching the myocardium, and is dependent

upon the amount of blood distending the ventricles at end-diastole. Starling's Law states that the greater the stretch, the greater the force of contraction. Left ventricular diastolic volume increase, all other factors remaining constant, would therefore increase ventricular systolic function (Otto 2012). Afterload is the force against which the heart must contract. Generally the heart will hypertrophy in response to increases in preload to normalize wall stress (Titcomb 2004). When hypertrophy is absent, afterload is increased within the volume overloaded LV (Boon 2011). Cardiac output (CO) can be calculated by multiplying heart rate and stroke volume. Increases in heart rate with no other changes will result in greater CO. Very high heart rates however can be detrimental to the heart itself and induce myocardial failure (Boon 2011).

Regarding the right ventricle, its optimal function allows the right atrium to maintain a low pressure for adequate venous return and to provide low-pressure perfusion of the pulmonary vasculature. Contraction of the right ventricle during systole results in slow continuous movement of blood into the lungs. Therefore right ventricular pressure remains low throughout systole (Mebazaa, Karpati et al. 2004). Isovolumic relaxation and contraction are shorter and ejection is longer than in the LV and continues even after pressure starts to decline. Acutely increased afterload results in dilation in order to maintain forward flow. Increased afterload also increases isovolumic contraction and ejection times (Mebazaa, Karpati et al. 2004).

1.3.4.1.1 - M-mode Evaluation of Systolic Function

Left ventricular fractional shortening (FS) is probably the most common echocardiographic measurement of left ventricular function. This parameter is calculated by subtracting the left ventricular systolic dimension from the diastolic dimension **(Fig.3)** and dividing by the diastolic dimension in order to obtain a percent change in left ventricular size between filling and emptying (FS= [(LVd – LVs)/LVd] x 100) (Boon 2011).

Fractional shortening (FS) however is not a measure of contractility but a measure of function. The three primary factors that affect this parameter the most are preload, afterload, and contractility. Each one of these may individually or together affect FS. When FS is low it may be secondary to poor preload, increased afterload, or decreased contractility (Otto 2012). Several studies showed a high correlation between M-mode derived volumes and cardiac output when using the Teicholz method in normal dogs (Uehara, Koga et al. 1995). The Teicholz equation and its use to calculate ejection fraction (EF) and stroke volume (SV) is based upon the assumption that the left ventricular chamber is an ellipse and is as displayed in **Figure 5**.

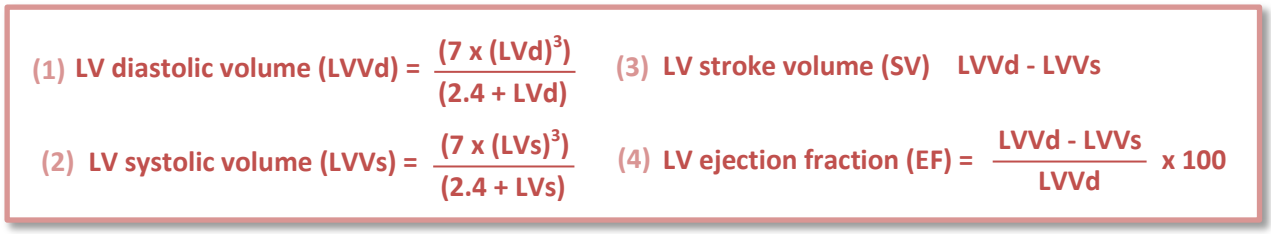


Figure 5: (1),(2) Teicholz equation to calculate LV diastolic and systolic volume; (3), (4) Derived equations to calculate stroke volume (SV) and ejection fraction (EF); LV = left ventricle; LVd = left ventricular diastolic dimension; LVs = left ventricular systolic dimension (adapted from Boon 2011).

1.3.4.1.2 - Spectral Doppler Evaluation of Systolic Function

Systolic time intervals (STI) may be better indicators of left ventricular systolic function than FS and have been shown to be as accurate as invasive methodology in humans (Atkins and Snyder 1992). The ejection time (ET) and PEP can both be measured from aortic or pulmonary flow profiles **(Fig.6)**. As with FS however, the STI are not indicators of contractility but rather function. Therefore, without first analyzing the effects of preload and afterload, contractility cannot be assessed accurately. When afterload is increased, the heart's workload is increased, and so, the time it takes to generate enough pressure in the LV before the aortic valve can open is longer. This time corresponds to the PEP. Decreases in afterload however allow the left ventricle to function easily, resulting in decreased PEP. Changes in preload can be approached the same way. High preload induces elongation of the fibers and function is enhanced (Frank Starling mechanism), shortening PEP and increasing LVET. Decreased preload however leads to the opposite (Boon 2011).

The myocardial performance index (MPI) is an index of global myocardial function and includes both diastolic and systolic time intervals. The MPI, also called the Tei index, correlates well with both systolic and diastolic function of the right and left ventricle and can be used to assess overall global function (Teshima, Asano et al. 2005; Teshima, Asano et al. 2006). This measurement uses ventricular ET and the isovolumic periods (contraction and relaxation) to derive an overall assessment of global ventricular function **(Fig.6)**. Using pulsed-wave Doppler, the time intervals are derived from different cardiac cycles (Boon 2011).

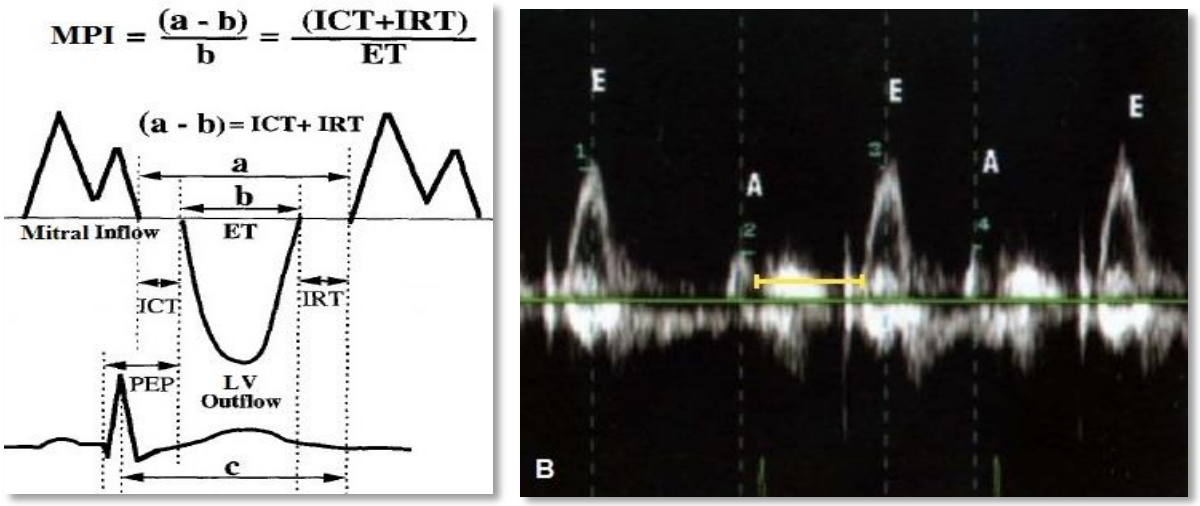


Figure 6: (A) Scheme of Doppler intervals. MPI is calculated by measuring two intervals: **a**, the interval between cessation and onset of mitral inflow, and **b**, the ejection time *(ET)* of left ventricular *(LT)* outflow; Isovolumic relaxation time *(IRT)* and Isovolumic contraction time *(ICT)* can be obtained by subtracting each one from (a - b). Pre-ejection period *(PEP)* is measured from onset of QRS wave to onset of LV ejection flow (adapted from Tei *et. al*, 1996);
(B) Normal mitral inflow pattern. The time from mitral valve closing (end of A wave) to mitral valve opening (start of E wave) is measured, representing IVCT+ET+IVRT (adapted from Schwarz 2008).

1.3.4.2 - Diastolic Function

Normal diastolic function allows the heart to fill appropriately at normal filling pressure. Diastolic failure is the outcome of increased resistance to filling and increased LV filling pressure. Diastolic dysfunction, however, simply refers to the presence of myocardial alterations during diastole but is not indicative of the patient's clinical status (Lester, Tajik et al. 2008).

