Published in final edited form as:

J Vet Cardiol. 2011 December ; 13(4): 231–242. doi:10.1016/j.jvc.2011.06.001.

Pharmacodynamic effects of ivabradine, a negative chronotropic agent, in healthy cats

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Abstract

Objective—To determine the pharmacodynamic effects of oral ivabradine in cats.

Animals—Eight healthy, adult domestic short hair cats.

Methods—Each cat underwent four study periods of 24 h, receiving either one dose of placebo or ivabradine (0.1 mg/kg, 0.3 mg/kg, and 0.5 mg/kg) in a single-blind randomized crossover study. Clinical tolerance was assessed hourly for the first 8 h, at 12 h, and at the end of the 24-h study period. Heart rate and blood pressure were monitored continuously for 18–24 h via radiotelemetry after each treatment. Response to stress (acoustic startle) was studied before ($t = 0$) and after treatment ($t = 4$ h). Statistical comparisons were made using a linear mixed models and 1-way and 2-way repeated measures ANOVA.

Results—Heart rate (min^{-1}) decreased significantly ($P < 0.05$) in a dose-dependent manner with peak negative chronotropic effects observed 3 h after ivabradine (mean $\pm$ SD; placebo, 144 ± 20 ; ivabradine 0.1 mg/kg, 133 ± 22 ; ivabradine 0.3 mg/kg, 112 ± 20 ; and ivabradine 0.5 mg/kg, 104 ± 11). Heart rate (min^{-1}) was still reduced ($P < 0.05$) 12 h after ivabradine (0.3 mg/kg; 128 ± 18 and 0.5 mg/kg; 124 ± 16) compared to placebo (141 ± 21). The tachycardic response to acoustic startle was significantly ($P < 0.01$) blunted at all 3 doses of ivabradine. Myocardial oxygen consumption estimated by the rate-pressure product was significantly reduced ($P < 0.05$) for all doses of ivabradine. No effect of ivabradine on systolic, diastolic, and mean blood pressure was identified and no clinically discernable side effects were observed.

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Conflict of interest

This study was funded by an American College of Veterinary Internal Medicine Cardiology Resident Research Grant and the Ohio Animal Health Foundation. Presented in part as an abstract at the 2010 ACVIM Forum in Anaheim, Ca. The authors have no conflict of interest. 240 R.E. Cober et al.

Conclusion—These findings indicate that a single oral dose of ivabradine predictably lowers heart rate, blunts the chronotropic response to stress, and is clinically well tolerated in healthy cats. This makes ivabradine potentially interesting in the treatment of feline heart disease where ischemia is of pathophysiologic importance.

Keywords

I_f inhibition; Heart rate; Tachycardia; Feline

Introduction

Hypertrophic cardiomyopathy (HCM) is the most common cardiac disease in cats.^{1–7} The progression of HCM is variable with many cats having a long asymptomatic period that may end with the abrupt development of congestive heart failure, arterial thromboembolism, or sudden cardiac death. Potential negative prognostic indicators for decompensation of HCM include increased left atrial size^{8,9} and elevated heart rate (HR).¹⁰ Tachycardia is a major contributor to increased myocardial oxygen consumption. High HR limits diastolic coronary blood flow decreasing myocardial perfusion, may induce myocardial ischemia ultimately leading to tissue fibrosis, decreases diastolic chamber filling, and increases LV end diastolic pressure. As HCM is a disease characterized by abnormal ventricular myocardium, ischemia, and replacement fibrosis, unwanted tachycardia may in fact be detrimental in cats with HCM. While the association between HR and outcome or disease severity has not yet been proven causal in cats with HCM, studies using logistic regression analysis found HR to be an independent variable of outcome in people with a variety of cardiovascular disorders including coronary artery disease.^{11,12} Although the pathogenesis of acute decompensation of otherwise clinically stable cats with HCM is not fully understood, anecdotal evidence suggests that stressful events leading to unwanted periods of tachycardia may lead to decompensation of previously stable asymptomatic patients with HCM to suddenly develop congestive heart failure.^{7,8,10,13}

Treatment of cats with preclinical HCM has been directed at relieving LV outflow tract obstruction and controlling tachycardia with beta-adrenergic receptor blockers and calcium channel antagonists via their negative chronotropic and inotropic properties. However, adverse effects and contra-indications exist for these medications. As a result other agents may be useful in controlling unwanted tachycardia in cats with HCM.

