Effects of Atenolol, Ivabradine and Pimobendan on Left Atrial and Left Atrial Appendage Function: An Echocardiographic Study in Healthy Cats

Master’s Thesis

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ABSTRACT

Left atrial (LA) and left atrial appendage (LAA) size and function can be altered in cats with cardiac disease. Decreased LA or LAA function and increased LA size are proposed risk factors for the development of thrombi within these chambers, which subsequently can result in arterial thromboembolism. Reduced LA function can also impair cardiac output, particularly when there is concurrent left ventricular diastolic dysfunction or reduced compliance. Although LA dysfunction has been reported in cats with cardiomyopathy, there are limited data regarding the effects of drugs on LA function in cats. The purpose of this echocardiographic study was to evaluate the effects of atenolol, pimobendan, and ivabradine on indices of LA function in healthy cats.

This prospective study used a double-blind, fully-crossed design in 9 healthy, sedated cats. LA function was evaluated by echocardiography over four study periods: control, atenolol (1.8-2.5 mg/kg q12h), pimobendan (0.2-0.3 mg/kg q12h), and ivabradine (0.3-0.5 mg/kg q12h). Treatments were randomized and continued for 7 days prior to measurements. Heart rate along with the following indices of LA and left ventricular (LV) size and function were evaluated: LA diameter, area and volume at end-systole and end-diastole; LA shortening fraction (SF), shortening area (SA) and ejection fraction (EF); peak LAA inflow and outflow velocities; atrial reversal wave velocity (AR\textsubscript{R}) and duration (AR\textsubscript{D}); LV internal dimension at end-diastole and end-systole; LV
shortening fraction and isovolumic relaxation time. Treatments were compared by repeated measures ANOVA followed by Holm Sidak multiple-comparison test. A linear mixed model (LMM) was performed to evaluate the effect of individual cats on LA function variables. Statistical significance was p<0.05.

Pimobendan significantly decreased end-diastolic variables of LA size while having minimal effects on LA and LAA function. Ivabradine significantly decreased LAA-inflow velocities (mean change of −21 cm/s, p<0.05) but otherwise had minimal effects. Atenolol significantly decreased (p<0.05) LA SA, EF, LAA inflow and outflow, and the AR₉ and increased the AR₅. HR was significantly decreased following atenolol and ivabradine (p<0.001). Subject had minimal influence on study variables.

These findings indicate that in these healthy cats pimobendan reduces LA size while having minimal effects on LA and LAA function. Ivabradine has minimal effects on LA and LAA function, while atenolol impairs LA and LAA function. Additional studies in cats with naturally occurring cardiac disease are warranted.
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CHAPTER 1
INTRODUCTION

Arterial thromboembolism (ATE) is a devastating consequence of cardiac disease in cats with most cases related to a form of cardiomyopathy. Reportedly ATE can develop in up to 33-48% of cats with hypertrophic cardiomyopathy (HCM), the most common heart disease in cats, and was diagnosed in 1 of 175 feline admissions in a referral hospital.¹⁻³ The classic clinical signs of ATE are pain and a reduction or loss of limb function, most frequently affecting both hindlimbs. ATE limits the long-term prognosis for life, can result in a prolonged hospitalization or limb amputation, and often prompts euthanasia.³,⁴ The overall survival rate for the initial episode of ATE, including euthanasia, in a study of 127 cats managed at a referral hospital was 35%, with 45% survival reported in cats that received treatment.³ In that study the median survival time was 117 days, while other studies report survival times of 51-184 days after discharge from the hospital.¹⁻³,⁵,⁶

There are a number of potential causes of thrombus formation predisposing to ATE in cats. Virchow’s triad describes the components that can result in thrombus formation, which include changes in blood flow (stasis), composition of the blood (hypercoagulability), and alterations in the endocardial surface.⁴ The thrombi in feline cardiomyopathies form mainly in the left atrium (LA), especially the left atrial appendage (LAA).²⁻⁴,⁷ Both increased LA size and diminished LA or LAA function are proposed as
significant risk factors for the development of thrombi. Increased left atrial size and stretch could potentially damage the endothelium, while both increased size and reduced function, can result in blood stasis.

Hypertrophic cardiomyopathy, the most common cardiac disease in cats, can result in left ventricular diastolic dysfunction, impedance to LV filling, increased LV stiffness, and increased LV end-diastolic pressure. These changes to the LV can have significant impact on both LA size and function. Patients with LV hypertrophy rely more on the atrial contribution to maintain diastolic LV filling. HCM was shown to result in increased LA preload, resulting in increased LA work and stimulation of the Frank Starling mechanism in the LA to augment the reduced early LV diastolic filling seen in these patients. Additionally, HCM results in increased afterload on the LA, which can reduce LA booster pump function over time. Furthermore, HCM increases LA chamber stiffness, limits LA reservoir function and thus impacts cardiac index, which could be further compromised when LA pump function is diminished.

The LA is located at the left caudodorsal aspect of the heart base and is divided into a main body and an appendage or auricle. The left LAA contains pectinate muscles along its internal surface that actively contract at end-diastole. The long and tubular LAA has a prominent junction with the venous component of the LA body. The LA and LAA are derived from different embryologic sources. The LAA develops as an outpouching from the atrial component of the primary heart tube, while the LA is derived from the outgrowth of the pulmonary veins.

There are three principle phases of mechanical LA function, which help to modulate LV filling and cardiovascular performance. These are the (1) reservoir phase,
where progressive pulmonary venous return leads to LA expansion during left ventricular (LV) systole and isovolumic contraction; (2) the conduit phase during which blood travels down a pressure gradient through the opened mitral valve from pulmonary veins to LV cavity; and (3) the atrial contractile phase during late LV diastole, which helps establish the LV end-diastolic volume. Under normal physiologic conditions the LA, as a “booster-pump”, contributes approximately 20-30% to the LV stroke volume at resting heart rates. This contribution becomes proportionally greater in the face of reduced LV compliance or elevated heart rate. Cardiac output is reduced with the development of atrial fibrillation and loss of active LA contraction by approximately 15-20%.

LA reservoir function is affected by venous pressures, LA relaxation and LA compliance. Early LA reservoir function is affected by LV systolic function due to descent of the LV base toward the apex during systole, pulling blood from the pulmonary veins into the LA. LA conduit function is dependent on LA compliance, LV diastolic function and normal mitral valve opening. LA systolic shortening is mainly dependent on LA preload and inotropic state. A number of factors influence the contribution of LA “booster-pump” function; these include: the volume of venous return, ventricular end-diastolic pressure and systolic reserve of the LV, the PR interval of the ECG and resultant timing of atrial systole, and autonomic nervous system balance. There is a complex interrelationship among variables determining LA mechanical function that include heart rate, loading conditions of the LA, inotropic state of the LA and LV, LA and LV relaxation and compliance, and intra-atrial conduction. Accordingly, there are multiple approaches to quantitation of LA function although the
atrial pressure-volume (or pressure area) relationship is considered the gold standard while also providing the most accurate information on atrial hemodynamics.\textsuperscript{18,24}

Recording of LA pressure requires a high fidelity intravascular pressure transducer placed into the LA chamber invasively. Various methods include transmural access across the LA body, LAA, or a proximal pulmonary vein; a transseptal catheter approach; or a retrograde catheterization of the LA through the mitral valve.\textsuperscript{18,25} The resultant LA pressure recordings demonstrate three major positive deflections and two descents, namely the 1) a wave, following the P-wave of the ECG and caused by LA contraction; 2) an x descent at longer PR intervals representing relaxation of the LA; 3) the c wave from closure and bulging of the mitral valve; 4) an x’ descent related to the suction caused by longitudinal shortening of the LV with tethering of the mitral annulus; 5) the v wave resulting from progressive LA filling against a closed mitral valve during LV systole; and 6) a y descent stemming from mitral valve opening and LA emptying.\textsuperscript{18,26,27}

Left atrial volume can be determined by multiple techniques including orthogonal epicardial sonomicrometry, two and three-dimensional echocardiography, including automated border detection algorithms, radionuclide angiography, computed tomography and magnetic resonance imaging.\textsuperscript{18} Simultaneous measurement of LA pressure and LA volume allows determination of LA function through the pressure volume loop. This graph is composed of two loops that are arranged in a horizontal figure-of-eight pattern. The A loop representing active atrial contraction and relaxation, the area of which is a measure of LA work\textsuperscript{27}; and the V loop representing passive LA reservoir function.\textsuperscript{17,18,28} Based on these analyses, LA end-diastolic and end-systolic volumes can be determined
and LA stroke volume and emptying fraction calculated; these are used to evaluate LA pump performance. However, these indices are highly dependent on loading conditions and therefore can not be used as surrogates for LA contractility. Contractile function can be assessed by time-varying elastance from the end-systolic pressure on the A loop, while the LA compliance can be evaluated from the V loop.

Generation of atrial pressure volume loops requires invasive techniques and thus precludes clinical application for assessment of LA function. The most common and non-invasive method used to evaluate LA function is echocardiography. The three phases of LA function (reservoir, conduit and atrial contraction), as discussed previously, can be evaluated separately by echocardiography. These transport function can be further divided into passive and active components. The passive component is represented by the amount of blood passing through the opened mitral valve prior to atrial contraction. This is due to energy stored by the LA during the reservoir phase. The active portion is related to the amount of blood ejected into the LV due to the contraction of the LA. In consideration of the above factors three discrete events can be marked to measure LA diameter, area or volume. These include in order: maximum LA size, LA size at the beginning of atrial contraction, and minimum LA size. Based on these measures, the active booster-pump and the passive functions of the LA can be determined. Total fractional shortening, fractional area change and emptying fraction can be used to evaluate active and passive components.