The echocardiographic assessment of diastolic function incorporates the evaluation of isovolumic relaxation, transmitral valve flow and pulmonary venous flow (Boon 2011). The time that elapse from the end of ventricular ejection, to when the mitral valve opens and diastolic flow into the LV begins is the isovolumic relaxation period. No change in volume occurs and all valves are closed, but pressure decreases and the myocardium relaxes (Lester, Tajik et al. 2008). Relaxation continues even after the mitral valve opens. Filling of the LV has several phases: a rapid ventricular filling phase, a slow ventricular filling phase, and filling secondary to atrial contraction. The peak flow velocity between the LA and LV is determined by the PG between the two chambers, being this reflected in the LV inflow profile (Boon 2011). Most of LV filling is completed by the end of the rapid ventricular filling phase. Consequently, E wave peak reflects the PG between the LA and LV at the beginning of diastole. As pressures equilibrate between the two chambers, a period of diastasis occurs and the time for pressures to equilibrate is reflected by the deceleration time of the E wave. Valve motion with atrial systole (A wave) reflects the PG between the LA and LV at the end of diastole (Lester, Tajik et al. 2008).

Chapter 2 – Materials and methods

The study was done after approval by the MSc plan by the thesis committee in Veterinary Medicine from the University of Trás-os-Montes e Alto Douro and the clinical direction from Hospital Veterinário do Porto.

In order to perform this study, ten healthy male cats of any breed, with 6 to 12 months of age and weighing between 2.5 and 5.5 kg, presented at our institution for routine elective orchiectomy were recruited. Most of the cats used in this study were provided by an animal protection association and some belonged to private owners, who gave the required consent.

The procedure included measuring indirect blood pressure, assessment of femoral artery pulse by palpation and transthoracic echocardiographic examination previously to sedation and subsequently under the effect of medetomidine.

Prior to sedation the cats were classified according to the American Society of Anesthesiologists (ASA) Physical Status Classification System, and only Class I animals were included in the study. All cats were fasted for at least 12 hours before anesthesia, being accommodated in individual cages at ambient temperature. Water was available *ad libitum* whenever the cat was awake.

Previously to sedation, each animal was subjected to:

- ✓ Evaluation of indirect blood pressure:
  - ✓ By using High Definition Oscillometry (HDO) – *Memo Diagnostic®;*
  - ✓ Mean based on five measurements;
  - ✓ Cuff placed on the left front leg;
  - ✓ Always performed by the same operator;
- ✓ Assessment of femoral artery pulse by palpation;
  - ✓ Always performed by the same operator;
- ✓ Transthoracic echocardiographic examination:
  - ✓ By using cardiovascular ultrasound GE Vivid 3 (GE Medical Systems) with 7 MHz, multifrequency phased array transducers;
  - ✓ Simultaneous lead II ECG recorded and superimposed on the monitor display;
  - ✓ Right and left lateral recumbence;
  - ✓ 3 to 5 measurements for each parameter;
  - ✓ Always performed by the same operator.

Sedation was performed with medetomidine (Domitor® Pfizer, Porto Salvo, Portugal; 1mg/ml) at a dose of 0,08 mg/kg intramuscularly (*longissimus dorsi* muscle). At 30 minutes when medetomidine reached the peak effect, evaluations were performed on the same parameters obtained in baseline conditions (blood pressure, pulse measurement by femoral palpation and echocardiographic assessment). After all parameters evaluated, ketamine (Imalgéne® Merial, Rio de Mouro, Portugal; 100mg/ml) was administered intramuscularly at a dose of 5mg/kg, and orchiectomy was performed. Once the procedure has been completed, the cats received a single intramuscular injection of atipamezole (Antisedan® Phizer, Portugal; 5mg/ml) at a dose of 0.04mg/kg.

2.1 - Ecocardiographic evaluation

Complete echocardiographic examination was performed in every cat using cardiovascular ultrasound GE Vivid 3 (GE Medical Systems) with 7 MHz, multifrequency phased array transducers. A simultaneous lead II ECG was recorded and superimposed on the monitor display (Lobo, Bussadori et al. 2008). The echocardiographic examination included two dimensional (2D) standard views, as recommended elsewhere (Thomas, Gaber et al. 1993), as well as M-mode measurements using the leading-edge of myocardial borders (Sahn, DeMaria et al. 1978). Colour flow Doppler and continuous and pulsed spectral Doppler was also used in all valves. Examinations were performed in right and left lateral recumbency and all data were stored in the system as cine-loops. For each measured parameter, various cine-loops were recorded, and 3 to 5 measurements were made in different consecutive heart cycles. The M-mode images of the left ventricle were recorded simultaneously with a B-mode real time display in a short axis at chordal level, immediately below the mitral valve (Lobo, Bussadori et al. 2008).
The following measurements were performed: calculation of left ventricular end-diastolic volume (LVEDV), left ventricular end-systolic volume (LVESV) and calculation of fractional shortening (FS). The ejection fraction (EF) was estimated using the following formula: (LVEDV – LVESV / LVEDV x 100). The stroke volume (SV) was calculated by measuring the difference between LVEDV and LVESV (SV = LVEDV – LVESV) and the cardiac output (CO) was calculated multiplying SV by heart rate (HR).
The left atrium (LA) and aortic (Ao) diameters were measured in short axis, from M-mode, at the level of the aortic valve, and ratio (LA/Ao) calculated.
Aortic peak velocity (AV peak) was measured by placing the cursor at the apex of the maximal downward motion of the valve and by tracing the flow profile in a parasternal left apical view that allowed a good alignment of the cursor with the left ventricular outflow tract. The same technique was used to trace the pulmonic valve profile in a right parasternal short axis view at

the pulmonic valve level, to measure pulmonic peak velocity (PV peak).The aortic pressure gradient and pulmonic pressure gradient were also measured (AVPG and PVPG) (Lobo, Bussadori et al. 2008).

The left apical four chamber view was used to measure mitral valve flow (Kirberger et al., 1992a), with the cursor placed at the apex of the maximal upward motion. Peak E and A wave velocities (MV E and MV A) were measured and the E/A index calculated (MV E/A).

Systolic time intervals, including the pre-ejection period (PEP), which is measured from the onset of the QRS complex to the onset of systolic flow, the left ventricular ejection time (LVET), which is measured from the onset of flow to the end of flow at the baseline (corresponding to aortic flow duration) and the PEP/LVET ratio were also assessed through Pulsed-Wave Doppler (PW). These parameters were obtained by placing the PW signal in the left ventricular outflow tract on apical four chamber imaging planes near the mitral valve and recording part of both the aortic flow profile and the transmitral flow profile. The isovolumic contraction time (IVCT) and the isovolumic relaxation time (IVRT) were also measured by the same method. The myocardial performance index (MPI) was calculated using the following equation: MPI=(IVRT+IVCT)/LVET (Boon 2011).

2.2 - Statistical analyses

Parametric data were analyzed using the "Paired sample test", while non-parametric data were analyzed with the "Wilcoxon test." All data were analyzed with SPSS 19 for Windows (IBM Corporation, Armonk, NY).

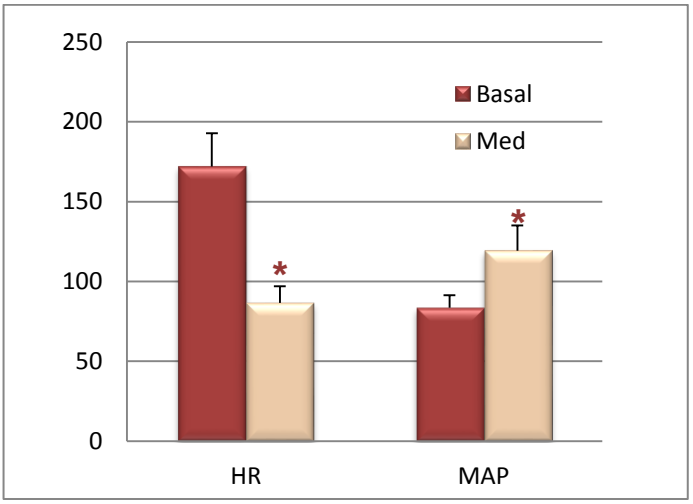
The null hypothesis (H0) was defined as absence of change in the mean of each parameter before and after sedation with MED and the alternative hypothesis (H1) was defined as the occurrence of variation in the mean of each parameter before and after sedation with MED. Statistical significance was set at $P \leq 0,05$. Therefore, in cases where the significance is ≤ 0,05 the null hypothesis is rejected and it is thus concluded that there was a statistically significant change.