The “funny” current (I_f) is abundant in the sinoatrial node and is a voltage-gated time-dependent non-selective cation inward current that becomes activated at hyperpolarized membrane potentials. Activation of I_f leads to increased membrane permeability to sodium and potassium causing a less negative membrane potential. It is considered to be the major current underlying spontaneous diastolic depolarization. The funny current also modifies the HR response to autonomic stimuli.^{14,15} Increased sympathetic tone leads to the formation of cyclic-adenosine-monophosphate through stimulation of beta-receptors. Cyclic-adenosine-monophosphate binds directly to I_f activating it at a less negative potential which increases the slope of early diastolic depolarization, and therefore increases HR. Parasympathetic stimulation does the opposite. Blockade of I_f, similar to vagal activation, decreases the slope

of spontaneous diastolic depolarization resulting in HR reduction. Ivabradine is a highly selective I_f current inhibitor approved for use in people with ischemic heart disease and stable angina and may be of use as a therapeutic agent in cats with HCM.

The objectives of this study were to determine the effects of a single dose of oral ivabradine on HR, blood pressure, surrogate measures of myocardial oxygen consumption, and stress-induced tachycardia in healthy cats. We hypothesized that ivabradine will reduce HR in a dose and time-dependent manner, will not affect systemic blood pressure, will blunt the tachycardic response to stress, and will reduce myocardial oxygen consumption as assessed by the rate-pressure product (RPP).

Animals, materials and methods

Animals

The study protocol (2008A0154) was approved by the Animal Care and Use Committee of The Ohio State University, and all cats were housed and treated in compliance with NIH Guidelines for the Care and Use of Laboratory Animals. Eight domestic short hair cats, acquired from an established in-house colony of healthy cats ($n = 3$) and cats with a history of feline interstitial cystitis (FIC; $n = 5$), were used in this study. There were 5 spayed females and 3 neutered male cats. Ages ranged from 4 to 9 years (mean $\pm$ SD, 6.3 ± 1.7 years) and body weight from 3 to 6.3 kg (mean $\pm$ SD, 5.1 ± 1.3 kg). All cats had previously been instrumented with telemetric transmitter devices^d capable of continuously recording invasive blood pressure (systolic, diastolic, and mean) and HR using proprietary software.^e All data were stored digitally for later review. Prior to enrollment, all cats underwent a thorough physical examination; resting ECG; 2D, M-Mode and Doppler echocardiography; systolic blood pressure (SBP) measurement; and blood biochemical analyses including total T4 concentration (in cats six years of age or older) to rule out pre-existing cardiac or systemic disease. Interstitial cystitis was judged to be controlled (non-active, asymptomatic) based on review of daily clinical observation sheets indicating lack of pollakiuria, dysuria, hematuria, inappetence or vomiting within the previous seven days and during the entire study period. None of the cats were on any medical treatment.

Study design

Repeated, randomized, single-blind, placebo-controlled study using a crossover design. This four-treatment four-period crossover study enrolled 8 cats, with each given a unique sequence of treatments. Each cat underwent four study periods of 24 h, and was randomized^f to receive either one dose of placebo or ivabradine^g (0.1 mg/kg, 0.3 mg/kg, and 0.5 mg/kg). The washout period between treatments was at least 48 h. All cats were housed in individual cages during the entire 24-h data acquisition period with the exception of two periods where stress was induced by acoustic startle. Telemetric devices were set to continuously record blood pressure and HR at a sampling rate of two per minute. Complete ECG data were also

^dPhysioTel D70PCTP, Data Science International, St. Paul, MN.

^eData Science International, St. Paul, MN.

^fGraphPad QuickCalc, GraphPad Software, Inc., La Jolla, CA.

^gIvabradine®, Servier, Les Laboratoires Servier, Neuilly-sur-Seine, France.

recorded and could be accessed for later data analysis. Baseline recordings were made over a time period of 30 min prior to acoustic startle with the cats resting quietly in their cages. The cats were then moved to a separate room where acoustic startle was applied for 15 min to induce stress leading to increased HR. Thereafter, the cats were returned to their cages and received placebo or ivabradine (Fig. 1). Medications were given orally, using Pill Pockets.^h Placebo was defined as a Pill Pocket not containing ivabradine. Cats were monitored for 5 min afterward to assure proper drug administration. The cats were then left in their cages and assessed hourly for 8 h, at 12 h, and at the end of the study period for adverse drug effects. Four hours after drug administration, the cats were again moved to the startle room to undergo another 15-min acoustic startle period. The cats were then returned to their cages for the remainder of the 24-h study period. Due to limited access of monitoring equipment only one cat per day was studied.