Doppler echocardiographic indices also can be used to evaluate LA function, with the focus on transmitral flow (TMF), mitral annular TDI and pulmonary venous flow (PVF) velocity profiles. There is a prominent influence of LA mechanical function, as
well as the compliance of the LV, on the A wave velocity of TMF.\textsuperscript{29,30} Furthermore, in people the A wave velocity time integral shows a good correlation with LA stroke volume determined from the LA-pressure-volume diagram.\textsuperscript{18} TMF patterns are influenced by many factors including age, heart rate, mitral regurgitation, LV compliance and filling pressures.\textsuperscript{29} LA systolic time intervals also can be determined from TMF included LA pre-ejection period (onset of P wave on ECG to beginning of A wave), LA ejection time and LA pre-ejection period-to-ejection time ratio, with a lower ratio indicating improvement in LA systolic function.\textsuperscript{29-32} Additionally, to evaluate atrial electromechanical activation, the time from the onset of the P wave to peak A wave, A wave acceleration time, and A wave acceleration rate have been used.\textsuperscript{30,33} Force exerted by the LA in accelerating blood into the LV during atrial systole is called the atrial ejection force and is based on the A velocity, blood density and mitral orifice area (based on Newton’s second law of motion: force = mass x acceleration).\textsuperscript{34} Atrial ejection force provides a physiologic assessment of atrial systolic function.\textsuperscript{17,34} LA kinetic energy can be attained non-invasively with echocardiography relating LA stroke volume and A wave velocity, and this variable has been correlated to LA stroke work index determined from the pressure-area relation.\textsuperscript{35} PVF atrial reversal wave (PVF A\textsubscript{R}) occurs when atrial contraction induces retrograde flow of blood into the pulmonary veins. Increased velocity of the PVF A\textsubscript{R} is observed with increases in LA contractile function, while LA mechanical failure decreases PVF A\textsubscript{R}.\textsuperscript{29} However, it is important to note that PVF is also very dependent on LA loading conditions, LV function, and LV end-diastolic pressure making interpretation of these variables somewhat complicated.\textsuperscript{18,29} Using tissue Doppler imaging at the mitral annulus the peak velocity during atrial contraction (A’) can be used
as an estimate of global LA function.\textsuperscript{19} Transmitral A` has been found to correlate well with LA ejection fraction, LA ejection force and LA kinetic energy in people with left ventricular hypertrophy.\textsuperscript{36}

Strain and strain rate (SR) are newer echocardiographic imaging modalities that describe myocardial wall deformation and rate of deformation. Strain and SR can be attained either by tissue Doppler imaging (TDI), or the non-Doppler technique of speckle tracking, based on 2D gray-scale imaging.\textsuperscript{37} TDI derived strain and SR provide one dimensional deformation and rate of deformation information of a myocardial segment. In this technology myocardial motion is analyzed by tracking speckles, which are natural acoustic markers, from frame to frame in the 2D image. The velocity of the speckles can be determined through changes in speckle position with shifts representing local tissue movement.\textsuperscript{37} The Aa-wave from atrial strain and SR imaging are regarded as a direct measure of regional active atrial contraction.\textsuperscript{38} The feasibility of 2D speckle-tracking of the left atrium was evaluated and found to be able to analyze global and regional LA longitudinal function in most people.\textsuperscript{39} It has not been reported for evaluation of LA function in small mammals such as cats.

In addition to echocardiography, LA function also can be evaluated by multi-slice computed tomography (CT) and magnetic resonance imaging (MRI). Despite the excellent spatial and temporal resolution of CT to determine LA volumes, this imaging modality is rarely used due to the inherent radiation exposure and need for contrast agents.\textsuperscript{40,41} MRI is considered the most accurate non-invasive technique for evaluating LA volumes and function due to the high spatial resolution and excellent myocardial border detection. However the need for anesthesia in cats, the long acquisition times,
need for breath holding, and extensive data analysis make this modality impractical for clinical practice.41

Owing to the heterogeneous anatomy and different embryologic origins of the LA and LAA, there are regional differences in function of the LA and LAA. The smooth venous LA cavern acts as the principal reservoir and conduit. The LAA also plays an important role as a reservoir, especially with increased pressure or volume in the LA, and has been shown to be more compliant than the LA body.16-18 The LAA has a distinct pattern of contraction compared to the LA, with greater shortening.16 LAA filling and emptying may be influenced by the LV through compression of the LAA wall against the pericardium and the suction effects of the LV.16 LA compliance and early LV filling are increased by pericardiectomy enhancing both conduit and reservoir functions.42 The contractile component of the LAA has particular importance in augmenting LV preload, and LAA function becomes especially important in the face of tachycardia and impaired LV filling.17,18 Movement of blood into and out of the LAA can be quantified noninvasively using Doppler echocardiography.8,14,43 These flow velocity patterns have been previously described in healthy cats and quantified by Schober et al14.

The late diastolic LAA ejection velocity profiles, found shortly after the P-wave on the electrocardiogram, are the Doppler echocardiographic manifestations of LAA contractile function.44 These echocardiographic variables are relatively easy to obtain,14 and part of the routine echocardiographic examination of cats in our clinical practice. However, LAA velocities are unlikely to be a good representation of global LA function. For example, an echocardiographic study in people revealed only a weak correlation between LAA contraction velocities and global LA function variables.45
Both LA size and function are altered in cats with cardiomyopathy (CM).\textsuperscript{8} Furthermore, cats presented with ATE are reported to have significantly larger left atria.\textsuperscript{2,4,7} Enlargement of the LA also has been linked to a shorter overall lifespan in cats with hypertrophic cardiomyopathy.\textsuperscript{46} The cause of LA enlargement and remodeling in cats with CM is probably multifactorial, and might include increased venous pressures, impaired diastolic function, greater fibrosis and chamber stiffness, mitral regurgitation, LV outflow tract obstruction, and neurohormonal activation.\textsuperscript{47} As the atrium enlarges, LA systolic function often declines, predisposing to blood stasis and increasing the risk of thrombus formation. It has been shown that cats with cardiomyopathy have reduced LAA function as measured by LAA flow velocities.\textsuperscript{8} Spontaneous LA echocardiographic contrast ("smoke") observed by 2D echocardiography is another possible marker of thromboembolic risk in human patients and in cats.\textsuperscript{8,16,48,49} This pattern, characterized by a visible echogenic swirling of blood components within the LA and LAA, is often observed in cats with advanced CM. In the clinical study of Schober and colleagues\textsuperscript{8}, the presence of spontaneous echocardiographic contrast was associated with reduced LAA flow velocities (<0.25 m/s); similar data have been reported in people.\textsuperscript{8,43,48} Although LA dysfunction in cats with cardiomyopathy has been reported,\textsuperscript{8,50} there are limited data regarding the effects of drugs on LA function in cats. For this reason, we evaluated in this echocardiographic study the effects of atenolol, pimobendan, and ivabradine on indices of LA function in healthy cats.

Beta-blocker therapy, including atenolol, is commonly used in cats with HCM, particularly in the face of left ventricular outflow or mid-ventricular obstructions. Beta-blockers result in negative inotropic, negative chronotropic and potentially beneficial
effects on ventricular filling. The use of beta-blockers continues to be controversial due to lack of efficacy data on disease progression or survival. However, the potential benefits of beta-blocker therapy include lowering of heart rate to indirectly increase diastolic filling time, reducing LV outflow tract or mid-ventricular obstruction, decreasing myocardial oxygen demand, and blunting sympathetic stimulating effects on the heart, along with antiarrhythmic effects. Atenolol is a hydrophilic, $\beta_1$-selective adrenergic receptor antagonist. Bioavailability of the drug in cats is 90% with a peak beta-blocking effect occurring at approximately one hour after oral administration. A decrease in LA function was reported in a recent study by Riesen et al. in cats after atenolol treatment. A study performed in people with mitral stenosis revealed a significant decrease in LAA function, and a significant increase in the presence of spontaneous echo contrast after two weeks of atenolol therapy. In addition, a case report in humans showed a decrease in LAA flow velocity after treatment with negative inotropic agents, including atenolol. Because both $\beta_1$ and $\beta_2$ receptors have been identified in the human atria and atrial appendages, it is likely that beta-antagonists can impact global atrial function. We would therefore expect atenolol to diminish LA function in normal cats in comparison to baseline and inotropic stimulating drugs. If that is the case, clinicians may need to consider a more cautious use of atenolol in cats with evidence of LA dysfunction while more widely applying LAA function tests in the evaluation of cats with CM. Furthermore, negative effects of atenolol on atrial function might recommend consideration of different classes of drugs for cats with LA dysfunction. These could include nearly pure negative chronotropes such as the funny channel blockers ivabradine and cilobradine, or positive inotropes such as pimobendan.
Ivabradine is a selective funny current (I\textsubscript{f}) inhibitor that induces negative chronotropy by decreasing the slope of diastolic (phase 4) depolarization in the sinoatrial node prolonging diastolic duration with minimal alteration of the action potential\textsuperscript{56,57}. The funny current is activated during hyperpolarization and is modeled as a mixed sodium/potassium inward current\textsuperscript{56}. The funny (f)-channels are composed of the hyperpolarization-activated, cyclic nucleotide gated (HCN) channels. Isoforms HCN-1 through 4 have been identified, and the HCN4 isoform is the most highly expressed in the sinoatrial node.\textsuperscript{56,58,59} A study recently performed in our laboratory by Riesen et al. revealed that HCN4 was expressed in the cat right atrium, right ventricle and LV, and expression was increased in the LV of cats affected with HCM compared to controls.\textsuperscript{a} Funny -channels can be directly activated by cyclic adenosine monophosphate (cAMP) and therefore, I\textsubscript{f} is modulated by both sympathetic (\beta) and vagal (muscarinic) stimulation resulting in an increase or decrease in heart rate, respectively.\textsuperscript{56,57,59} Ivabradine is a “pure” negative chronotrope resulting in the potential benefits of improving coronary blood flow and reducing myocardial oxygen consumption (increasing the ischemic threshold), while preserving inotropy.\textsuperscript{56} Ivabradine is increasingly used as an anti-anginal therapy in people. Telemetry data from a study performed at our institution by Cober et al.\textsuperscript{b} showed a reliable dose-dependent reduction of heart rate with no appreciable adverse effects in healthy cats at doses of 0.3 to 0.5 mg/kg PO, with the peak effects occurring at approximately three hours after administration.