Chapter 3 – Results

In the following section the results obtained in the present study will be presented. Data displayed in the following tables and graphics will be regarding heart rate, mean arterial pressure and the already mentioned echocardiographic parameters, under baseline conditions and after medetomidine administration. Values are expressed as mean ± standard deviation and statistical significance set at $P \leq 0,05$.

Table 1: Heart rate (HR) in beats per minute and mean arterial pressure (MAP) in mmHg results under baseline conditions and after medetomidine administration.
Values are expressed as mean ± standard deviation.
Statistical significance set at $P \leq 0,05$.

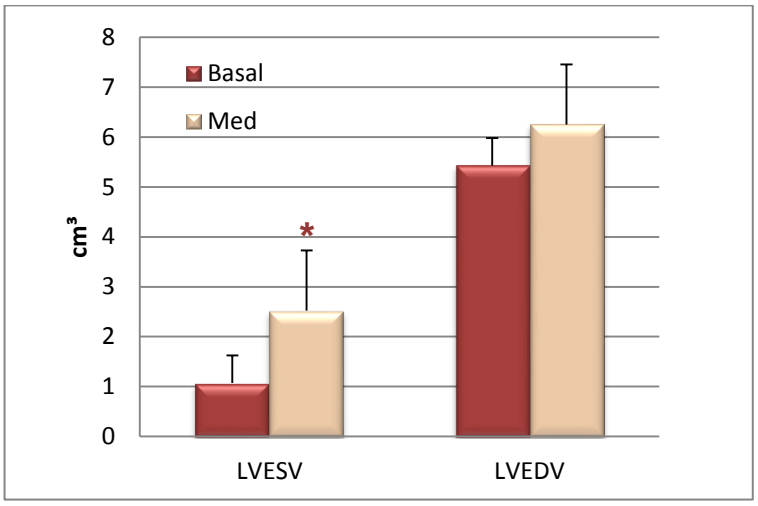
	Baseline	Medetomidine	*P*
HR	172±20,7	86,6±10,9	0,005
MAP	83,5±7,8	119,2±13,3	0,005



Graphic 1: Heart rate (HR) in beats per minute and mean arterial pressure (MAP) in mmHg results under baseline conditions and after medetomidine administration.
Values are expressed as mean ± standard deviation.
* $P < 0,05$ vs baseline

Table 2: Left ventricular end-systolic volume (LVESV) and left ventricular end-diastolic volume (LVEDV) in cm^3 results under baseline conditions and after medetomidine administration.
Values are expressed as mean ± standard deviation.
Statistical significance set at $P \leq 0,05$.

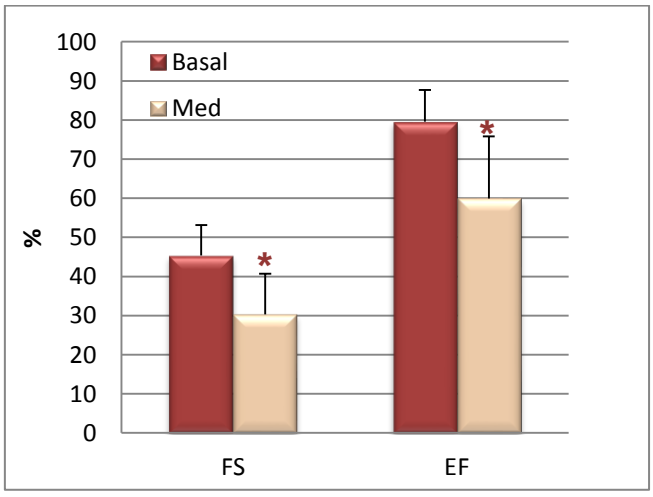
	Basal	Medetomidine	*P*
LVESV	1,07±0,55	2,52±1,20	0,005
LVEDV	5,43±2,61	6,25±1,64	0,169

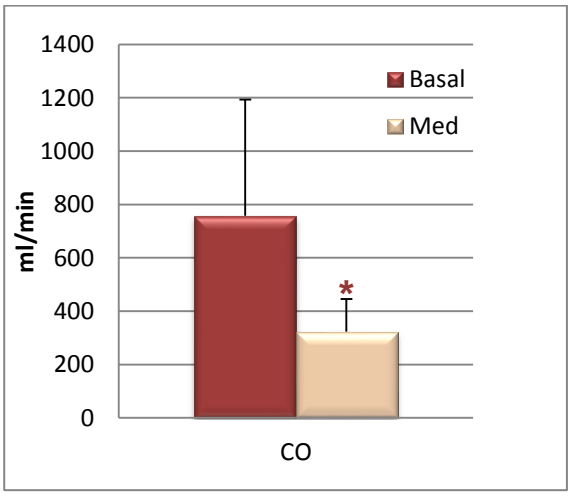


Graphic 2: Left ventricular end-systolic volume (LVESV) and left ventricular end-diastolic volume (LVEDV) in cm^3 results under baseline conditions and after medetomidine administration.
Values are expressed as mean ± standard deviation.
* $P < 0,05$ vs baseline

Table 3: Fractional shortening (FS) and ejection fraction (EF) in percentage; cardiac output (CO) in milliliters per minute; results under baseline conditions and after medetomidine administration. Values are expressed as mean ± standard deviation.
Statistical significance set at $P \leq 0,05$.

	Basal	Medetomidine	*P*
FS	45,35±7,75	30,27±10,40	0,003
EF	79,57±8,08	59,93±15,87	0,003
CO	757,55±436,2	323,38±122,69	0,005

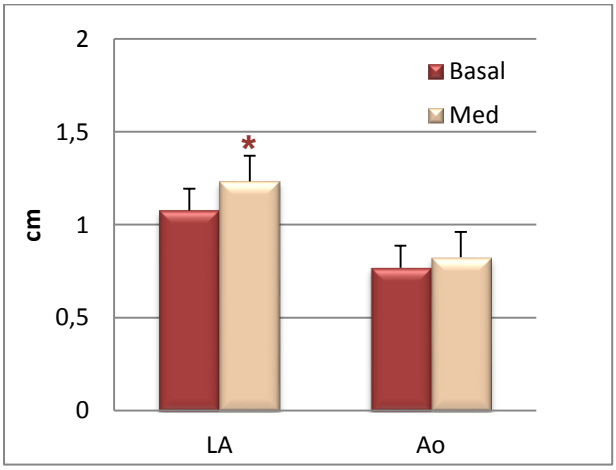


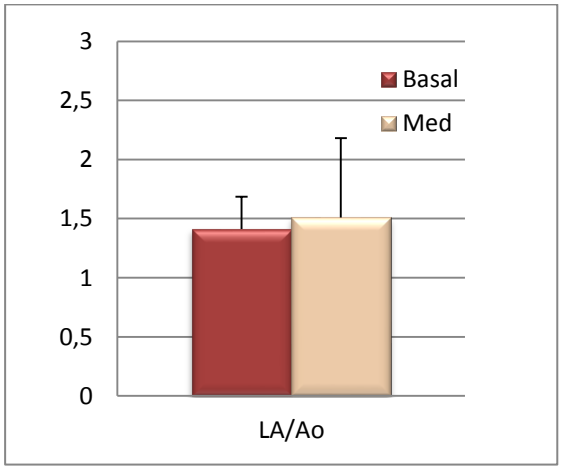


Graphics 3 and 4: Fractional shortening (FS) and ejection fraction (EF) in percentage; cardiac output (CO) in milliliters per minute; results under baseline conditions and after medetomidine administration. Values are expressed as mean ± standard deviation.
* $P < 0,05$ vs baseline

Table 4: Aortic diameter (Ao) and left atrium diameter (LA) in centimeters; LA/Ao ratio (LA/Ao); results under baseline conditions and after medetomidine administration.
Values are expressed as mean ± standard deviation.
Statistical significance set at $P \leq 0,05$.