Acoustic Startle

Response to acoustic startle was studied using a custom-built wooden chamber platform (35 × 70 × 2.5 cm) to which an open wire cage (20 × 29 × 26 cm) was attached. Testing was performed in a quiet room with an ambient noise level of 60–65 dB. Labtec speakersⁱ were positioned approximately 12 cm from each end of the cage. The speakers were connected to a 250 W amplifier^j capable of delivering a computer generated white noise acoustic pulse of varying intensity (80–120 dB), with a 2.5 ms rise and fall time. For testing, cats were placed into the wire cage on the platform within 5 min of leaving their home cage. They were given a 5-min acclimation period followed by a 118 dB pulse delivered randomly twice per minute for 15 min. At the end of the startle period, the cats returned to their original location. This method has recently been validated to stimulate the sympathetic nervous system leading to increased sympathetic tone and HR in cats (Buffington CAT, personal communication). For final data analysis of the startle response, four 15-min periods were considered: Pre-startle 1 (baseline before first startle), Startle 1 (first startle), Pre-startle 2 (baseline before second startle), and Startle 2 (second startle; Fig. 1).

Clinical findings

Daily observation sheets were generated for each cat during each study period and compared to observations made prior to the study. Quantitative and qualitative variables evaluated were related to food and water intake, bowel movements, and urinations. All cats were also evaluated for vomiting, ocular or nasal discharge, shedding, grooming, hair coat quality, vocalizations, weakness or signs of other abnormalities including salivation, oral or skin lesions, itching, pain, or increased respiratory rate and effort.

Heart rate

Telemetric devices were programmed using the Dataquest ART 3.1 software^f to record, store, and average HRs and tabulate data in a Microsoft Office Excel^k worksheet. Heart

^hGreenies, Franklin, TN.

ⁱLabtec, Vancouver, WA – range 70 Hz-20 kHz.

^jTandy Corp., Fort Worth, TX.

^kMicrosoft Corporation, Redmond, WA.

rates were recorded for the entire study period of approximately 24 h and averaged into hourly HRs. For purposes of data analysis, a baseline period and post-treatment hours 1, 2, 3, 4, 8, and 12 were analyzed and compared. The first 30 min of the study (prior to Pre-startle 1) were averaged to obtain a resting baseline HR. Heart rates during each 15-min pre-startle and startle periods (Pre-startle 1, Startle 1, Pre-startle 2, and Startle 2) were also averaged. Pre-startle 1 was used as a separate baseline for comparison to Startle 1 and Pre-startle 2 was used as a separate baseline for comparison to Startle 2. Hourly HRs were also averaged to obtain an average HR over the entire study period. The minimum instantaneous HR (defined as the lowest 30 s-averaged HR recorded during the entire study period) was determined for all cats at all drug doses. The mean and range of all minimum instantaneous HRs for each treatment period was then calculated.

Blood pressure and rate-pressure product

Telemetric devices were programmed to record, store, and average systolic, diastolic, and mean arterial blood pressure and transfer data to a Microsoft Office Excel^k worksheet. Blood pressure was then averaged into hourly blood pressures. As a surrogate measure of myocardial oxygen consumption,¹⁶ the RPP was calculated from the mean hourly HRs and the mean hourly systolic blood pressures: $RPP = HR \times SBP$.

ECG analysis

All QRS complexes of all studies ($n = 32$) were reviewed to identify the total number and type of ectopic complexes and periods of other arrhythmias present during each study period.

Statistical analysis

Statistical analyses were performed with commercially available software.^{l,m} Data were evaluated for normality with the D'Agostino and Pearson test and are reported as mean $\pm$ SD, unless stated otherwise. Linear mixed-effects models were used to analyze serial HR and blood pressure (systolic, diastolic, and mean). The models included fixed effects of treatment dose (placebo, and ivabradine 0.1, 0.3, and 0.5 mg/kg), time after treatment (1 h, 2 h, 3 h, 4 h, 8 h, and 12 h), the interaction of dose and time, order of drug administration, baseline measures as a covariate, and animal as a random effect. A carry-over effect was deemed unlikely and thus was not considered in our statistical analyses. The 48-h washout period seemed sufficiently long based on the results of a previously performed pharmacokinetic study in healthy cats¹⁷ and reports from studies in people and experimental animals.^{18–20} A 2-way repeated measures ANOVA and a Holm-Sidak post-hoc test were used to evaluate differences between the treatments and the pre-startle and startle periods, and to determine if there were interactions between treatment and startle response. Differences among treatment groups with regard to average HR and RPP during the whole study period were determined using a 1-way repeated measures ANOVA and a Tukey's post-hoc test. Values of $P \leq 0.05$ were considered significant for all analyses.

^lGraphpad Prism, Graphpad Software, Inc., La Jolla, CA.

^mSAS version 9.1, SAS Institute Inc, Cary, NC.