The effects of ivabradine on left atrial function in vivo have not been published. However, a study on guinea pig isolated cardiac preparations revealed that ivabradine exerted no negative inotropic effect on atrial tissues at concentrations required to induce
negative chronotropy. More recently, ivabradine was shown to have either negative or positive inotropic effects in a small number of human isolated atrial preparations. Additionally, a positive inotropic effect was seen in spontaneously beating mouse right atrial preparations, speculated to be due to involvement of the L-type Ca$^{2+}$ channel. However, these positive inotropic effects were seen at much higher concentrations of ivabradine than those required to induce negative chronotropy. In a small number of anesthetized cats evaluated by Riesen et al. at our institution, heart rate was markedly reduced while only fractional area change of the LA was increased in both HCM and control cats. Other atrial function variables were unaffected. If a prospective evaluation of ivabradine on left atrial function reveals no adverse atrial effects, these data could provide support for evaluating this drug clinically in management of feline CM.

Pimobendan is a benzimidazole-pyridazinone derivate with both positive inotropic and vasodilatory effects as a calcium sensitizer and phosphodiesterase (PDE) III inhibitor respectively. The calcium sensitization effect is due to an increased affinity of troponin C binding sites for calcium. This drug is commonly used in canine patients with congestive heart failure with studies showing improved survival in patients with both dilated cardiomyopathy and degenerative mitral valve disease. Pimobendan is increasingly used in an extra-label manner in cats with congestive heart failure. The pharmacokinetics of a single oral dose of pimobendan in a small number of healthy cats has been reported. It was shown that pimobendan is rapidly absorbed, with maximum plasma concentrations in healthy cats of 11.1-59.4 ng/mL which is approximately four times higher than those in dogs. Additionally, the elimination half-life was $1.5 \pm 0.2$
hours, which is approximately three times longer than in dogs. Pharmacodynamic information for pimobendan in cats has not been reported at this time. A small study evaluating the use of pimobendan (0.23 ± 0.07 mg/kg PO q 12h) in cats with heart failure secondary to cardiomyopathy, congenital heart disease and endocarditis showed that the drug appeared safe, well tolerated, and may have improved survival. A more recent report retrospectively evaluated the use of pimobendan in 161 cats with naturally occurring heart disease (mainly cardiomyopathy) and showed that the drug (median dose 0.23 mg/kg PO q 12h) was well tolerated, with only five cats showing mild adverse effects, however these cats were receiving other congestive heart failure therapy concurrently. Pimobendan exerts a positive inotropic effect on feline left ventricular function, but the effect of pimobendan on LA function in vivo in cats has not been reported. Levosimendan, similar in drug mechanism of action to pimobendan, increases the force of contraction in the guinea pig LA. Furthermore, this same drug was shown to improve LA performance, while reducing LA volumes in human patients with ischemic heart failure, and those with decompensated heart failure (ischemic and nonischemic). The current study evaluates whether LA function is altered in healthy cats with inotropic stimulation from oral administration of pimobendan. A demonstrated effect of enhanced atrial function might promote additional studies assessing the cardiac effects of pimobendan in cats with CM and in particular on LA function and risk of ATE.

The objectives of this study were to evaluate the effects of pimobendan, ivabradine and atenolol on LA and LAA function in healthy cats using transthoracic echocardiography. We hypothesized that pimobendan would improve, atenolol would
depress, and ivabradine would demonstrate minimal effects on LA and LAA function in healthy cats.
CHAPTER 2
MATERIALS AND METHODS

Animals: Ten healthy, female-spayed, domestic shorthair cats from an established research colony were studied. The cats were 2-7 years old. All cats were acquired from a commercial vendor (Cat source: Liberty Research Inc., Waverly, NY). The study protocol was reviewed and approved by the Animal Care and Use Committee and the College of Veterinary Medicine Review Board of the Ohio State University. The cats were housed in approved University Laboratory Animal Facilities. All animals were treated in compliance with the National Institutes of Health guidelines on the care and use of laboratory animals.

Study Design: This was a prospective study using a double-blind, randomized, fully-crossed design. Prior to baseline echocardiographic data acquisition, each cat was subjected to a complete clinical evaluation including physical examination, complete blood count and serum biochemistry, 6 lead electrocardiogram (ECG: MAC 8 resting ECG analysis system, Marquette Electronics, Milwaukee, WI), indirect systolic blood pressure measurement (Ultrasonic Doppler Flow Detector 811-AL, Parks Medical Electronics Inc, Aloha, OR), and transthoracic echocardiography (Vivid 7 Vantage, GE Medical Systems, Milwaukee, WI). One cat was found to have systolic anterior motion of the mitral valve resulting in significant left ventricular outflow tract obstruction and was excluded from the study. Therefore, only nine cats were included in the final analysis.
LA function was evaluated by echocardiography over four study periods: control (no drugs given), atenolol (Atenolol, Mallinckrodt Inc., St. Louis, MO; (1.8-2.5 mg/kg q12h), pimobendan (Vetmedin®, Boehringer Ingelheim Vetmedica Inc); (0.2-0.3 mg/kg q12h), and ivabradine (Procoralan®, Les Laboratoires Servier, 22 Rue Garnier, 92200 Neuilly-sur-Seine, France); (0.3-0.5 mg/kg q12h). Prior to randomization the drugs at the appropriate doses were prepared for each cat and subsequently filled in opaque capsules (Capsules 3 blue, Gallipot Inc, St. Paul, MN) assuring blinding of the investigators. The control period consisted of three baseline echocardiographic evaluations on three consecutive days. After completion of the control period the cats were randomized to receive one of the three treatments: atenolol, ivabradine or pimobendan. Each treatment was given to each cat for seven consecutive days followed by a seven-day wash out period before the next treatment period. Treatment order was randomized and cats were treated for 7 days prior to measurements. Echocardiographic examinations were performed three hours after the morning dose of drug on the seventh day. An accidental evening dose was given to one cat on the sixth day during the first treatment period. After discovery of the error, the cat received the intended study drug that evening and in the morning prior to echocardiographic evaluation. After unblinding of treatments, it was determined that the cat received ivabradine instead of the intended pimobendan that evening.

_Echocardiography:_ To facilitate echocardiography the cats were sedated with acepromazine (Acepromazine maleate injection, Boehringer Ingelheim Vetmedica inc, St. Joseph, MO; 0.1 mg/kg), butorphanol (Torbugesic, Fort Dodge Laboratories, Fort Dodge, IA; 0.25 mg/kg) and ketamine (Ketaset, Fort Dodge Laboratories, Fort Dodge,
IA; 3 mg/kg), all given by intramuscular injection. Acepromazine and butorphanol were given 20 minutes and ketamine 5 minutes before initiation of the echocardiographic examinations. All cats were given the same sedation protocol prior to each echocardiographic examination. Echocardiographic studies were performed by one investigator (AK) using a GE Vivid 7 Dimension echocardiographic system with 10 MHz and 7 MHz nominal frequency transducers preset for optimal feline imaging and Doppler studies. 2D images were recorded at >80 frames/s, and PW Doppler was recorded at 200 mm/sec sweep speed. A simultaneous one-lead ECG was recorded and used for heart rate measurement. Pulsed Doppler flow recordings were guided by 2D color Doppler imaging with appropriate settings to observe low velocity signals. Measurements were performed off-line from digitized images using the embedded software and calculation packages (EchoPac software package, Version BT06, GE Medical Systems, Milwaukee, WI). The mean of three cardiac cycles was used for each measured variable. Right parasternal long and short-axis and left apical imaging views were acquired for optimal recording of the LA, the LV, transmittal flow, pulmonary venous flow, LAA flow, and isovolumic relaxation time. Measured two-dimensional LA variables included LA diameter (LAD; from the right parasternal, long axis image plane), LA length and width (LAL and LAW respectively; from the left apical imaging plane), and LA area (from left apical imaging plane) at ventricular end-diastole and end-systole. Both peak LAA inflow (LAA-in) and outflow (LAA-out) velocities were obtained from the left craniodorsal image plane using a 3 mm sample volume placed at the mid-junction of the atrium and auricle. Pulmonary venous flow patterns were recorded from the left apical long axis (three or four chamber) or right short axis image planes and atrial reversal peak velocity (PVF A_R)
and duration of the reversal wave (PVF A<sub>D</sub>) measured. LV internal dimension at end-diastole (LVID<sub>d</sub>) and end-systole (LVID<sub>s</sub>) were determined from M-mode recordings obtained from right parasternal short axis.

Transmitral flow velocity (TMF) and mitral annular tissue Doppler imaging (TDI) at the lateral annulus were recorded; however, owing to the rapid feline heart rate, early- and late-diastolic waveforms were fused in the majority of studies precluding further analysis. Additionally, 2D speckle-tracking was attempted on the LA wall to quantify cyclic myocardial deformation. However, this technique was unsuccessful as the software algorithm could not effectively track the thin LA wall of the cats.