	Basal	Medetomidine	*P*
Ao	0,77±0,12	0,83±0,07	0,284
LA	1,08±0,12	1,23±0,14	0,005
LA/Ao	1,41±0,17	1,51±0,22	0,359

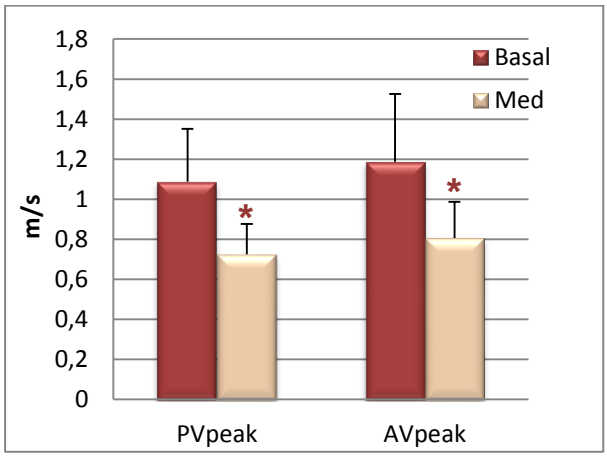


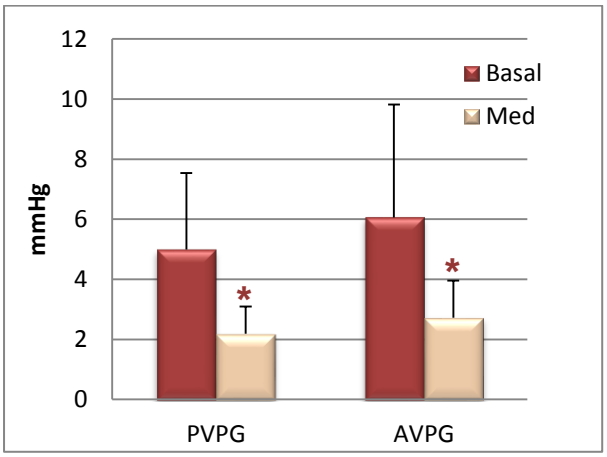


Graphics 5 and 6: Aortic diameter (Ao) and left atrium diameter (LA) in centimeters; LA/Ao ratio (LA/Ao); results under baseline conditions and after medetomidine administration.
Values are expressed as mean ± standard deviation.
* $P < 0,05$ vs baseline

Table 5: Pulmonic valve peak velocity (PVpeak) and aortic valve peak velocity (AVpeak) in meters per second; pulmonic valve pressure gradient (PVPG) and aortic valve pressure gradient (AVPG) in mmHg; results under baseline conditions and after medetomidine administration.
Values are expressed as mean ± standard deviation.
Statistical significance set at $P \leq 0,05$.

	Basal	Medetomidina	*P*
PV peak	1,09±0,27	0,73±0,15	0,002
AV peak	1,19±0,34	0,81±0,18	0,007
PVPG	4,99±2,54	2,19±0,90	0,004
AVPG	6,06±3,76	2,73±1,23	0,007





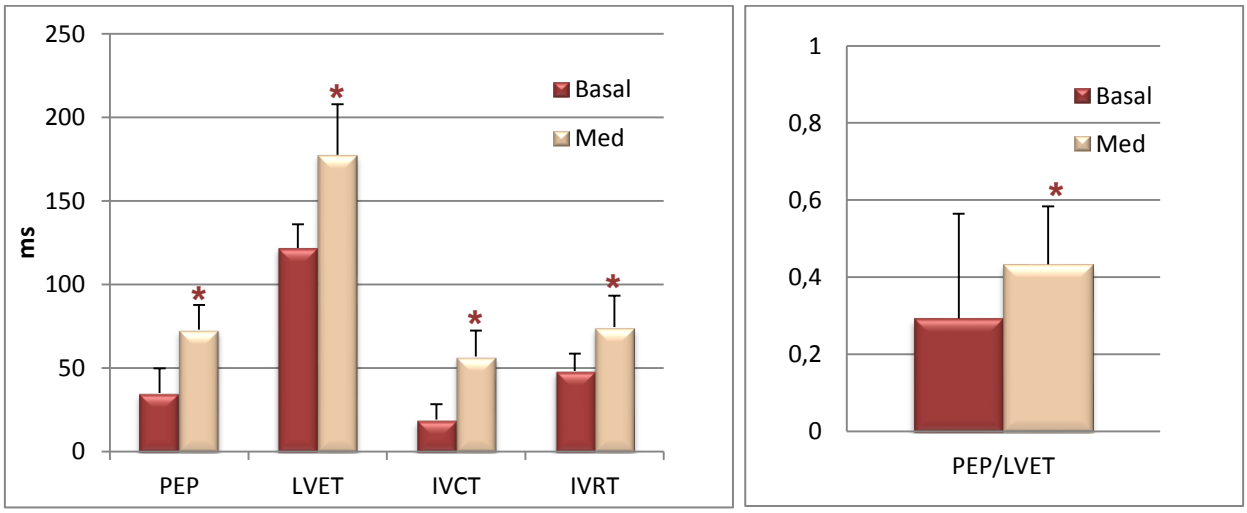
Graphics 7 and 8: Pulmonic valve peak velocity (PVpeak) and aortic valve peak velocity (AVpeak) in meters per second; pulmonic valve pressure gradient (PVPG) and aortic valve pressure gradient (AVPG) in mmHg; results under baseline conditions and after medetomidine administration.
Values are expressed as mean ± standard deviation.
* $P < 0,05$ vs baseline

Table 6: Pre-ejection period (PEP), left ventricular ejection time (LVET), isovolumic contraction time (IVCT) and isovolumic relaxation time (IVRT) in milliseconds; PEP/LVET ratio; results under baseline conditions and after medetomidine administration.

Values are expressed as mean ± standard deviation.

Statistical significance set at $P \leq 0,05$.

	Basal	Medetomidine	*P*
PEP	35,00±14,67	73,00±14,61	0,000
LVET	121,8±14,12	177,5±30,37	0,002
IVCT	19±9,20	56,9±15,39	0,000
IVRT	48,2±10,26	74,4±18,80	0,007
PEP/LVET	0,29±0,13	0,43±0,15	0,044



Graphic 9 and 10: Pre-ejection period (PEP), left ventricular ejection time (LVET), isovolumic contraction time (IVCT) and isovolumic relaxation time (IVRT) in milliseconds; PEP/LVET ratio; results under baseline conditions and after medetomidine administration.

Values are expressed as mean ± standard deviation.

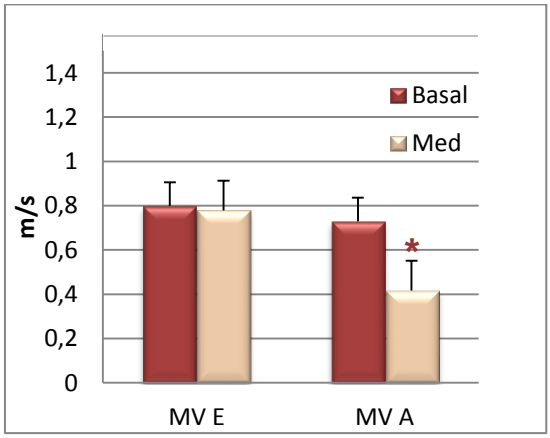
* $P < 0,05$ vs baseline

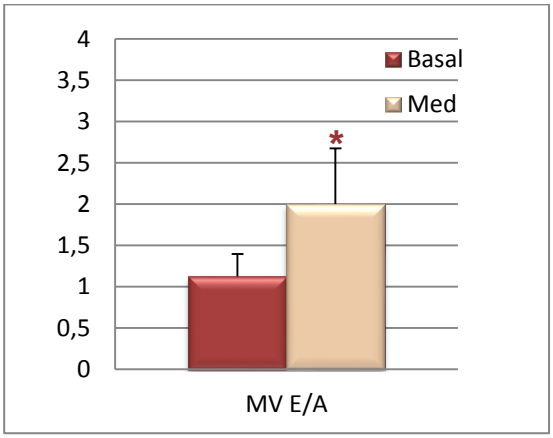
Table 7: Mitral valve E wave peak velocity (MV E) and mitral valve A wave peak velocity (MV A) in meters per second; E/A ratio (MV E/A); results under baseline conditions and after medetomidine administration.