Results

Heart rate, ECG, and blood pressure data were continuously recorded for at least 22 h after drug for all cats and doses ($n = 32$ studies). In six instances (placebo, $n = 2$; ivabradine 0.1 mg/kg, $n = 1$; ivabradine 0.3 mg/kg, $n = 1$; and ivabradine 0.5 mg/kg, $n = 2$) less than 22 h of data were recorded. The lack of data recording was due to cats moving beyond the maximal wireless connection between the telemetry transmitter and the recording plate of the data acquisition system. The lack of recording periods occurred sporadically between hours 18 and 24 corresponding with sleep activity.

Clinical findings

No major adverse effects were seen during the study period. A total of seven days of decreased appetite was seen in three out of the eight study cats. Placebo was administered on three of these days and ivabradine on four days. One day of decreased appetite corresponded to the administration of ivabradine 0.1 mg/kg, two days to ivabradine 0.3 mg/kg, and one day to ivabradine 0.5 mg/kg. One cat had a single episode of diarrhea and another cat vomited once. The diarrhea was seen on the day of administration of ivabradine 0.3 mg/kg whereas the vomiting occurred after treatment with placebo.

Heart rate

Administration of ivabradine induced a time-dependent negative chronotropic effect compared to baseline and placebo that lasted for at least 12 h with the lowest HR occurring approximately 3 h after drug administration (Fig. 2; Table 1). Heart rate was also affected in a dose-dependent manner, with lower HRs at higher dosages of ivabradine (Fig. 2). Compared to placebo, HR was significantly lower ($P < 0.05$) after ivabradine 0.1 mg/kg (at hours 2, 4, and 8), ivabradine 0.3 mg/kg (at hours 1, 2, 3, 4, 8, and 12), and ivabradine 0.5 mg/kg (at hours 1, 2, 3, 4, 8, and 12). Compared to ivabradine 0.1 mg/kg, HR was significantly lower ($P < 0.05$) after ivabradine 0.3 mg/kg and ivabradine 0.5 mg/kg at hours 2, 3, 4, 8 and 12 except for ivabradine 0.3 mg/kg at hour 12. Ivabradine 0.5 mg/kg also significantly lowered ($P < 0.05$) HR compared to ivabradine 0.3 mg/kg at hours 3 and 4 (Table 1).

Average HR recorded over the entire study period was decreased for all doses of ivabradine (Fig. 3). More specifically, for the 22-h duration of recording, mean HR after ivabradine 0.1 mg/kg ($138 \pm 7 \text{ min}^{-1}$), 0.3 mg/kg ($132 \pm 10 \text{ min}^{-1}$), and 0.5 mg/kg ($130 \pm 13 \text{ min}^{-1}$) were significantly ($P < 0.05$) decreased compared to placebo ($148 \pm 7 \text{ min}^{-1}$). Both ivabradine 0.3 mg/kg ($132 \pm 10 \text{ min}^{-1}$) and 0.5 mg/kg ($130 \pm 13 \text{ min}^{-1}$) significantly ($P < 0.05$) decreased HR compared to ivabradine 0.1 mg/kg ($138 \pm 7 \text{ min}^{-1}$), but no significant ($P > 0.05$) differences were found between HR after ivabradine 0.3 mg/kg and ivabradine 0.5 mg/kg.

The minimum instantaneous HR for all drug doses was above 80 min^{-1} for all cats. Placebo and ivabradine 0.3 and 0.5 mg/kg were associated with instantaneous HRs below 90 min^{-1} (mean and min-max, 112 min^{-1} and $84\text{--}134 \text{ min}^{-1}$; 94 min^{-1} and $83\text{--}114 \text{ min}^{-1}$; and 88 min^{-1} and $81\text{--}104 \text{ min}^{-1}$; respectively). The minimum instantaneous HR for ivabradine 0.1 mg/kg was 100 min^{-1} (mean and min-max, 107 min^{-1} and $100\text{--}133 \text{ min}^{-1}$). The minimum

instantaneous HR for placebo, ivabradine 0.1, 0.3, and 0.5 mg/kg occurred approximately 2 h 10 min, 5 h 5 min, 7 h 12 min, and 5 h 20 min after drug administration, respectively.