Calculated LA variables included: LA % shortening fraction from LAD \{(LAD<sub>S</sub> – LAD<sub>D</sub>/LAD<sub>S</sub>) x 100\};\textsuperscript{14} LA % shortening area \{(LA Area<sub>S</sub> – LA Area<sub>D</sub>/LA Area<sub>S</sub>) x 100\};\textsuperscript{14} and LA volumes (LAV). Left atrial volumes were obtained in atrial end-diastole and end-systole using both automated methods (Simpson’s calculation from a single traced left apical image) and by calculation of LA volume using the prolate-ellipsoid (PE) method \{(0.523 x D<sub>1</sub> x D<sub>2</sub> x D<sub>3</sub>)/1000, where D1= LAD; D2= LAL; D3= LAW\}.\textsuperscript{76} LA ejection fraction (EF) was obtained from LA volumes (using both the modified Simpson’s method and PE method) as: LA Vol<sub>S</sub> – LA Vol<sub>D</sub>/LA Vol<sub>S</sub>. The LV shortening fraction was calculated from the LV internal dimensions as: LVID<sub>d</sub> – LVID<sub>s</sub>/LVID<sub>d</sub>. Heart rate was calculated for each study period by measuring instantaneous R-R intervals at the midpoint of each examination.

**Statistical Analysis:** Statistical analysis was performed by use of commercially available software (GraphPad Prism 5.02, GraphPad Software, La Jolla, CA; SigmaPlot for Windows Version 11.0.0.75., Systat Software 2008, San Jose, CA; SPSS 19, IBM
Corporation, Somers, NY). The data were tested for normality using D’Agostino and Pearson and Kolmogorov-Smirnov tests. Descriptive statistics were calculated for all clinical and echocardiographic variables; these are presented as mean ± standard deviation (SD) unless stated otherwise. Variability in values for each individual cat obtained over the three day baseline examinations were quantified by calculating a coefficient of variation for each cat where: Subject CV = Subject SD/Subject mean x 100%. The coefficients of variation for each individual cat were averaged to obtain the overall CV for each variable. To compare the data over the four study periods (baseline, atenolol, ivabradine and pimobendan) a one way ANOVA for repeated measures was used. When a significant F was determined, a Holm Sidak test was used for multiple comparisons between treatments. Statistical significance was set at alpha=0.05. Based on our previous experience with these variables in experimental and clinical studies in horses,30 and dogs,77 as well as the normal variation reported for key variables in the literature,8,14 we believed that 10 cats in a repeated measures design limited to 4 study periods would provide sufficient statistical power to identify clinically important differences between means for our most important variables such as left atrial appendage emptying velocities and left atrial diameter. For variables with higher coefficients of variation, it was accepted that the study might be underpowered to see statistically significant differences. (It should be noted that a priori power calculations were conducted on 10 cats, but one cat was eliminated from the study after uncovering cardiac disease). In addition to the standard univariate repeated measures ANOVA, a linear mixed model analysis was performed using treatment as a fixed effect and cat (subject) identification as a random effect. This was done to evaluate the impact of individual cats
on the statistical model over the four treatment periods. Finally, simple correlation (Spearman) was used to identify relationships between heart rate and key measured and calculated variables. Further modeling (such as repeated measures linear regression or analysis of covariance) was not done as atenolol and ivabradine influence heart rate directly; therefore, HR could not be considered an independent predictor from treatment effect.\textsuperscript{78}
CHAPTER 3

RESULTS

The mean echocardiographic variables obtained from these 9 cats over the three baseline measurement periods were relatively consistent despite individual day to day variation. These results are summarized in Tables 1 to 4 and Figures 1 to 21 and described more fully below. Treatment effects on measured and calculated variables were evident with each of the three drugs and are summarized in Tables 5 to 8 and Figures 22 to 42.

Heart rate

Results of the three baseline heart rate measurements are summarized in Table 1 and Figure 1. The mean heart rate for the three baseline exams was 223 +/- 27.3 per minute (bpm) with no significant difference evident between the days (p=0.289). Statistically significant correlations were identified by Spearman’s method between baseline HR and LAA-in (r=0.649), PVF A_D (r=-0.295). LAA-out (r=0.523), and PVF A_R (r=0.456).

Results of the heart rate measurements over the four treatment periods are shown in Table 5 and Figure 22. Atenolol resulted in a significant decrease in heart rate compared to baseline and pimobendan (p<0.05). Ivabradine significantly decreased heart rate compared to baseline, pimobendan, and atenolol (p<0.05).
There was no significant statistical difference in heart rate between baseline and pimobendan.

**Baseline Echocardiography**

Mean values for the echocardiographic variables studied were not significantly different across the three baseline periods with the exception of LVIDd. There was good repeatability with low subject day-to-day variability (CV 5-15%) for HR, IVRT, LVIDd, LA diameter, at end-systole and end-diastole, LA area at end-systole and end-diastole, LA volume by the modified Simpson's method at end-systole and end-diastole, LA volume at end-systole by the PE method, LA SA, LA EF (by both Simpson's and PE methods), LAA-in, LAA-out, and PVF $A_D$. There was greater day-to-day variability (CV 15-25%) for LVIDs, LA volume at end-diastole by the PE method, LA SF and PVF $A_R$.\(^{30}\)

**LA and LV size** There were no significant differences in LA size at (ventricular) end-systole or (ventricular) end-diastole between the three baseline periods for the variables LA diameter, LA area, and LA volume, as estimated by the modified Simpson's and PE methods (Table 2; Figures 2 to 9). There was a statistically significant difference in LVIDd noted between days 1 and 3 (Table1; Figure 10); this difference averaged 1.3 mm. There was no significant difference in LVIDs between the baseline periods (Table1; Figure 11).

**Baseline global LA function and LV function** There were no significant differences evident across the three baseline periods for LA EF (by modified Simpson's or PE methods) or for left atrial shortening fraction or shortening area (Table 3; Figures 12 to 15). For the left ventricle, there were no significant differences across the
baseline periods for LV shortening fraction (p=0.706) or for IVRT (p=0.321; Table 1; Figures 16 to 17).

*Baseline Doppler echocardiographic indices of LA and LAA function* There were no significant differences between any of the baseline Doppler variables (LAA-in, LAA-out, PVF A_R, PVF A_D) across the three baseline examinations (Table 4; Figures 18 to 21).

**Effects of Treatments on Echocardiographic Variables**

Significant differences in left atrial and ventricular size and function were observed following treatments with pimobendan, atenolol, and ivabradine. When comparing results obtained for the repeated measures ANOVA and the linear mixed model, there was a small change in the p-value (ANOVA p = 0.045 versus linear mixed model p = 0.050) for LA ejection fraction (modified Simpson’s method) rendering the differences between treatments nonsignificant using the latter analysis. Otherwise, statistical differences between treatment periods were similar for the repeated measures ANOVA and linear mixed model analyses.

*Treatment effects on LA and LV size* Ivabradine did not significantly change LAD at (ventricular) end-systole or (ventricular) end-diastole when compared to baseline. Pimobendan did not change end-systolic LA diameter when compared to baseline, and atenolol did not change LAD at end-systole (p=0.088). Atenolol resulted in a significant increase in (ventricular) end-diastolic LA diameter compared to baseline, pimobendan, and ivabradine. However, there were no significant differences in end-diastolic LAD between baseline, pimobendan or ivabradine (Table 2; Figures 23 to 24).
Pimobendan treatment decreased the maximum LA area measured at (ventricular) end-systole when compared to baseline, ivabradine and atenolol. End-systolic LA area was not significantly altered by ivabradine or atenolol compared to baseline. Atenolol resulted in a significant increase in area at ventricular end-diastole, compared to baseline, and was also significantly greater than pimobendan and ivabradine. There was no significant difference in LA end-diastolic area after pimobendan or ivabradine (Table 2; Figures 25 to 26).

The (ventricular) end-systolic LA volume was significantly decreased with pimobendan treatment when compared to baseline, ivabradine and atenolol (as measured by both modified-Simpson’s and PE methods). There was no significant change with atenolol or ivabradine compared to baseline by either method. The (ventricular) end-diastolic LA volume was significantly increased by atenolol treatment when compared to baseline, ivabradine and pimobendan. LA end-diastolic volume when measured by the modified-Simpson’s method was not changed by pimobendan, however was significantly decreased when measured by the PE method (p<0.001; Table 2; Figures 27 to 30).

LVIDd was significantly increased by ivabradine compared to baseline. LVIDd was significantly decreased after pimobendan treatment when compared to ivabradine and atenolol, while atenolol did not significantly affect LVIDd. LVIDs was significantly greater after atenolol compared to baseline; whereas, LVIDs was significantly decreased after pimobendan when compared to ivabradine and atenolol (Table 1; Figures 31 to 32).
Global LA function and LV function  Atenolol significantly decreased LA SF and LA SA compared to baseline. There was no significant difference between baseline, pimobendan or ivabradine (Table 7; Figures 33 to 34). Atenolol significantly decreased LA EF, by the modified Simpson's method, compared to ivabradine, however there was no significant difference compared to baseline. Ivabradine and pimobendan did not significantly alter LA EF derived by the modified Simpson's method (Table 7; Figure 35).

Atenolol also significantly decreased LA EF as measured by the PE method compared to baseline and ivabradine. There was no significant difference in LA EF by PE method between pimobendan, ivabradine and baseline (Table 7; Figure 36). The LV FS also was significantly decreased during atenolol treatment when compared to pimobendan and ivabradine, but the other periods were not significantly different from each other (Table 5; Figure 37).

IVRT was significantly prolonged by atenolol when compared to baseline and pimobendan. No significant differences were evident between pimobendan, ivabradine and baseline (Table 5; Figure 38).