Values are expressed as mean ± standard deviation.

Statistical significance set at $P \leq 0,05$.

	Basal	Medetomidine	*P*
MV E	0,80±0,11	0,79±0,12	0,715
MV A	0,73±0,11	0,42±0,13	0,005
MV E/A	1,12±0,27	2,00±0,27	0,005





Graphics 11 and 12: Mitral valve E wave peak velocity (MV E) and mitral valve A wave peak velocity (MV A) in meters per second; E/A ratio (MV E/A); results under baseline conditions and after medetomidine administration.

Values are expressed as mean ± standard deviation.

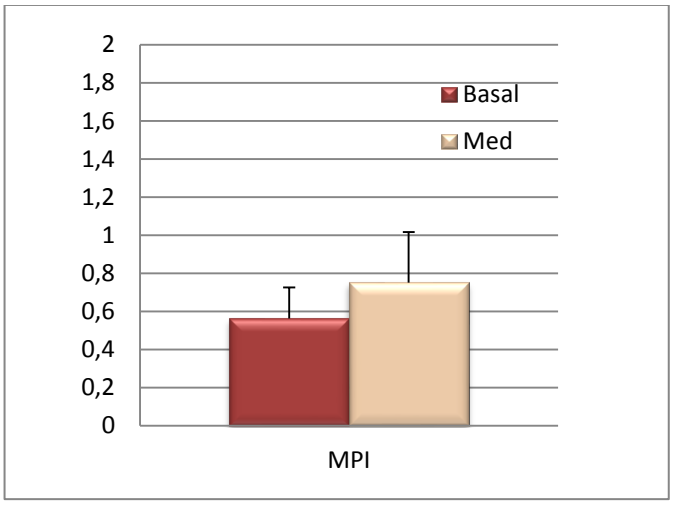
* $P < 0,05$ vs baseline

Table 8: Myocardial performance index (MPI) results under baseline conditions and after medetomidine administration.

Values are expressed as mean ± standard deviation.

Statistical significance set at $P \leq 0,05$.

	Basal	Medetomidina	*P*
MPI	0,562±0,16	0,751±0,27	0,114



Graphic 13: Myocardial performance index (MPI) results under baseline conditions and after medetomidine administration.

Values are expressed as mean ± standard deviation.

* $P < 0,05$ vs baseline

Chapter 4 – Discussion

This study was designed to give continuity to a previous investigation on the cardiovascular effects of DEX, in which the same variables as the present study were assessed. So the discussion will incorporate a comparison of the echocardiographic changes induced by MED with those caused by the sedation with DEX (as displayed in Appendix 2).

In the present study heart rate (HR) decreased significantly after MED administration from 172±20,7 bpm to 86,6±10,9 bpm. In the study performed with DEX similar results were verified, having HR decreased from 184±24 bpm to 82,6±24,1 bpm (Carvalho, 2008). As to mean arterial pressure (MAP), it increased after MED administration from 83,5±7,8 mmHg to 119,2±13,3 mmHg, such as after DEX, which caused an increase from 88,6±11,7 mmHg to 119,8±20,4 mmHg (Carvalho,2008).

The changes in HR and MAP, induced by both of these drugs, reflect the response to peripheral vasoconstriction in combination with the sympatholytic effect of the α_2-agonists used.

Regarding systolic function, there were significant changes in several echocardiographic parameters for its evaluation.

Both MED and DEX promoted very similar significant effects in fractional shortening (FS) and ejection fraction (EF). After MED administration FS diminished from 45,35±7,75% to 30,27±10,40% and EF from 79,57±8,08% to 59,93±15,87%. DEX sedation led FS to reduce from 45,9±5,9% to 30,6±4,1% and EF from 80,2±5,6% to 61,5±6,2% (Carvalho, 2008).

The significant decrease in FS associated with sedation is directly related to the increase in left ventricular dimensions at end-systole (LVs) and the significant decrease in EF related with the increased left ventricle end-systolic volume (LVESV). The primary factors that affect these parameters the most are preload, afterload, and contractility. Each one of these may individually or together affect FS. When FS is low it may be secondary to poor preload, increased afterload, or decreased contractility (Otto 2012) The presence of hypertension (increased afterload), as recorded in both of these studies, can lead to an increase in telesystolic volume, justifying the reduction in FS and EF, which is unrelated to contractility.

As to cardiac output (CO), MED sedation induced a significant reduction in this parameter comparing with the baselines values (from 757,55±436,2 ml/min to 323,38±122,69 ml/min). Although CO has not been evaluated in the study on DEX cardiovascular effects, it is expected for this anesthetic agent to produce a similar reduction.

A precise mechanism accounting for the reduction in CO produced by α_2-agonists remains unclear, even though some mechanisms have been suggested. These mechanisms included a direct myocardial depressant effect, drug-induced decrease of metabolic demands, and decrease in response to α_2-agonist-mediated increase in afterload. Other mechanisms also

included the decrease in heart rate, myocardial hypoxia and dysfunction as a result of coronary vasoconstriction, and decrease in plasma circulating catecholamines. It was suggested that several of these mechanisms may be involved together to decrease CO as a result of α_2-agonist administration (Murrell and Hellebrekers, 2005; Bloor *et al*., 1992; Housmans, 1990). However, various research articles have already demonstrated that the drop in CO is not due to a direct negative action of the α_2-agonist on myocardial contractility, but secondary to the increased systemic vascular resistance and reduced HR (Autran de Morais *et al*., 1995; Schmeling, Kampine, et al. 1991; Muir and Piper 1977). A study with MED in autonomically (pharmacologically) blocked dogs showed that the cardiac depressor effect of MED is most likely attributable to an increase in peripheral vascular resistance caused by postsynaptic activation of α_2-receptors in the peripheral vasculature. In the mentioned study, MED did not produce any direct myocardial negative inotropic effect (Autran de Morais *et al*., 1995). Supporting these conclusions, other study demonstrated that DEX administered in isolated dog hearts (peripheral α_2-receptors ruled out) did not demonstrated depressant effects (Flacke *et al*., 1992). Another study concluded that DEX did not seem to produce direct negative inotropic or chronotropic myocardial effects (Housmans, 1990).

Regarding to the systolic time intervals (STI), pre-ejection period (PEP), isovolumic contraction time (IVCT) and left ventricle ejection time (LVET), both MED and DEX promoted very similar statistically significant changes comparatively to base line values. MED increased PEP from 35±14,67 ms to 73±14,61 ms, and DEX from 34,4±18,8 ms to 61,4±6,8 ms. IVCT raised from 19±9,20 ms to 59,9±15,39 ms with MED, and from 23,3±10,4 ms to 61,5±28,2 ms following DEX administration. MED also raised LVET from 121,8±14,12 ms to 177,5±30,37 ms, while DEX caused an increase from 137,9±13,9 ms to 183,5±21,8 ms (Carvalho, 2008).

Once LVET is affected by HR, a PEP to LVET ratio was calculated in the present study of MED's effects, in order to reduce this influence. The calculation of this ratio is recommended, as it's considered to be a more accurate indicator of the LV function (Boon 2011). In this case PEP/LVET ratio increased from 0,29±0,13 to 0,43±0,15.

However, just as with FS, the STI are not indicators of contractility but rather function. Moreover, these parameters are affected by several factors, including the afterload which, in this case, is increased (hypertension). When afterload is increased, the heart's workload also increases, and consequently, the time it takes to generate enough pressure within the LV before the aortic valve can open is longer. This time corresponds to the PEP which will be consequently increased. This will also tend to increase LVET (Boon 2011). The significant increase in the mentioned parameters (PEP, IVCT and LVET) indicates a decrease in the LV performance (systolic dysfunction), as these parameters allow us to infer it noninvasively.