Acoustic Startle

No significant ($P > 0.05$) difference in HR between groups was found during Pre-startle 1 nor was there a significant ($P > 0.05$) difference in HR between groups during Startle 1 (Fig. 4). In all groups, the 15-min baseline startle (Startle 1) significantly elevated HR compared to Pre-startle 1 ($P < 0.001$; Fig. 4). Heart rate decreased significantly for all treatment groups between Startle 1 and Pre-startle 2 ($P < 0.05$; Fig. 4). During Pre-startle 2, HR after ivabradine 0.3 mg/kg and ivabradine 0.5 mg/kg was significantly lower than HR after placebo and ivabradine 0.1 mg/kg ($P < 0.001$). However, there was no statistical difference between placebo and ivabradine 0.1 mg/kg or ivabradine 0.3 mg/kg and 0.5 mg/kg ($P = 0.886$ and $P = 0.683$, respectively; Fig. 4; Table 1). Heart rate was significantly higher during Startle 2 compared to the Pre-startle 2 for all treatments ($P < 0.001$; Fig. 4). However, HR during Startle 2 was significantly lower than during Startle 1 for all doses of ivabradine ($P < 0.01$; Fig. 5). Heart rates after placebo were not significantly different between Startle 1 and Startle 2 ($P = 0.941$). During Startle 2, HR was significantly lower after ivabradine 0.1 mg/kg, 0.3 mg/kg, and 0.5 mg/kg compared to placebo ($P < 0.05$). Ivabradine 0.3 mg/kg and ivabradine 0.5 mg/kg caused significantly lower HRs than ivabradine 0.1 mg/kg (both $P < 0.01$; Fig. 4; Table 1), whereas no HR difference between ivabradine 0.3 and ivabradine 0.5 mg/kg was found ($P = 0.171$).

Blood pressure and rate-pressure product

Compared to placebo, no significant differences ($P > 0.05$) between treatments were found for SBP at hours 1, 2, 3, 4, 8, and 12 except for ivabradine 0.3 mg/kg at hour 12 (Fig. 6). No significant difference ($P > 0.05$) between treatments was found between diastolic blood pressure at hours 1, 2, 3, 4, 8, and 12 except for ivabradine 0.3 mg/kg at hours 1 and 12 and ivabradine 0.5 mg/kg at hour 12 compared to placebo. No significant differences ($P > 0.05$) between treatments were found between mean blood pressure at hours 1, 2, 3, 4, 8, and 12 except for ivabradine 0.3 mg/kg at hour 12 compared to placebo. Ivabradine 0.1 mg/kg ($15,148 \pm 1010 \text{ mmHg} \cdot \text{min}^{-1}$), ivabradine 0.3 mg/kg ($14,444 \pm 1603 \text{ mmHg} \cdot \text{min}^{-1}$), and ivabradine 0.5 mg/kg ($14,977 \pm 1932 \text{ mmHg} \cdot \text{min}^{-1}$) significantly decreased the whole study RPP compared to placebo ($P < 0.0003$; $16,415 \pm 1132 \text{ mmHg} \cdot \text{min}^{-1}$; Fig. 7). There were no significant differences in the RPP ($P > 0.05$) between ivabradine 0.1 mg/kg, 0.3 mg/kg, or 0.5 mg/kg (Fig. 7).

ECG

A total of 14 single uniform ventricular premature complexes (VPCs) were noted for all eight cats at all doses administered. Three VPCs were associated with two cats given placebo, nine with two cats given ivabradine 0.1 mg/kg, and two with one cat given ivabradine 0.5 mg/kg. No other arrhythmias were noted.

Discussion

The results of this study indicate that a single, oral dose of ivabradine in healthy cats: (1) is clinically well tolerated; (2) decreases HR in a time and dose-dependent manner without clinically relevant effects on systemic blood pressure; (3) blunts stress-induced increases in HR; (4) may reduce myocardial oxygen consumption; and (5) does not induce ventricular ectopy.

Ivabradine has been shown to have similar effects on HR in other species including rabbits, rats, dogs, and people. These effects are related to the selective inhibition of I_f currents in the sinoatrial node leading to a decrease in the slope of diastolic depolarization, thus reducing HR.^{18–22} Ivabradine primarily suppresses the sinoatrial node with only mild or no effect on other myocardial tissues.¹⁹ Consistently, ivabradine has been shown to be devoid of direct negative inotropic, lusitropic or dromotropic effects in healthy people and animals.^{19–27} However, a recent study in anesthetized cats with HCM performed in our laboratory suggested that ivabradine, administered intravenously, has mild negative inotropic and lusitropic effects.²⁸

Our findings indicate that in cats, similar to other species, oral ivabradine has a time-dependent effect on HR with peak HR reduction occurring approximately 3 h after administration and duration of action lasting at least 12 h. This is in agreement with ivabradine's pharmacokinetic properties recently reported from healthy cats.¹⁷ Ivabradine also reduces HR in a dose-dependent manner with higher doses (0.3 and 0.5 mg/kg) causing statistically significant and clinically relevant larger reductions of HR compared to a lower dose of ivabradine (0.1 mg/kg).