Doppler echocardiographic indices of LA and LAA function  Both ivabradine and atenolol caused a significant reduction in LAA-in compared to baseline and pimobendan. Atenolol resulted in a further decrease in LAA-in when compared to ivabradine (Table 8; figure 39). Mean LAA-out velocities were 85.0 (± 22.6) cm/s at baseline; 101.4 (± 30.6) cm/s following pimobendan; 81.2 (± 22.6) cm/s after ivabradine; and 39.4 (± 8.2) cm/s after atenolol, which was significantly decreased compared to other treatments (Table 8, Figure 40). Atenolol resulted in a significant
decrease in PVF $A_r$ and a significant increase in PVF $A_d$ compared to baseline, pimobendan and ivabradine. There were no statistically significant differences in PVF $A_r$ and $A_d$ after pimobendan or ivabradine administration compared to baseline (Table 8; Figures 41 to 42).
<table>
<thead>
<tr>
<th>Variable</th>
<th>n</th>
<th>Day 1</th>
<th>Day 2</th>
<th>Day 3</th>
<th>Grand Mean</th>
<th>P</th>
<th>CV (%)</th>
<th>CV Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>HR (bpm)</td>
<td>9</td>
<td>228.7 (35.3)</td>
<td>214.4 (26.5)</td>
<td>226.1 (32.5)</td>
<td>223.1</td>
<td>0.289</td>
<td>8.4</td>
<td>2.3-13.0</td>
</tr>
<tr>
<td>IVRT (ms)</td>
<td>9</td>
<td>56.7 (4.6)</td>
<td>53.5 (7.8)</td>
<td>55.5 (4.6)</td>
<td>55.2</td>
<td>0.321</td>
<td>6.9</td>
<td>0.5-19.0</td>
</tr>
<tr>
<td>LVIDd (mm)</td>
<td>9</td>
<td>9.4 (1.0)</td>
<td>10.2 (1.3)</td>
<td>10.7 (1.6) *</td>
<td>10.1</td>
<td>0.025</td>
<td>9.0</td>
<td>4.0-18.0</td>
</tr>
<tr>
<td>LVIDs (mm)</td>
<td>9</td>
<td>4.1 (0.9)</td>
<td>4.6 (1.2)</td>
<td>4.5 (1.4)</td>
<td>4.4</td>
<td>0.401</td>
<td>16.0</td>
<td>11.0-24.0</td>
</tr>
<tr>
<td>LV FS (%)</td>
<td>9</td>
<td>55.9 (10.9)</td>
<td>55.4 (8.9)</td>
<td>57.9 (11.0)</td>
<td>56.4</td>
<td>0.706</td>
<td>10.0</td>
<td>2.0-22.0</td>
</tr>
</tbody>
</table>

Table 1. Heart rate and echocardiographically-derived indices of left ventricular function during three baseline periods performed on consecutive days. Mean and intra-day standard deviation (SD) are shown for the individual study periods. The grand mean and SD over the three baseline days are also indicated along with the P value from the repeated-measures ANOVA. * indicates a significant difference (p<0.05) between day 1 and day 3. CV mean = average of individual CV determined for each of 9 cats over three days; CV range = lowest to highest CV for individual cats over three study days.
<table>
<thead>
<tr>
<th>Variable</th>
<th>n</th>
<th>Day 1</th>
<th>Day 2</th>
<th>Day 3</th>
<th>Grand Mean</th>
<th>P</th>
<th>CV(%)</th>
<th>CV Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>LA diameter-S (mm)</td>
<td>9</td>
<td>11.4 (1.5)</td>
<td>11.5 (1.4)</td>
<td>11.4 (1.5)</td>
<td>11.4</td>
<td>0.944</td>
<td>5.7</td>
<td>0.8-11.0</td>
</tr>
<tr>
<td>LA diameter-D (mm)</td>
<td>9</td>
<td>8.3 (1.5)</td>
<td>8.2 (1.4)</td>
<td>8.1 (1.3)</td>
<td>8.2</td>
<td>0.933</td>
<td>9.1</td>
<td>5.8-12.0</td>
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<tr>
<td>LA Area-S (cm²)</td>
<td>9</td>
<td>1.20 (0.20)</td>
<td>1.24 (0.21)</td>
<td>1.28 (0.27)</td>
<td>1.24</td>
<td>0.221</td>
<td>7.3</td>
<td>2.6-15.0</td>
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<tr>
<td>LA Area-D (cm²)</td>
<td>9</td>
<td>0.66 (0.18)</td>
<td>0.64 (0.12)</td>
<td>0.71 (0.17)</td>
<td>0.67</td>
<td>0.167</td>
<td>9.3</td>
<td>3.8-23.0</td>
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<tr>
<td>LA Vol Simp-S (mL)</td>
<td>9</td>
<td>0.88 (0.22)</td>
<td>0.93 (0.24)</td>
<td>0.96 (0.31)</td>
<td>0.92</td>
<td>0.352</td>
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<td>5.6-19.0</td>
</tr>
<tr>
<td>LA Vol Simp-D (mL)</td>
<td>9</td>
<td>0.36 (0.17)</td>
<td>0.34 (0.11)</td>
<td>0.39 (0.15)</td>
<td>0.36</td>
<td>0.223</td>
<td>13.0</td>
<td>5.6-34.0</td>
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<tr>
<td>LA Vol PE-S (mL)</td>
<td>9</td>
<td>0.90 (0.21)</td>
<td>0.92 (0.23)</td>
<td>0.95 (0.27)</td>
<td>0.93</td>
<td>0.556</td>
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<tr>
<td>LA Vol PE-D (mL)</td>
<td>9</td>
<td>0.36 (0.15)</td>
<td>0.34 (0.09)</td>
<td>0.38 (0.15)</td>
<td>0.36</td>
<td>0.455</td>
<td>15.0</td>
<td>8.5-33.0</td>
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</table>

Table 2: Echocardiographic measurements and calculations of left atrial size during three baseline periods performed on consecutive days. Mean and intra-day standard deviation (SD) are shown for the individual study periods. The grand mean and SD over the three baseline days are also indicated along with the P value from the repeated-measures ANOVA. CV mean = average of individual CV determined for each of 9 cats over three days; CV range = lowest to highest CV for individual cats over three study days.
### Table 3

<table>
<thead>
<tr>
<th>Variable</th>
<th>n</th>
<th>Day 1</th>
<th>Day 2</th>
<th>Day 3</th>
<th>Grand Mean</th>
<th>P</th>
<th>CV(%)</th>
<th>CV Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>LA SF (%)</td>
<td>9</td>
<td>27.7 (5.0)</td>
<td>28.7 (5.1)</td>
<td>28.2 (6.2)</td>
<td>28.2</td>
<td>0.897</td>
<td>15.0</td>
<td>4.0-30.0</td>
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<td>LA SA (%)</td>
<td>9</td>
<td>45.1 (7.4)</td>
<td>47.8 (6.5)</td>
<td>44.8 (7.2)</td>
<td>45.9</td>
<td>0.508</td>
<td>12.0</td>
<td>4.0-23.0</td>
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<tr>
<td>LA EF Simp</td>
<td>9</td>
<td>0.61 (0.10)</td>
<td>0.64 (0.08)</td>
<td>0.60 (0.10)</td>
<td>0.62</td>
<td>0.391</td>
<td>10.0</td>
<td>2.2-21.0</td>
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<tr>
<td>LA EF PE</td>
<td>9</td>
<td>0.61 (0.09)</td>
<td>0.63 (0.04)</td>
<td>0.61 (0.07)</td>
<td>0.62</td>
<td>0.629</td>
<td>8.5</td>
<td>1.5-18.0</td>
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Table 3. Echocardiographically-derived indices of global LA function during three baseline periods performed on consecutive days. Mean and intra-day standard deviation (SD) are shown for the individual study periods. The grand mean and SD over the three baseline days are also indicated along with the P value from the repeated-measures ANOVA. CV mean = average of individual CV determined for each of 9 cats over three days; CV range = lowest to highest CV for individual cats over three study days.

### Table 4

<table>
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<th>Variable</th>
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<th>Day 1</th>
<th>Day 2</th>
<th>Day 3</th>
<th>Grand Mean</th>
<th>P</th>
<th>CV(%)</th>
<th>CV Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>LAA-in (cm/s)</td>
<td>9</td>
<td>82.8 (13.2)</td>
<td>82.0 (17.2)</td>
<td>84.3 (17.2)</td>
<td>83.0</td>
<td>0.882</td>
<td>11.0</td>
<td>1.4-19.0</td>
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<tr>
<td>LAA-out (cm/s)</td>
<td>9</td>
<td>83.8 (24.6)</td>
<td>89.7 (20.5)</td>
<td>81.4 (21.6)</td>
<td>85.0</td>
<td>0.182</td>
<td>12.0</td>
<td>3.3-29.0</td>
</tr>
<tr>
<td>PVF-A_R vel (cm/s)</td>
<td>9</td>
<td>27.9 (12.1)</td>
<td>25.2 (4.2)</td>
<td>27.0 (6.3)</td>
<td>26.7</td>
<td>0.655</td>
<td>16.0</td>
<td>4.8-46.0</td>
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<tr>
<td>PVF-A_R dur (ms)</td>
<td>9</td>
<td>48.9 (7.5)</td>
<td>54.3 (5.4)</td>
<td>51.1 (4.7)</td>
<td>51.4</td>
<td>0.082</td>
<td>9.0</td>
<td>2.7-18.0</td>
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Table 4. Echocardiographically-derived Doppler indices of left atrial and left atrial appendage function during three baseline periods performed on consecutive days. Mean and intra-day standard deviation (SD) are shown for the individual study periods. The grand mean and SD over the three baseline days are also indicated along with the P value from the repeated-measures ANOVA. CV mean = average of individual CV determined for each of 9 cats over three days; CV range = lowest to highest CV for individual cats over three study days.
<table>
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<th>Variable</th>
<th>n</th>
<th>Baseline</th>
<th>Pimobendan</th>
<th>Ivabradine</th>
<th>Atenolol</th>
<th>Univariate</th>
<th>Mixed Model</th>
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</thead>
<tbody>
<tr>
<td><strong>HR</strong></td>
<td>9</td>
<td>223.1 (27.3)</td>
<td>215.4 (37.1)</td>
<td>125.3 (26.9)</td>
<td>146.2 (19.9)</td>
<td>90.26</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>IVRT (ms)</strong></td>
<td>9</td>
<td>55.2 (4.7)</td>
<td>54.8 (8.8)</td>
<td>60.0 (10.3)</td>
<td>70.7 (6.6)</td>
<td>9.64</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>LVIDd (mm)</strong></td>
<td>9</td>
<td>10.1 (1.1)</td>
<td>9.1 (0.8)</td>
<td>11.9 (2.4)</td>
<td>11.0 (1.8)</td>
<td>6.51</td>
<td>0.002</td>
</tr>
<tr>
<td><strong>LVIDs (mm)</strong></td>
<td>9</td>
<td>4.4 (1.0)</td>
<td>3.4 (1.0)</td>
<td>4.9 (1.6)</td>
<td>5.8 (1.5)</td>
<td>7.80</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>LV FS (%)</strong></td>
<td>9</td>
<td>56.4 (8.8)</td>
<td>62.0 (10.3)</td>
<td>61.3 (10.4)</td>
<td>48.3 (8.4)</td>
<td>4.93</td>
<td>0.008</td>
</tr>
</tbody>
</table>