As to diastolic function, the isovolumic relaxation time (IVRT) is considered a useful tool to the estimation of the active or isovolumic phase of the diastole, being the increase of this parameter associated with a decreased ability of the LV to relax (impaired relaxation). The IVRT increased secondarily to MED sedation from 48,2±10,26 ms to 74,4±18,80 ms, while DEX raised from 40,6±9,7 ms to 84,6±9,9 ms (Carvalho, 2008), reflecting an impaired relaxation. The observed increase of IVRT can also be associated with increased aortic pressure (due to hypertension), decreased LA pressure and decrease in HR, as witnessed in both of these studies.

The myocardial performance index (MPI) is an index of global myocardial function and includes both diastolic and systolic time intervals. This parameter correlates well with both systolic and diastolic function of the right and left ventricle and can be used to assess overall global function (Teshima, Asano et al. 2005; Teshima, Asano et al. 2006). The MPI increased from 0,56±0,16 to 0,75±0,27 after MED administration, however, this change was not statistically significant. In the DEX study the MPI increased significantly from 0,4±0,1 to 0,8±0,2. This increase may be in part due to the increase in IVRT and IVCT, even if LVET had also risen.

With regard to transmitral flow pattern for diastolic function assessment, MED induced a significant decrease in the A wave peak velocity or MV A (from 0,73±0,11 m/s to 0,42±0,13 m/s) and accordingly an increase in the E/A ratio or MV E/A (from 1,12±0,27 m/s to 2,00±0,27 m/s). Although the E wave peak velocity has diminished as a result of MED sedation, this change was not statistically significant. In the DEX study, both MV A and MV E have decreased significantly (MV E from 0,80±0,10 m/s to 0,60±0,10 m/s and MV A from 0,64±0,10 m/s to 0,32±0,10 m/s), and as to the E/A ratio, it has raised significantly (from 1,28±0,30 m/s to 2,10±0,50 m/s) (Carvalho, 2008).

The MV E, MV A and E/A ratio determination enables the assessment of diastolic function and varies with HR, being that when HR is decreased the E/A ratio increases (Feigenbaum 2005). The changes in the parameters obtained from transmitral flow can be associated to the bradycardia induced by these two α_2-agonists, like as already been described in a study on cats sedated with MED (Lamont, L. A., et al. 2002).

Regarding aortic and pulmonary artery flow assessment, both MED and DEX induced a significant decrease in aortic valve peak velocity (AVpeak), pulmonic valve peak velocity (PVpeak), and the corresponding pressure gradients (AVPG and PVPG). With MED the AVpeak decreased from 1,19±0,34 m/s to 0,81±0,18 m/s, the AVPG from 6,06±3,76 mmHg to 2,73±1,23 mmHg, the PVpeak from 1,09±0,27 m/s to 0,73±0,15 m/s and the PVPG from 4,99±2,54 mmHg to 2,19±0,90 mmHg. Similarly, DEX promoted a decrease of the AVpeak from 1,0±0,15 m/s to 0,68±0,07 m/s, the AVPG from 4,5±1,3 mmHg to 1,9±0,4 mmHg, the PVpeak from 0,94±0,16 m/s to 0,58±0,13 m/s and the PVPG from 3,6±1,3 mmHg to 1,4±0,67 mmHg (Carvalho, 2008).

The observed changes in the mentioned parameters may be associated with the observed bradycardia and with the increase in LVESV, which therefore leads to a decrease in pressure on these valves.

Among the changes verified in the developed study with MED are also included valvular dysfunctions. The development of valvular insufficiencies (aortic and mitral), associated with sedation, is possibly a result of increased pressure at the aorta, consequent from high blood pressure due to the action of the studied drug. It was also observed the development of pulmonary insufficiency associated with sedation with MED, which may be indicative of pulmonary hypertension due to an increase in pulmonary vascular resistance. The left atrial diameter (LA), assessed only in the MED study, exhibited a significant increase, being this variation frequently observed in animals with mitral insufficiency at an early stage, as verified in most animals of this study.

In human anesthesia α_2-agonists are increasingly being utilized to improve hemodynamic stability, alleviate stress and prevent tachyarrhythmias (Vainio 1997; Maze 1992; Flacke 1989). There are clear divergences in the cardiovascular effects of α_2-agonists in veterinary and human patients, adding to the differences in species, economics and anesthesia sophistication. However, the major difference between how α_2-agonists are used in animals and humans is simply a dose matter. The doses used in humans are much lower than label dose ranges in animals. And even with recognizable species differences, lower doses of α_2-agonists are usually adequate in veterinary species when they are used in combination with other sedatives, and they are still being used with considerable success in many practices (Sinclair 2003). Decreased doses of MED have been combined with various preanesthetics (i.e. butorphanol, buprenorphine) to enhance sedation and analgesia, while potentially reducing the duration of the associated adverse cardiovascular effects. Although lowered doses of MED or DEX will not prevent cardiovascular depression (Pypendop and Verstegen 1998), it will promote greater patient safety. In the other hand, a recent study suggested that MED may be a suitable sedative-analgesic for cats with left ventricular outflow tract (LVOT) obstruction since the drug decreases HR, LVOT velocity and LVOT pressure gradient (Lamont et al., 2002). Subsequently, adding to the utilization of adequate doses, proper case selection is particularly important.

Chapter 5 – Conclusions

Overall significant changes were observed in the different evaluated echocardiographic parameters, associated to the sedation with MED, particularly in those related to systolic function. We therefore accept the alternative hypothesis (H1), defined as the occurrence of variation in the mean of each parameter before and after sedation with MED. DEX sedation promoted very similar changes, leading to the conclusion that these anesthetic agents have very similar effects in feline cardiac function.

The changes observed in the present study, confirm that the extracardiac effects of MED and DEX affect the heart's loading condition in a very similar way. The verified systolic and diastolic cardiac dysfunctions are certainly deleterious in cats with underlying heart disease, with the referred exception, for which these drugs should be avoided or used cautiously in cats in which sudden increase in afterload could be detrimental.

Even with these findings and conclusions, α_2-agonists are still considered fairly safe. Their reliable sedation, analgesia, muscle relaxation and anxiolysis, and the decrease in the anesthetic requirements of injectable and inhalant agents, make them a sustainable option in small animal anesthesia.

The future successful use of MED and DEX will continue to involve lowered doses and combinations with other sedatives to promote a balanced anesthesia, in combination with oxygen administration, appropriate monitoring and reversal with atipamezole, to promote greater patient safety (Sinclair 2003).

The verified cardiovascular effects should be taken into consideration and remind the care that should be taken with α_2-agonists utilization, particularly in cardiac patients to prevent perioperative anesthetic complications.

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Appendix 1

ECHOCARDIOGRAPHIC ASSESSMENT OF CARDIOVASCULAR DEPRESSANT EFFECTS OF MEDETOMIDINE SEDATION IN CATS

Experimental Protocol

Objectives:

Assessment of the cardiovascular response to medetomidine administration in cats.

Animals:

10 healthy male cats, presented for routine elective orchiectomy

Date: __ / __ /____

Animal's identification: _____

Sex: M / F BW: _____ Kg Age: _____

Stage 1 (before the administration of medetomidine)

1- Anesthetic risk classification according to the American Society of Anesthesiologists (ASA) Physical Status Classification System – only Class I animals included.

2- Monitoring (quiet environment)

1.1 - Heart rate (femoral artery pulse by palpation): _____ bpm

1.2 - Blood pressure - High Definition Oscillometry; Cuff placed on the left front leg;

SP	DP	MAP	
			MEAN

2- Transthoracic echocardiographic examination

Right and left lateral recumbence; 3 to 5 measurements for each parameter.