Ivabradine was clinically well tolerated without evidence of adverse effects. The most commonly reported side effects in people treated with ivabradine include visual symptoms (luminous phenomena) and bradycardia. Less commonly reported are VPCs, headache, and nausea.^{20,29–32} The visual symptoms are described as increases in brightness in limited areas of the visual field in people and are related to ivabradine's inhibition of another hyperpolarization-activated cyclic nucleotide channel (I_h) in the retina.³¹ The visual effects appear to be dose related and transient in nature. Changes in vision were not directly examined in our cats; however, none of the cats appeared to have obvious visual impairment or deficits during the study period. Sinus bradycardia occurred in 3.7% of people during long-term safety and efficacy trials using oral ivabradine (5.0–7.5 mg, q 12 h) however, only 0.2% experienced clinically significant symptomatic bradycardia.²⁰ These results were not different from patients treated with atenolol. While the lowest instantaneous HR in our cats was 81 min⁻¹ with ivabradine and 84 min⁻¹ after placebo, there was no evidence of symptoms associated with bradycardia such as weakness, fatigue, hypotension, or syncope. Furthermore, the lowest instantaneous HR after placebo was not different from that observed after the maximum dose of ivabradine. Although we did not find any clinical signs of bradycardia, such as weakness and fatigue, our cats were not housed or allowed to exercise in the manner of a typical pet cat. It is possible that if the cats were allowed to exercise freely they may have exhibited clinical signs. Future studies are needed to fully elucidate potential side effects of ivabradine.

Although ventricular arrhythmias were reported after administration of ivabradine in people, the incidence of such events was not different from placebo, amlodipine, or atenolol and most likely was caused by concurrent disease rather than the drug administered.²⁰ Our cats experienced a very low number of VPCs during the entire study period, and a dose–effect relationship was not observed. Furthermore, the number of VPCs in this study is no different than the number of VPCs over 24 h as previously published in normal cats.^{31,32}

Nausea is a reported side effect in people receiving ivabradine.³² The most common gastrointestinal sign in the cats of this study were decreased appetite occurring in 3 cats for a total of 7 (22%) study days. Inappetance, however, was not only associated with administration of ivabradine but also placebo, with no difference in frequency between the two treatments. Therefore, it is unlikely that the decreased appetite observed was solely related to ivabradine.

The normal average daily HR in healthy cats has previously been studied using 24-h Holter ECG monitoring.^{33,34} Average daily HRs of 165 min⁻¹ and 157 min⁻¹ have been reported with³³ and without³⁴ effects of age on mean HR. Results from our study with regard to mean 22-h HR in the placebo group (148 min⁻¹) are in agreement with the findings from previous studies.^{33,34} Furthermore, compared to the mean daily HR in the placebo group and results of mean daily HR in other studies,³⁴ all doses of ivabradine decreased mean 22-h HR in our cats, indicating that it has a consistent negative chronotropic effect in healthy cats.

MacGregor et al³⁵ and Quinones et al³⁶ evaluated the pharmacokinetic and pharmacodynamic effects of orally administered atenolol in healthy cats. These studies revealed that atenolol induces a time-dependent effect on HR that lasts for at least 12 h with peak serum concentrations and HR-lowering effects observed one to 2 h after administration.^{35,36} This led to the conclusion that atenolol should be administered twice daily for effective HR control in cats. Our study revealed a similar effect of ivabradine on mean HR in healthy cats with a slightly different peak effect, but a comparable duration of action. These findings indicate that ivabradine given at a dose of 0.3 and 0.5 mg/kg may have similar negative chronotropic effects as atenolol. Assuming a lack of drug accumulation with repeated dosing¹⁷ twice daily administration may be appropriate for clinical use.²⁸

In people, elevated HR is considered an independent risk factor for cardiovascular mortality. A landmark study in people, the BEAUTIFUL trial,¹¹ concluded that patients with coronary artery disease, LV dysfunction, and a 24-h average HR >70 min⁻¹ had an increased risk of cardiovascular death, admission to the hospital for heart failure, and admission for myocardial infarction.^{11,37} In one retrospective study of 56 cats with HCM,¹⁰ a HR >200 min⁻¹ at admission was a negative prognostic indicator for survival, although this finding was not reported from other retrospective studies on feline HCM.^{8,9} Potential reasons for the devastating effect of non-physiologic HR is that tachycardia may decrease myocardial perfusion by limiting diastolic coronary blood flow and increase myocardial oxygen consumption and thereby induce or worsen myocardial ischemia. Ischemia in turn aggravates diastolic dysfunction, causes Ca²⁺ overload, triggers apoptosis and arrhythmias, and induces myocardial fibrosis; changes that all may lead to progression of heart disease.