Table 5. Heart rate and echocardiographically-derived indices of left ventricular function at baseline and after 7 days of treatment with pimobendan, ivabradine or atenolol. Mean (SD). * indicates significant difference compared to baseline. † indicates significant difference compared to pimobendan. ‡ indicates significant difference compared to ivabradine. § indicates significant difference compared to atenolol.
Table 6. Echocardiographically-derived 2D indices of left atrial size at baseline and after 7 days of treatment with pimobendan, ivabradine, or atenolol. * indicates significant difference compared to baseline. Mean (SD) ‡ indicates significant difference compared to pimobendan. ^ indicates significant difference compared to ivabradine. † indicates significant difference compared to atenolol.
<table>
<thead>
<tr>
<th>Variable</th>
<th>n</th>
<th>Baseline</th>
<th>Pimobendan</th>
<th>Ivabradine</th>
<th>Atenolol</th>
<th>Univariate F</th>
<th>Univariate p</th>
<th>Mixed Model p</th>
</tr>
</thead>
<tbody>
<tr>
<td>LA SF (%)</td>
<td>9</td>
<td>28.2 (3.9)</td>
<td>24.9 (6.3)</td>
<td>25.6 (5.1)</td>
<td>19.5 (8.2)*</td>
<td>3.30</td>
<td>0.037</td>
<td>0.026</td>
</tr>
<tr>
<td>LA SA (%)</td>
<td>9</td>
<td>45.9 (5.2)</td>
<td>45.1 (8.4)</td>
<td>47.5 (7.3)</td>
<td>38.8 (7.8)^</td>
<td>3.372</td>
<td>0.035</td>
<td>0.040</td>
</tr>
<tr>
<td>LA EF Simp</td>
<td>9</td>
<td>0.62 (0.07)</td>
<td>0.61 (0.10)</td>
<td>0.64 (0.08)</td>
<td>0.54 (0.10)^</td>
<td>3.120</td>
<td>0.045</td>
<td>0.050</td>
</tr>
<tr>
<td>LA EF PE</td>
<td>9</td>
<td>0.62 (0.05)</td>
<td>0.58 (0.08)</td>
<td>0.60 (0.08)</td>
<td>0.49 (0.12)**</td>
<td>4.64</td>
<td>0.011</td>
<td>0.013</td>
</tr>
</tbody>
</table>

Table 7. Echocardiographically-derived indices of LA function at baseline and after 7 days of treatment with pimobendan, ivabradine or atenolol. Mean (SD). * indicates significant difference compared to baseline. ^ indicates significant difference compared to pimobendan. ^ indicates significant difference compared to ivabradine.

<table>
<thead>
<tr>
<th>Variable</th>
<th>n</th>
<th>Baseline</th>
<th>Pimobendan</th>
<th>Ivabradine</th>
<th>Atenolol</th>
<th>Univariate F</th>
<th>Univariate p</th>
<th>Mixed Model p</th>
</tr>
</thead>
<tbody>
<tr>
<td>LAA-in (cm/s)</td>
<td>9</td>
<td>83.0 (13.7)</td>
<td>90.0 (25.2)</td>
<td>62.0 (9.3)^+</td>
<td>45.5 (8.1)^++</td>
<td>26.28</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>LAA-out (cm/s)</td>
<td>9</td>
<td>85.0 (20.9)</td>
<td>101.4 (30.6)</td>
<td>81.2 (22.6)</td>
<td>39.4 (8.2)^++</td>
<td>24.00</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>PVF-A_R vel (cm/s)</td>
<td>9</td>
<td>26.7 (6.3)</td>
<td>26.3 (8.2)</td>
<td>26.2 (7.3)</td>
<td>16.8 (3.9)^++</td>
<td>5.03</td>
<td>0.008</td>
<td>0.009</td>
</tr>
<tr>
<td>PVF-A_R dur (ms)</td>
<td>9</td>
<td>51.4 (4.6)</td>
<td>51.4 (7.5)</td>
<td>58.5 (7.4)</td>
<td>68.0 (10.0)^++</td>
<td>10.88</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Table 8. Echocardiographically-derived Doppler indices of left atrial and left atrial appendage function at baseline and after 7 days of treatment with pimobendan, ivabradine, or atenolol. Mean (SD). * indicates significant difference compared to baseline. ^ indicates significant difference compared to pimobendan. ^ indicates significant difference compared to ivabradine.
Figure 1. A) Baseline heart rate measured on three consecutive days. B) Baseline heart rate displayed as mean; error bars indicate standard error of the mean.

Figure 2. A) Baseline measurement of LA diameter (mm) at ventricular end-systole performed on consecutive days. B) Baseline measurement of LA diameter (mm) at ventricular end-systole displayed as mean; error bars indicate standard error of the mean.
Figure 3. A) Baseline measurement of LA diameter (mm) at ventricular end-diastole performed on consecutive days. B) Baseline measurement of LA diameter (mm) at ventricular end-diastole displayed as mean; error bars indicate standard error of the mean.

Figure 4. A) Baseline measurement of LA area (cm$^2$) at ventricular end-systole performed on consecutive days. B) Baseline measurement of LA area (cm$^2$) at ventricular end-systole displayed as mean; error bars indicate standard error of the mean.
Figure 5. A) Baseline measurement of LA area (cm$^2$) at ventricular end-diastole performed on consecutive days. B) Baseline measurement of LA area (cm$^2$) at ventricular end-diastole displayed as mean; error bars indicate standard error of the mean.

Figure 6. A) Baseline LA volume (mL) measured by modified Simpson’s method at ventricular end-systole performed on consecutive days. B) Baseline LA volume (mL) measured by modified Simpson’s method at ventricular end-systole displayed as mean; error bars indicate standard error of the mean.
Figure 7. A) Baseline LA volume (mL) measured by modified Simpson’s method at ventricular end-diastole performed on consecutive days. B) Baseline LA volume (mL) measured by modified Simpson’s method at ventricular end-diastole displayed as mean; error bars indicate standard error of the mean.

Figure 8. A) Baseline LA volume (mL) measured by prolate ellipsoid method at ventricular end-systole performed on consecutive days. B) Baseline LA volume (mL) measured by prolate ellipsoid method at ventricular end-systole displayed as mean; error bars indicate standard error of the mean.
Figure 9. A) Baseline LA volume (mL) measured by prolate ellipsoid method at ventricular end-diastole performed on consecutive days. B) Baseline LA volume (mL) measured by prolate ellipsoid method at ventricular end-diastole displayed as mean; error bars indicate standard error of the mean.

Figure 10. A) Baseline LV internal dimension (mm) at end-diastole on consecutive days. B) Baseline LV internal dimension (mm) at end-diastole displayed as mean; error bars indicate standard error of the mean. * indicates significant difference compared to day 1.
Figure 11. A) Baseline LV internal dimension (mm) at end-systole on consecutive days. B) Baseline LV internal dimension (mm) at end-systole displayed as mean; error bars indicate standard error of the mean.

Figure 12. A) Baseline calculated LA shortening fraction (%) on three consecutive days. B) Baseline calculated LA shortening fraction (%) displayed as mean; error bars indicate standard error of the mean.
Figure 13. A) Baseline calculated LA shortening area (%) on three consecutive days. B) Baseline calculated LA shortening area (%) displayed as mean; error bars indicate standard error of the mean.

Figure 14. A) Baseline calculated LA ejection fraction derived from modified Simpson’s method on three consecutive days. B) Baseline calculated LA ejection fraction derived from modified Simpson’s method displayed as mean; error bars indicate standard error of the mean.
Figure 15. A) Baseline calculated LA ejection fraction derived from prolate ellipsoid method on three consecutive days. B) Baseline calculated LA ejection fraction derived from prolate ellipsoid method displayed as mean; error bars indicate standard error of the mean.

Figure 16. A) Baseline calculated LV shortening fraction (%) on consecutive days. B) Baseline calculated LV shortening fraction (%) displayed as mean; error bars indicate standard error of the mean.
Figure 17. A) Baseline measured isovolumic relaxation time (ms) on consecutive days. B) Baseline measured isovolumic relaxation time (ms) displayed as mean; error bars indicate standard error of the mean.

Figure 18. A) Baseline measured LAA inflow velocity (cm/s) on consecutive days. B) Baseline measured LAA inflow velocity (cm/s) displayed as mean; error bars indicate standard error of the mean.
Figure 19. A) Baseline measured LAA outflow velocity (cm/s) on consecutive days. B) Baseline measured LAA outflow velocity (cm/s) displayed as mean; error bars indicate standard error of the mean.