- ✓ **Parameters evaluated**
  - Lead II ECG
  - Left ventricular end-diastolic volume (LVEDV)
  - Left ventricular end-systolic volume (LVESV)
  - Fractional shortening (FS)

- Ejection fraction (EF) [formula: LVEDV - LVESV / LVEDV x 100]
- Heart rate (HR)
- Cardiac Output (CO)
- Aortic diameter (Ao)
- Left atrium diameter (LA)
- LA/Ao ratio (LA/Ao)
- Pulmonic valve peak velocity (PVpeak)
- Aortic valve peak velocity (AVpeak)
- Pulmonic valve pressure gradient (PVPG)
- Aortic valve pressure gradient (AVPG)
- E peak - mitral valve E wave peak velocity (MV E)
- A peak - mitral valve A wave peak velocity (MV A)
- E/A ratio (MV E/A)
- Pre-ejection period (PEP)
- Left ventricular ejection time (LVET)
- PEP/LVET ratio
- Isovolumic contraction time (IVCT)
- Isovolumic relaxation time (IVRT)
- Myocardial performance index (MPI)

Stage 2 (administration of medetomidine at a dose of 0,08 mg/Kg: _____ ml)

1- Monitoring (quiet environment, 30 minutes until reaching the peak effect)

1.1 - Heart rate (femoral artery pulse by palpation): _____ bpm;

1.2 - Blood pressure - High Definition Oscillometry; Cuff placed on the left front leg;

SP	DP	MAP	
			MEAN

2- Transthoracic echocardiographic examination

Assessment of the same parameters obtained in baseline conditions;

Ketamine administration (IM) at a dose of 5mg/kg: _____ ml;

Orchiectomy;

Atipamezol single injection (IM) at a dose of 0,04mg/kg: _____ ml.

Appendix 2

	MEDETOMIDINE		DEXMEDETOMIDINE (Carvalho, 2008)	
	BASELINE	SEDATION	BASELINE	SEDATION
HR (bpm)	172±20,7	86,6±10,9*	184±24	82,6±24,1*
MAP (mmHg)	83,5±7,8	119,2±13,3*	88,6±11,7	119,8±20,4*
LVESV (cm^3)	1,07±0,55	2,52±1,20*	1.4±0,9	3,5±1,3*
LVEDV (cm^3)	5,43±2,61	6,25±1,64	6,8±2,7	8,9±2,1*
FS (%)	45,35±7,75	30,27±10,40*	45,9±5,9	30,6±4,1*
EF (%)	79,57±8,08	59,93±15,87*	80,2±5,6	61,5±6,2*
CO (ml/min)	757,55±436,2	323,38±122,69*	NM	NM
Ao (cm)	0,77±0,12	0,83±0,07	NM	NM
LA (cm)	1,08±0,12	1,23±0,14*	NM	NM
LA/Ao	1,41±0,17	1,51±0,22	NM	NM
PV peak (m/s)	1,09±0,27	0,73±0,15*	0,94±0,16	0,58±0,13*
PVPG (mmHg)	4,99±2,54	2,19±0,90*	3,6±1,3	1,4±0,67*
AV peak (m/s)	1,19±0,34	0,81±0,18*	1,0±0,15	0,68±0,07*
AVPG (mmHg)	6,06±3,76	2,73±1,23*	4,5±1,3	1,9±0,4*
PEP (ms)	35,0±14,67	73,0±14,61*	34,4±18,8	61,4±6,8*
LVET (ms)	121,8±14,12	177,5±30,37*	137,9±13,9	183,5±21,8*
PEP/LVET	0,29±0,13	0,43±0,15*	NM	NM
IVCT (ms)	19±9,20	59,9±15,39*	23,3±10,4	61,5±28,2*
IVRT (ms)	48,2±10,26	74,4±18,80*	40,6±9,7	84,6±9,9*
MV E (m/s)	0,80±0,11	0,79±0,12	0,80±0,1	0,6±0,1*
MV A (m/s)	0,73±0,11	0,42±0,13*	0,64±0,1	0,32±0,1*
MV E/A	1,12±0,27	2,0±0,27*	1,28±0,3	2,1±0,5*
MPI	0,56±0,16	0,75±0,27	0,46±0,1	0,81±0,2*

Values are expressed as mean ± standard deviation.

Statistical significance set at $P \leq 0,05$; * $P < 0,05$ vs baseline;

NM – not measured.

Appendix 3 – Clinical research poster presented at IX Congresso do Hospital Veterinário Montenegro - Medicina e Cirurgia Felina

EFEITOS DEPRESSORES CARDIOVASCULARES DA SEDAÇÃO COM MEDETOMIDINA EM GATOS

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INTRODUÇÃO

A manutenção da integridade cardiovascular em animais sob anestesia é de extrema importância, visto que as alterações a este nível podem comprometer a saúde do animal.

A sedação, por interferir com a função cardiovascular, requer cuidados específicos entre os quais uma avaliação pré-anestésica e monitorização durante e após a anestesia, que incluam os parâmetros cardiovasculares.

Sendo a medetomidina um sedativo frequentemente utilizado para indução da anestesia geral em gatos é fundamental estudar os efeitos que este agente anestésico provoca no aparelho cardiovascular e assim prevenir/reduzir o desenvolvimento de complicações cardiovasculares potencialmente fatais.

OBJETIVOS

- Observar/analisar a ocorrência de efeitos depressores cardiovasculares associados à sedação com recurso a medetomidina, com vista a manter a integridade ao nível do aparelho cardiovascular;
- Contribuir para a prevenção/redução de complicações anestésicas peri-operatórias associadas ao uso de medetomidina na prática clínica.

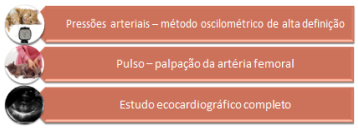
MATERIAL E MÉTODOS

Animais:

- ✓ Gatos machos (n=10), de qualquer raça, saudáveis, com idades entre os 6 e os 12 meses e peso corporal entre os 2,5 e os 5,5Kg; apresentados ao HVP para orquiectomia;
- ✓ Alojamento em jaulas individuais, à temperatura ambiente, com restrição de comida durante 12 horas;

Procedimentos prévios à sedação:

- ✓ Classificação de acordo com o sistema de classificação da Sociedade Americana de Anestesiologia - apenas incluídos gatos: Classe I e II;
- ✓ Avaliação dos seguintes parâmetros:



Sedação dos gatos com medetomidina (Domitor® Phizer, Portugal; 1mg/ml) na dose de 0.08 mg/kg, por via intramuscular (no músculo *longissimus dorsi*);

Aguardaram-se 30 minutos, até atingir o pico do efeito, e foram avaliados os mesmos parâmetros medidos em condições basais (pressões arteriais, pulso por palpação femoral e avaliação ecocardiográfica);

Depois de avaliados todos os parâmetros, seguiu-se a administração de ketamina (Imalgène® Merial, Portugal; 100mg/ml) 5mg/kg, via intramuscular, e foi realizada a orquiectomia;

Assim que o procedimento foi concluído, os gatos receberam uma injeção única de Atipamezol (Antisedan® Phizer, Portugal; 5mg/ml) na dose de 0.04mg/kg para reverter os efeitos da medetomidina.

Análise estatística

Os dados paramétricos foram analisados com o "Paired sample test", enquanto que os dados não paramétricos foram analisados com o "Wilcoxon test". Todos foram analisados no SPSS 19 para o Windows (IBM Corporation, Armonk, NY). As diferenças são considerados estatisticamente significativas quando p≤0.05.