In this study, acoustic startle was used to increase HR and thus was applied to mimic the naturally-occurring sympathetic stimulation observed after stress. Previous studies evaluating pharmacologically-induced or physical stress on HR in normal cats revealed that isoproterenol, physical restraint, and hospitalization are effective in increasing HR.^{36,38,39} In this study, acoustic startle increased HR in all cats supporting the concept that this method leads to sympathetic stimulation. The results of this study also indicate that ivabradine blunts peak HR response to acoustic startle in healthy cats. Moreover, while ivabradine was able to diminish peak HR response to startle it did not completely nullify the positive chronotropic response to startle in these cats. Similar to ivabradine, atenolol reduced the HR response after isoproterenol challenge in cats³⁶ suggesting comparable effects of both drugs in their ability to blunt tachycardic responses to sympathetic activation. These results are of clinical relevance as ivabradine may be useful in the prevention of sudden and unwanted periods of tachycardia.

Experimental studies of ivabradine in people, dogs, and rats have shown that it does not affect systemic arterial blood pressure,^{23,27,40} findings confirmed in this study. Although ivabradine at 0.3 mg/kg and 0.5 mg/kg reduced blood pressure at 12 h, the magnitude of the reduction observed did not appear to be clinically relevant, and a true cause-effect relationship between ivabradine administration and blood pressure reduction could not clearly be demonstrated. As a pure negative chronotrope in normal cats,²⁸ no overall direct effect on cardiac output or blood pressure would be expected with I_f inhibition by ivabradine. In dogs and rats, direct effects on vasoreactivity were not observed with ivabradine.^{23,40}

There are limitations to this study. First, to reduce the number of tests and to maintain statistical power for detection of meaningful differences, statistical comparisons were only made for selective time points or were derived from pooled data for the entire study period. As a result, we may have missed significant changes for HR and blood pressure at other time points. Due to the lack of data analysis beyond 12 h after administration of ivabradine, the exact duration of the effect of a single dose of oral ivabradine cannot be stated. Another limitation is that 5 out of 8 cats used in this study had previously been diagnosed with FIC. Interstitial cystitis may be associated with higher baseline sympathetic tone as determined by increases in plasma norepinephrine concentrations in cats with FIC compared to healthy controls.⁴¹ Cats with symptomatic FIC may also have an exaggerated response to acoustic startle as demonstrated in people with FIC.⁴² Finally, cats with HCM, the disease in which ivabradine may potentially be clinically useful, were not studied. Therefore, caution is advised in the extrapolation of our findings to cats with naturally-acquired HCM.

In conclusion, our study indicates that ivabradine can be safely administered to healthy cats at single doses of 0.1, 0.3, and 0.5 mg/kg, PO. Ivabradine 0.3 mg/kg and ivabradine 0.5 mg/kg consistently reduces HR and the tachycardic response to stress. Furthermore, it will most likely have to be administered twice daily for clinical use. Further studies in cats with HCM are needed to clinically validate our findings.

Abbreviations

FIC	Feline Interstitial Cystitis
HCM	Hypertrophic Cardiomyopathy
HR	Heart Rate
LV	Left Ventricle
RPP	Rate-Pressure Product
SBP	Systolic Blood Pressure
VPC	Ventricular Premature Contraction

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Figure 1.

Study timeline. A: Pre-startle 1–15-min time period before first acoustic startle; B: Startle 1–15 min time period during first acoustic startle; C: Pre-startle 2–15-min time period before second acoustic startle; and D: Startle 2–15-min time period during second acoustic startle.

Figure 2.

Mean hourly heart rate (min^{-1}) in eight cats determined before (baseline) and after oral administration of placebo and one dose of ivabradine (0.1 mg/kg, 0.3 mg/kg, and 0.5 mg/kg; A). Mean $\pm$ SD hourly heart rate (min^{-1}) before and after oral administration of placebo and ivabradine (0.1 mg/kg, B); ivabradine (0.3 mg/kg, C); and ivabradine (0.5 mg/kg, D). *, significant differences ($P < 0.05$) compared to placebo. †, significant differences ($P < 0.05$) compared to ivabradine (0.1 mg/kg). ‡, significant differences ($P < 0.05$) compared to ivabradine (0.3 mg/kg). Data were compared statistically only at hours 0, 1, 2, 3, 4, 8, and 12. ●, placebo; ■, ivabradine (0.1 mg/kg); ▲, ivabradine (0.3 mg/kg); and ◆ ivabradine (0.5 mg/kg).

Figure 3.

Mean $\pm$ SD 22-h average heart rate (min^{-1}) in eight cats after oral administration of placebo and one dose of ivabradine (0.1 mg/kg, 0.3 mg/kg, and 0.5 mg/kg). See Fig. 2 for remainder of key.

Figure 4.