Figure 20. A) Baseline measured PVF atrial reversal wave velocity (cm/s) on consecutive days. B) Baseline measured PVF atrial reversal wave velocity (cm/s) displayed as mean; error bars indicate standard error of the mean.
Figure 21. A) Baseline measured PVF atrial reversal wave duration (ms) on consecutive days. B) Baseline measured PVF atrial reversal wave duration (ms) displayed as mean; error bars indicate standard error of the mean.
Figure 22. Mean baseline and post-treatment heart rate. A) Raw data of measured baseline heart rate and after treatment with pimobendan, ivabradine and atenolol. B) Baseline and post-treatment heart rate displayed as the mean; error bars indicate standard error of the mean. * indicates significant difference compared to baseline. + indicates significant difference compared to pimobendan. ^ indicates significant difference compared to ivabradine.
Figure 23. A) Mean baseline and post-treatment LA diameter (mm) at ventricular end-systole. B) Baseline and post-treatment LA diameter (mm) at ventricular end-systole displayed as mean; error bars indicate standard error of the mean.

Figure 24. A) Mean baseline and post-treatment LA diameter (mm) at ventricular end-diastole. B) Baseline and post-treatment LA diameter (mm) at ventricular end-diastole displayed as mean; error bars indicate standard error of the mean. * indicates significant difference compared to baseline. + indicates significant difference compared to pimobendan. ^ indicates significant difference compared to ivabradine.
Figure 25. A) Mean baseline and post-treatment LA area (cm$^2$) at ventricular end-systole. B) Baseline and post-treatment LA area (cm$^2$) at ventricular end-systole displayed as mean; error bars indicate standard error of the mean. * indicates significant difference compared to baseline. ^ indicates significant difference compared to ivabradine. ◆ indicates significant difference compared to atenolol.
Figure 26. A) Mean baseline and post-treatment LA area (cm²) at ventricular end-diastole. B) Baseline and post-treatment LA area (cm²) at ventricular end-diastole displayed as mean; error bars indicate standard error of the mean. See figure 14 for reminder of key.

Figure 27. A) Mean baseline and post-treatment LA volume (mL) at ventricular end-systole measured by modified Simpson’s method. B) Baseline and post-treatment LA volume (mL) measured by modified Simpson’s method at ventricular end-systole displayed as mean; error bars indicate standard error of the mean. See figure 15 for reminder of key.
Figure 28. A) Mean baseline and post-treatment LA volume (mL) at ventricular end-diastole measured by modified Simpson’s method. B) Baseline and post-treatment LA volume (mL) at ventricular end-diastole measured by modified Simpson’s method displayed as mean; error bars indicate standard error of the mean. See figure 14 for reminder of key.

Figure 29. A) Mean baseline and post-treatment LA volume (mL) at ventricular end-systole measured by prolate ellipsoid method. B) Baseline and post-treatment LA volume (mL) measured by prolate ellipsoid method at ventricular end-systole displayed as mean; error bars indicate standard error of the mean. See figure 15 for reminder of key.
Figure 30. A) Mean baseline and post-treatment LA volume (mL) at ventricular end-diastole measured by prolate ellipsoid method. B) Baseline and post-treatment LA volume (mL) at ventricular end-diastole measured by prolate ellipsoid method displayed as mean; error bars indicate standard error of the mean. See figure 14 for reminder of key.

Figure 31. A) Mean baseline and post-treatment LV internal dimension (mm) at end-diastole. B) Baseline and post-treatment LV internal dimension (mm) at end-diastole displayed as mean; error bars indicate standard error of the mean. See figure 15 for reminder of key.
Figure 32. A) Mean baseline and post-treatment LV internal dimension (mm) at end-systole. B) Baseline and post-treatment LV internal dimension (mm) at end-systole displayed as mean; error bars indicate standard error of the mean. See figure 15 for reminder of key.

Figure 33. A) Mean baseline and post-treatment LA shortening fraction (%). B) Baseline and post-treatment LA shortening fraction (%) displayed as mean; error bars indicate standard error of the mean. * indicates significant difference compared to baseline.
Figure 34. A) Mean baseline and post-treatment LA shortening area (%). B) Baseline and post-treatment LA shortening area (%) displayed as mean; error bars indicate standard error of the mean. ^ indicates significant difference compared to ivabradine.

Figure 35. A) Mean baseline and post-treatment calculated LA ejection fraction derived from modified Simpson’s method. B) Baseline and post-treatment calculated LA ejection fraction derived from modified Simpson’s method displayed as mean; error bars indicate standard error of the mean.
Figure 36. A) Mean baseline and post-treatment calculated LA ejection fraction derived from prolate ellipsoid method. B) Baseline and post-treatment calculated LA ejection fraction derived from prolate ellipsoid method displayed as mean; error bars indicate standard error of the mean. * indicates significant difference compared to baseline. ^ indicates significant difference compared to ivabradine.
Figure 37. A) Mean baseline and post-treatment calculated LV shortening fraction (%). B) Baseline and post-treatment calculated LV shortening fraction (%) displayed as mean; error bars indicate standard error of the mean. + indicates significant difference compared to pimobendan. ^ indicates significant difference compared to ivabradine.

Figure 38. A) Mean baseline and post-treatment LV isovolumic relaxation time (ms). B) Baseline and post-treatment isovolumic relaxation time (ms) displayed as mean; error bars indicate standard error of the mean. See figure 14 for reminder of key.
Figure 39. A) Mean baseline and post-treatment LAA inflow velocity (cm/s). B) Baseline and post-treatment LAA inflow velocity (cm/s) displayed as mean; error bars indicate standard error of the mean. See figure 14 for reminder of key.

Figure 40. A) Mean baseline and post-treatment LAA outflow velocity (cm/s). B) Baseline and post-treatment LAA outflow velocity (cm/s) displayed as mean; error bars indicate standard error of the mean. See figure 14 for reminder of key.
Figure 41. A) Mean baseline and post-treatment PVF atrial reversal wave velocity (cm/s). B) Baseline and post-treatment PVF atrial reversal wave velocity (cm/s) displayed as mean; error bars indicate standard error of the mean. See figure 14 for reminder of key.

Figure 42. A) Mean baseline and post-treatment calculated PVF atrial reversal wave duration (ms). B) Baseline and post-treatment PVF atrial reversal wave duration (ms) displayed as mean; error bars indicate standard error of the mean.
CHAPTER 4

DISCUSSION

The results of this study demonstrate that in healthy, consciously sedated cats: (1) atenolol significantly depresses global LA and LAA function; (2) pimobendan does not significantly alter indices of LA and LAA function but does decrease LA size; (3) ivabradine has minimal effects on LA and LAA function; and (4) both ivabradine and atenolol decrease heart rate with a greater reduction seen with ivabradine treatment at the doses used.

Although pimobendan has been reported to increase heart rate,\textsuperscript{63,71,79} this effect was not evident in this study. Similarly, there was no consistent or statistically significant change in left atrial function related to pimobendan therapy. Although there was a trend for increases in LAA outflow velocities with pimobendan (Table 8), this did not reach statistical significance ($p = 0.084$). The positive inotropic effects of pimobendan are a result of phosphodiesterase III inhibition resulting in an increase in intracellular calcium, and calcium sensitization of troponin C resulting in an increase in the extent of contraction for a given concentration of cytosolic calcium.\textsuperscript{64} Pimobendan has been shown to increase contractility of isolated papillary muscle preparations and increase LV dP/dt in vivo in cats.\textsuperscript{71,80} It would be anticipated that both LV and LA systolic function might improve following pimobendan, even when noninvasive methods of assessment are used. Although effects of pimobendan on LA function in dogs have not been reported to our
knowledge, the reported changes in LV systolic function in dogs evaluated by echocardiography (FS and EF) have been modest.\textsuperscript{65,81,82} To our knowledge no data have been published describing the effects of pimobendan on LA function in cats or people. However, the calcium sensitizer, levosimendan, has been shown to improve indices of LA function in people with ischemic and decompensated heart failure.\textsuperscript{73,74}

Experimentally, left atrial loading conditions have been found to affect LAA flow velocities in dogs.\textsuperscript{83} As pimobendan reduced LA size in this study, it is possible that the lack of statistically demonstrated positive effect on LA function was due to reduced preload and a negative Frank-Starling effect; Starling’s law has been shown to apply to the atrium.\textsuperscript{84,85} It is also possible that any potential positive effects on LA and LAA function were masked by the administration of ketamine for sedation. Ketamine is classified as a dissociative anesthetic, and the mechanism of action is mainly through antagonism of the N-methyl-D-aspartate (NMDA) receptor.\textsuperscript{86} The cardiovascular effects of ketamine are related to indirect cardiovascular stimulation secondary to sympathomimetic effects through inhibition of sympathetic nerve ending uptake of catecholamines, sympathomimetic effects mediated within the central nervous system and negative inotropic effects on the myocardium. Although there is a direct negative effect on myocardial contractility, increased sympathetic efferent activity increases heart rate, cardiac output and mean arterial pressure in ketamine-anesthetized cats, dogs and people.\textsuperscript{86,87} Additionally, the myocardial substrate in this study was presumably normal; it is possible that the response in diseased tissue would be different. Finally, the number of cats studied was relatively small and while the mean increase with pimobendan
compared to control was approximately 20 cm/s, the statistical power to identify significant differences from other groups may have been insufficient.

In this study pimobendan decreased LA size and volume compared to baseline with significant differences compared to the other treatments. This might be due to the venodilation properties from phosphodiesterase III inhibition reducing preload.\textsuperscript{71,79} Decreases in LA and LV size have been seen previously in studies of pimobendan in dogs with cardiac disease.\textsuperscript{65,82} Additionally, levosimendan, drug similar to pimobendan, resulted in significant decreases in LA volume in people with ischemic heart failure.\textsuperscript{73} Whether this same effect might occur in cats with diseased atria would require further investigation. However, if atrial size were to be decreased by pimobendan in cats with cardiac disease this may impart some protection against development of LA spontaneous echocardiographic contrast and thrombus formation. This could also have potential negative effects as reduced preload could decrease LV filling and cause a reduction in stroke volume. This effect could be particularly detrimental for cats with HCM and LV hypertrophy. Additional investigation of pimobendan on feline LA size and function in the setting of cardiomyopathy and LA enlargement are required to better characterize these effects.