RESULTADOS

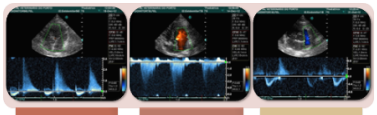
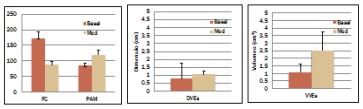
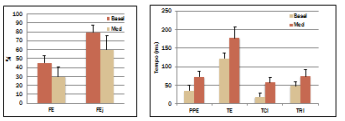


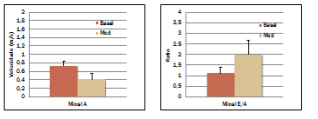
Fig. 1: Vista paraesternal esquerda apical. Modo 2D e Doppler espectral: Insuficiência aórtica

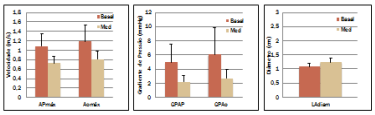
Fig. 2: Vista paraesternal esquerda apical. Modo 2D e Doppler espectral: Insuficiência mitral

Fig. 3: Vista paraesternal direita de eixo-curto. Modo 2D e Doppler espectral: Insuficiência pulmonar









	Basal	Medetomidina	*P*
FC	172±20,7	86,6±10,9	0,005
PAM	83,5±7,8	119,2±13,3	0,005
DVEs	0,77±0,14	1,1±0,19	0,002
VVEs	1,07±0,55	2,52±1,20	0,005
FE	45,35±7,75	30,27±10,40	0,003
FEj	79,57±8,08	59,93±15,87	0,003
APmáx	1,09±0,27	0,73±0,15	0,002
GPAP	4,99±2,54	2,19±0,90	0,004
Aomáx	1,19±0,34	0,81±0,18	0,007
GPAo	6,06±3,76	2,73±1,23	0,007
PPE	35,00±14,67	73,00±14,61	0,000
TE	121,8±14,12	177,5±30,37	0,002
TCI	19±9,20	56,9±15,39	0,000
TRI	48,2±10,26	74,4±18,80	0,007
Mitral A	0,73±0,11	0,42±0,13	0,005
Mitral E/A	1,12±0,27	2,00±0,27	0,005
LAdiam	1,08±0,12	1,23±0,14	0,005

*Apenas apresentados os resultados com diferença significativas (p≤0,05)

DISCUSSÃO DOS RESULTADOS

- ✓ A diminuição significativa da frequência cardíaca e o aumento da pressão arterial após a administração de medetomidina sugerem uma resposta à vasoconstrição periférica em combinação com o efeito simpaticolítico do α2-agonista utilizado.
- ✓ Relativamente à função sistólica, verificaram-se alterações significativas nos diversos parâmetros ecocardiográficos para a sua avaliação. A diminuição significativa da fração de encurtamento (FE) associada à sedação está diretamente relacionada com o aumento das dimensões do ventrículo esquerdo no final da sístole (DVEs) e a diminuição significativa da fração de ejeção (Fej) com o aumento do volume ventricular em sístole (VVEs).
- ✓ Apesar destes valores serem indicadores indiretos de contratilidade, sugerindo uma diminuição desta, dependem da pós-carga pelo que um aumento desta, por exemplo por aumento da pressão arterial sistémica como verificado, pode levar a um aumento do volume telesistólico, justificando a diminuição da FE e da FEj.
- ✓ Os aumentos significativos do período de pré-ejeção (PPE), do tempo de contração isovolumétrico (TCI) e do tempo de ejeção (TE), indicam uma diminuição da performance do ventrículo esquerdo (disfunção sistólica), já que estes parâmetros o permitem inferir de forma não invasiva.
- ✓ O tempo de relaxamento isovolumétrico (TRI) é considerado uma ferramenta útil para estimar a fase ativa ou isovolumétrica da diástole, sendo o aumento deste parâmetro associado a uma diminuição da capacidade de relaxamento do ventrículo esquerdo. O aumento do TRI observado pode ainda encontrar-se associado ao aumento da pressão aórtica (por aumento da pressão arterial sistémica), à diminuição da pressão atrial esquerda e à diminuição da frequência cardíaca, como se verificou no presente estudo.
- ✓ Relativamente ao padrão de fluxo transmitral, para avaliação da função diastólica, verificou-se uma diminuição significativa da velocidade do pico da onda A (Mitral A) e consequentemente um aumento do ratio E/A . Correspondendo a onda A à diástole ativa (sístole atrial), esta variação parece ser indicativa de disfunção sistólica do átrio esquerdo.
- ✓ Quanto à avaliação dos fluxos transaórtico e transpulmonar, a diminuição significativa verificada da velocidade no pico aórtico (Aomáx), da velocidade no pico da artéria pulmonar (APmáx) e dos correspondentes gradientes de pressão (GPAo e GPAP), poderá estar relacionada com a bradicardia induzida pela medetomidina e pelo facto de ter ocorrido um aumento do VVEs, o que por sua vez leva a uma diminuição da pressão nestas válvulas.
- ✓ Dentro das alterações verificadas no estudo desenvolvido incluem-se ainda as disfunções valvulares. O desenvolvimento de insuficiências valvulares, aórtica e mitral, associado à sedação, é possivelmente consequência do aumento da pressão ao nível da aorta, derivada da hipertensão arterial decorrente da ação do fármaco em estudo. Foi ainda verificado o desenvolvimento de insuficiência pulmonar associada à sedação com medetomidina, o que poderá ser indicativo de hipertensão pulmonar, por aumento da resistência vascular pulmonar.
- ✓ O diâmetro do átrio esquerdo (LAdiam) apresentou um aumento significativo, sendo esta alteração frequentemente observada em animais com insuficiência mitral em fase inicial, como se verificou em grande parte dos animais do presente estudo.

CONCLUSÃO

Em termos globais foram verificadas variações significativas dos diversos parâmetros avaliados, associadas à sedação com medetomidina, especialmente aqueles relacionados com a função sistólica. Os mecanismos compensatórios que se encontram na base destas alterações, bem como uma possível ação direta deste fármaco ao nível do miocárdio, aumentam o esforço cardíaco, o que se poderá tornar clinicamente significativo em pacientes com comprometimento cardiovascular, quando são utilizadas doses elevadas deste tipo de fármaco, ou quando estamos perante as duas situações.

Assim, os efeitos depressores cardiovasculares verificados deverão ser tidos em consideração, tanto em pacientes cardíacos como em pacientes saudáveis, para a prevenção de complicações anestésicas peri-operatórias associadas ao uso de medetomidina na prática clínica.

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- RA, H., *Echocardiography and Doppler Ultrasound*, in *Manual of Canine and Feline Cardiology*, G.J. Tilley LP, Editor, W.B. Saunders Company: Philadelphia USA.
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- ANSAH, O. B., *Use of the alpha-2-adrenoceptor agonists medetomidine and dexmedetomidine in the sedation and analgesia of domestic cats*, Faculty of Veterinary Medicine, Department of Veterinary Clinical Sciences, University of Helsinki, Finland, 2004;

Appendix 4 – Clinical Research Abstract submitted for oral presentation at IV Encontro de Formação OMV

ECHOCARDIOGRAPHIC ASSESSMENT OF MEDETOMIDINE-INDUCED CARDIOVASCULAR EFFECTS IN CATS

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5 Centro de Estudos de Ciência Animal – Universidade do Porto (CECA-UP)

Medetomidine is frequently used for induction of general anesthesia in cats. Its interference on cardiovascular function is known, but data is sparse in this specie. We postulate that medetomidine could have depressant effects on feline cardiac function.
To perform this study, ten healthy male cats presented at Hospital Veterinário do Porto were recruited. The procedure included measuring indirect blood pressure, assessment of femoral artery pulse by palpation and transthoracic echocardiographic examination previously to sedation and subsequently under the effect of medetomidine (0.08 mg/kg intramuscular).

Overall statistically significant changes were observed between base line and sedation values. Significant decrease of heart rate and increase of blood pressure occurred. Fractional shortening and ejection fraction decreased, whereas pre-ejection period, isovolumic contraction time and left ventricular ejection time increased, reflecting systolic dysfunction. Isovolumic relaxation time increased, implying an impairment of left ventricular relaxation. Mitral valve A wave peak velocity decreased and E/A ratio increased, which may suggest systolic dysfunction of the left atrium. Left atrium diameter increased significantly. Aortic and pulmonic valve peak velocities and the respective pressure gradients decreased significantly. Valvular insufficiencies (aortic, mitral and pulmonic) associated to sedation were also observed.

Our study shows that medetomidine has a significant depressant effect on feline cardiac function, being the reflex of altered loading conditions secondary to medetomidine increased systemic vascular resistance and bradycardia effects. In conclusion, medetomidine may be deleterious in cats with underlying heart disease. In these cases it should be avoided or used cautiously, as sudden changes in the loading conditions can be detrimental.