Mean $\pm$ SD 15-min average heart rate (min^{-1}) in eight cats before and after acoustic startle.

A) Baseline periods: before first startle (Pre-startle 1) and during first startle (Startle 1); B)

Treatment periods: before second startle (Pre-startle 2) and during second startle (Startle 2).

See Fig. 2 for remainder of key.

Figure 5.

Mean $\pm$ SD 15-min average heart rate (min^{-1}) in eight cats during first (Startle 1) and second acoustic startle (Startle 2). *See Figs. 2 and 4 for remainder of key.*

Figure 6.

Mean $\pm$ SD hourly systolic arterial blood pressure (mmHg) in eight cats determined after oral administration of placebo or one dose of ivabradine (0.1 mg/kg, 0.3 mg/kg, and 0.5 mg). See Fig. 2 for remainder of key.

Figure 7.

Mean $\pm$ SD 22-h rate-pressure product (mmHg*min⁻¹) in eight cats after oral administration of placebo and one dose of ivabradine (0.1 mg/kg, 0.3 mg/kg, and 0.5 mg/kg). *See* Fig. 2 for remainder of key.

Table 1

Mean $\pm$ SD hourly heart rate (min^{-1}) in 8 cats after oral administration of placebo and one dose of ivabradine (0.1 mg/kg, 0.3 mg/kg, and 0.5 mg/kg).

Time (h)	Placebo	Ivabradine (mg/kg)		
		0.1	0.3	0.5
Baseline	147 $\pm$ 21	153 $\pm$ 8	154 $\pm$ 20	158 $\pm$ 12
1	156 $\pm$ 27	152 $\pm$ 24	149 $\pm$ 19 ^{a,b}	144 $\pm$ 23 ^{a,b}
2	146 $\pm$ 19	133 $\pm$ 16 ^a	119 $\pm$ 18 ^{a,b}	109 $\pm$ 15 ^{a,b}
3	144 $\pm$ 20	133 $\pm$ 22	112 $\pm$ 20 ^{a,b}	104 $\pm$ 11 ^{a,b,c}
4	157 $\pm$ 24	141 $\pm$ 19 ^a	120 $\pm$ 13 ^{a,b}	116 $\pm$ 14 ^{a,b,c}
5	167 $\pm$ 29	139 $\pm$ 18	128 $\pm$ 20	118 $\pm$ 14
6	156 $\pm$ 30	133 $\pm$ 20	128 $\pm$ 14	117 $\pm$ 11
7	157 $\pm$ 29	139 $\pm$ 18	131 $\pm$ 19	119 $\pm$ 15
8	157 $\pm$ 26	144 $\pm$ 16 ^a	127 $\pm$ 23 ^{a,b}	126 $\pm$ 19 ^{a,b}
9	148 $\pm$ 20	150 $\pm$ 28	135 $\pm$ 11	130 $\pm$ 26
10	146 $\pm$ 16	144 $\pm$ 22	124 $\pm$ 11	129 $\pm$ 22
11	146 $\pm$ 25	138 $\pm$ 15	125 $\pm$ 15	128 $\pm$ 19
12	141 $\pm$ 21	135 $\pm$ 16	128 $\pm$ 18 ^a	124 $\pm$ 16 ^{a,b}
13	143 $\pm$ 18	137 $\pm$ 17	126 $\pm$ 20	133 $\pm$ 17
14	145 $\pm$ 17	132 $\pm$ 14	132 $\pm$ 26	137 $\pm$ 21
15	143 $\pm$ 17	132 $\pm$ 16	133 $\pm$ 20	132 $\pm$ 20
16	149 $\pm$ 25	140 $\pm$ 22	135 $\pm$ 16	138 $\pm$ 20
17	149 $\pm$ 25	135 $\pm$ 12	136 $\pm$ 17	140 $\pm$ 21
18	142 $\pm$ 21	133 $\pm$ 15	138 $\pm$ 18	141 $\pm$ 27
19	139 $\pm$ 16	132 $\pm$ 14	144 $\pm$ 25	143 $\pm$ 25
20	141 $\pm$ 16	140 $\pm$ 25	134 $\pm$ 23	149 $\pm$ 25
21	141 $\pm$ 22	133 $\pm$ 11	131 $\pm$ 18	132 $\pm$ 15
22	142 $\pm$ 19	134 $\pm$ 11	141 $\pm$ 28	126 $\pm$ 17

^a Significant differences ($P < 0.05$) compared to placebo.

^b Significant differences ($P < 0.05$) compared to ivabradine (0.1 mg/kg).

^c Significant differences ($P < 0.05$) compared to ivabradine (0.3 mg/kg). Data were compared only at hours 0, 1, 2, 3, 4, 8, and 12.