Both atenolol and ivabradine are negative chronotropic drugs due to their ability to reduce the slope of diastolic depolarization.\textsuperscript{88} However, the mechanism by which negative chronotropy is accomplished is different between these drugs. Atenolol, a $\beta_1$-adrenergic receptor blocker reduces heart rate through competitive inhibition of $\beta_1$-adrenoreceptors due to its structural similarity to catecholamines.\textsuperscript{89} The proposed important mechanisms of heart rate acceleration by catecholamines include both the L-
type Ca\(^{2+}\) current (I\(_{Ca-L}\)) and I\(_f\) due to an increase in intracellular cAMP, as cAMP activates the \(f\)-channels.\(^{90}\) Because \(\beta\)-blockers decrease intracellular cAMP levels, a reduction in the I\(_f\) current explains a large proportion of the heart rate lowering effect of this drug class.\(^{56}\) In addition to the effects on chronotropy, \(\beta\)-blockers also negatively impact inotropy, lusitropy and dromotropy.\(^{89}\) However, ivabradine, a selective I\(_f\)-current inhibitor through \(f\)-current blockade, appears to exert only pure negative chronotropic effects at clinically relevant dosages.\(^{56}\)

In this study ivabradine resulted in a significantly greater reduction in heart rate than atenolol in healthy cats at the dosages used. The effects of atenolol and ivabradine on heart rate in healthy cats have also been compared in a recent study (Riesen SC, et al).\(^{91}\) In that study ivabradine and atenolol were administered for four weeks in healthy cats and there was no significant difference on heart rate reduction between the two treatments, with both treatments significantly decreasing heart rate compared to baseline. The mean post-treatment heart rates were not statistically different in that study similar in that study (ivabradine: 135/min; atenolol: 144/min) when compared to the present study (ivabradine: 125.3/min; atenolol: 146.2/min). However, the drug dosages were different and higher in the present study compared to the study of Riesen and colleagues (ivabradine: 0.3 to 0.5 mg/kg q 12h versus 0.3 mg/kg q 12h; atenolol: 1.0 to 1.7 mg/kg versus 1.8 to 2.5 mg/kg q 12h versus 1.0-1.7 mg/kg q 12h).

Atenolol reduced while ivabradine did not significantly alter LA function studies. Prior studies also have shown a reduction in LA systolic function indices following atenolol in cats,\(^{91,d}\) while ivabradine has been shown to preserve global LA function after four weeks of treatment.\(^{91}\) In the current study, after one week of atenolol administration,
Doppler indices of LA and LAA function (LAA-in, LAA-out, PVF A_R and A_D) were depressed. In people LAA flow velocities were also decreased after β-blocker treatment in the setting of atrial fibrillation and mitral stenosis. Additionally, this study showed that global indices of LA function were depressed by atenolol compared to baseline (LA SF and EF by PE method) and ivabradine (LA SA and EF by Simpson’s method). Moreover, the negative effects on LA and LAA function also resulted in increases in LA diameter, area and volume at end ventricular diastole (the minimum LA dimension). Although atenolol and ivabradine are both negative chronotropic drugs and prolong filling time they did not significantly alter LA size indices at ventricular end-systole (maximum LA dimension). Additionally, unlike the negative inotrope atenolol, ivabradine did not affect ventricular end-diastolic LA size. Based on these effects on LA function and size, this study further supports the concern that atenolol could increase the risk for thrombus formation and ultimately arterial thromboembolism. Therefore caution is recommended when using atenolol, particularly in the face of underlying LA enlargement, reduced LA function, or presence of spontaneous echocardiographic contrast or thrombus within the LA or LAA.

Ivabradine as an I_f current inhibitor is considered solely a negative chronotrope. However, it has been shown to have some effect on inotropy, although at doses greatly exceeding those required for negative chronotropic effects. Thus the overall lack of significant effects on LA function in this study was not unexpected. Ivabradine did however significantly reduce LAA inflow velocities, although to a lesser extent than the reduction seen after atenolol. One proposed mechanism for this is slower, more gradual filling at the slower heart rate induced by ivabradine. This effect could also contribute to
the reduction in LAA inflow velocities observed after atenolol, along with the negative effects of beta blockade on myocardial relaxation. To our knowledge, the effects of If-inhibitors on LA or LAA function in people have not been reported. In the study performed by Riesen, et al

91, ivabradine also affected LA function minimally, with only pulmonary venous flow S:D decreased after four weeks of ivabradine administration. In an invasive study evaluating effects of ivabradine on LV and LA function indices in healthy cats and in cats with HCM, a measure of LV contractility (+dP/dt) was decreased by ivabradine in cats with HCM, however other variables of systolic function were not affected. Furthermore, ivabradine had minimal effects on LA performance with only LA fractional area change being significantly increased.5 Based on those findings and those of the present study, ivabradine may be a suitable alternative to atenolol as a negative chronotrope in cats, especially if there is impaired LA function. However, additional studies evaluating the long-term effects in cats with cardiomyopathy are required; particularly effects on mortality, thromboembolic complications, outflow obstruction, and congestive heart failure.

Average within-subject day to day repeatability was acceptable for most of the variables used to assess LA size and function in this study. However, other variables showed lower repeatability during the baseline period based on the calculated coefficients of variation.30 Furthermore, not all cats in this study responded similarly in terms of directional change or percent change during the treatment periods (see Figures). There will be inherent biologic variability related to echocardiographic recordings with influences from physiologic effects, behavioral reactions to environment and stress responses.30,93 However, it is also possible that there was biologic variability in how the
cats responded to the drugs, or the combined effects of the drugs and the sedative protocol. There is additionally, recording variability with echocardiography that is influenced by compliance of the patient during the study, transducer placement, echo system settings, imaging planes, and other sonographer-based factors. In this study we attempted to control for potential sources of error related to recording variability by standardizing recording system settings, using a standard sedation protocol, and performing echocardiograms in the same quiet environment for the duration of the study.

The administration of sedation also may have impacted evaluation of LA and LAA function. Ketamine, has been shown to increase sympathetic outflow increasing systemic and pulmonary arterial blood pressure, heart rate, cardiac output, cardiac work, and myocardial oxygen consumption, while decreasing peripheral vascular resistance. A study evaluating the effects of ketamine on m-mode echocardiographic values in cats revealed a reduction in LVIDd and shortening fraction, while LVIDs and LA dimensions were unchanged. Acepromazine, a phenothiazine sedative, decreases mean arterial pressure within 30 minutes of IM administration in conscious cats. In conscious dogs decreases in stroke volume, cardiac output and mean arterial blood pressure occur after IV administration. Butorphanol, an agonist-antagonist opioid, has the least cardiovascular side effects of the three sedative drugs used. The sedation protocol was given at a standardized dosage, at the same time prior to echocardiography and administered by the same investigator; thus, the side effects should have been constant between and within cats.

Several study limitations, in addition to the effects of sedation, must be acknowledged. This study was performed in healthy cats with presumably normal left
atrial function. It is possible that the effects of these drugs on left atrial size and function could be very different in cats affected with cardiac disease. Another limitation of this study was the relatively small sample size of nine cats, which limited statistical power for identifying differences. This might have affected results for LAA outflow velocities, which might be expected to increase with pimobendan treatment (Figure 40).

Echocardiographic examinations were limited by these normal cats owing to high heart rates and relatively small atria: each of these factors make border detection more difficult, particularly in the ventricular end-diastolic frames when atrial size is the smallest. Furthermore, due to the high heart rates in the baseline and pimobendan treatment periods, transmitral flow and diastolic tissue Doppler velocity profiles exhibited fused E and A waves, precluding further analysis of these diastolic events. Additionally the maximal LA size occurred during or after the P-wave on simultaneous ECG so that passive and active components of LA transport function could not be separated. There was no gold standard (magnetic resonance imaging, or invasive measures) used for the assessment of LA size and function and no attempt was made to index variables to changing heart rate, in part because we could not isolate the combined effects (inotropic, chronotropic, vascular and autonomic) during atenolol and ivabradine therapies. Variables were no indexed for changing heart rate. Lastly, there was only one dosage administered for each study drug and it is possible that dose response effects could have been observed if different dosages were compared. The accidental misdosage of ivabradine in one cat that was to receive pimobendan was unlikely to have significantly affected the results. Mean heart rate during pimobendan treatment was compared with that cat excluded from analysis and there was minimal difference between means (223 ±
27/min compared to 221 ± 35/min). Additionally, mean LAA-out was also insignificantly changed (101.4 cm/s versus 104 ± 31 cm/s). Statistical analysis results were unchanged for the pimobendan treatment period for these two variables.

In conclusion, this study indicates that pimobendan reduced LA and LV size although LA function indices were not significantly changed in these healthy cats. The reduction in chamber dimensions could impart some protective effect in cats with cardiomyopathy and LA dilation, however further studies in cats with naturally occurring disease are warranted. Ivabradine resulted in minimal effects on LA and LAA function while significantly reducing heart rate suggesting this drug may be a safer negative chronotropic agent compared to atenolol in cats with HCM, particularly in the face of LA dilation and dysfunction. Atenolol results in a reduction in LA and LAA function, which could impart an increased risk for development of thromboembolic complications.
FOOTNOTES


bCober RE. Effects of ivabradine, a new selective If current inhibitor, on heart rate in cats. Master’s Thesis, 2010, The Ohio State University, Columbus, OH

cRiesen SC. Effects of ivabradine on heart rate and left ventricular function in healthy cats and cats with hypertrophic cardiomyopathy. PhD Dissertation: Studies on Myocardial Funny Channels and the Funny Current Inhibitor Ivabradine in Healthy Cats and Cats with Hypertrophic Cardiomyopathy, 2010, The Ohio State University, Columbus, OH: 56-96.

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