J Vet Intern Med 2014;28:838–846

Acute Effects of Ivabradine on Dynamic Obstruction of the Left Ventricular Outflow Tract in Cats with Preclinical Hypertrophic Cardiomyopathy

K.A. Blass, K.E. Schober, X. Li, B.A. Scansen, and J.D. Bonagura

Background: Ivabradine is a negative chronotropic drug with minimal effects on central hemodynamics. Its effect on dynamic obstruction of the left ventricular outflow tract (LVOT) in cats with hypertrophic cardiomyopathy (HCM) remains unknown.

Hypothesis/Objectives: Ivabradine reduces dynamic obstruction of the LVOT in cats with HCM.

Animals: Twenty-eight client-owned cats with preclinical HCM and dynamic LVOT obstruction.

Methods: Randomized, double-blind, active-control single dose study. Cats received a single dose of either ivabradine (0.3 mg/kg PO) or atenolol (2 mg/kg PO). Heart rate, echocardiographic variables, and systolic blood pressure (SBP) were recorded before and 3 hours after drug administration. Statistical comparisons were made using ANCOVA.

Results: Peak velocity in the LVOT was significantly decreased compared to baseline for both drugs; however, the effect was more prominent with atenolol (mean reduction 2.53 m/s; 95% CI 2.07–3.13 m/s) compared to ivabradine (mean reduction 0.32 m/s; 95% CI −0.04 to 0.71 m/s; $P < .0001$). Echocardiographic indices of systolic function were largely unchanged by ivabradine, but significantly reduced by atenolol.

Conclusions and Clinical Importance: A single dose of ivabradine decreases dynamic LVOT obstruction in cats with HCM, but the clinical effect is negligible and inferior compared to that achieved by atenolol.

Key words: Atenolol; Feline; I_f current; Systolic anterior motion.

Hypertrophic cardiomyopathy (HCM) is the most common cardiac disease in cats.[1] The majority of cats with HCM develop dynamic obstruction of the left ventricular (LV) outflow tract (LVOT) and secondary mitral regurgitation (MR) as a result of hyperdynamic LV function and systolic anterior motion (SAM) of the anterior, and rarely posterior, mitral valve leaflet,[2] potentially leading to clinical signs and disease progression.[3]

Presence of SAM is a negative prognostic indicator in people with HCM and is an independent predictor of disease progression, heart failure status, and risk for worsening of exercise tolerance, stroke, and death attributable to cardiac disease.[3] Whereas similar studies addressing adverse clinical outcomes associated with dynamic LVOT obstruction in cats are sparse, with conflicting results on the prognostic importance of SAM from retrospective studies reported,[2,4,5] comparative aspects of human and feline HCM make it appealing to believe that reduction of moderate and severe SAM would also be beneficial in cats.

Abbreviations:

AMVL	anterior mitral valve leaflet
Ao V_{max}	peak flow velocity at the level of the aortic valve
CW	continuous wave
DE	Doppler echocardiographic
ET	left ventricular ejection time
HCM	hypertrophic cardiomyopathy
HR	heart rate
IVS	interventricular septum
LA	left atrial
LA_{area} s	maximum left atrial area at end-systole
LAD	maximum left atrial cranial-caudal dimension
LV	left ventricular
$LVID_d$	maximum left ventricular internal dimension at end-diastole
$LVID_s$	maximum left ventricular internal dimension at end-systole
LVOT V_{max}	peak flow velocity in the left ventricular outflow tract
LVOT	left ventricular outflow tract
LVPW	left ventricular posterior wall
MR	mitral regurgitation
PEP : ET	ratio of left ventricular pre-ejection period to ejection time
PEP	left ventricular pre-ejection period
PW	pulsed wave
S_a	peak systolic velocity of the lateral mitral annulus
SAM	systolic anterior motion
SBP	systolic blood pressure
SF	left ventricular shortening fraction

The most commonly prescribed medications used to reduce dynamic LVOT obstruction in cats are beta-adrenergic blockers, particularly atenolol. Beta-blockers exhibit both negative inotropic and chronotropic effects, thus leading to reduction in LVOT obstruction, as well as improvement in LV filling and coronary perfusion times. However, these drugs may also induce

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Submitted August 19, 2013; Revised November 27, 2013; Accepted January 20, 2014.

DOI: 10.1111/jvim.12331

adverse effects on inotropy and lusitropy, and the long-term use of beta-blockers in feline HCM continues to be controversial because of lack of efficacy data on clinical signs, disease progression, or survival.[6,7]

Ivabradine is a novel heart rate (HR) lowering agent that acts by selectively inhibiting the pacemaking I_f current in the sinoatrial node.[8] Ivabradine's unique HR lowering properties and minimal effects on myocardial function are evident in healthy cats and cats with HCM.[9,10] The drug is apparently safe, enhances left atrial (LA) function, and short- and long-term administration is not inferior to atenolol with regard to effects on cardiac performance.[10–13] However, the effects of ivabradine on dynamic LVOT obstruction in cats with HCM have not been studied and comparative data from studies in other species are lacking. If ivabradine was able to reduce LVOT obstruction to a clinically relevant degree, it might become a potential new treatment option for cats with preclinical HCM. The objectives of this study were to compare the effects of a single dose of ivabradine or atenolol on dynamic LVOT obstruction in cats with preclinical HCM. We hypothesized that ivabradine reduces dynamic obstruction of the LVOT in cats with HCM.

Materials and Methods

Animals

Twenty-eight consecutive client-owned cats examined between 2011 and 2013 with preclinical HCM and dynamic LVOT obstruction were enrolled in this study. For all cats, HCM was previously diagnosed based upon idiopathic LV hypertrophy (global or regional diastolic LV wall thickness ≥6 mm)[2] as determined by 2D echocardiography. Dynamic obstruction of the LVOT was defined for this study by a resting LV to aortic root systolic pressure gradient >25 mmHg or midventricular obstruction with a midventricular systolic pressure gradient >25 mmHg as determined by 2D and Doppler echocardiography (DE)[2] using peak velocity in the LVOT and the modified Bernoulli equation. Echocardiographic criteria for SAM included an abrupt bend of the tips of the anterior or both mitral valve leaflets, with the distal tip of the respective leaflet approaching or contacting the interventricular septum (IVS) in systole, and evidence of flow turbulence and increased LVOT velocities with a dagger-shaped flow signal reflecting dynamic obstruction.[2,14] Criteria for mid-LV obstruction included the presence of a mid-LV systolic pressure gradient unrelated to SAM as detected by DE. Peak flow velocity in the LVOT (LVOT V_{max}) was measured from a left apical LV outflow view[15] using continuous wave (CW) Doppler.

Before enrollment, health status was determined in all cats based on physical examination; 2D, M-mode, and DE; systolic blood pressure (SBP) measurement; and plasma thyroid hormone (T4) analysis in cats older than 6 years as well as younger cats if clinical signs suggestive of hyperthyroidism were observed. Exclusion criteria included the presence of any cardiac disease other than HCM based on established echocardiographic criteria,[16] systemic hypertension (SBP >170 mmHg),[17] hyperthyroidism, concurrent pulmonary or bronchial disease, renal disease, any other systemic disease, a resting HR <120 bpm or resting SBP <100 mmHg, brady- and tachyarrhythmias, congestive heart failure, intracardiac thrombi, LA spontaneous echocardiographic contrast, ongoing treatment with other cardiac medications, and poor animal compliance. All screening examinations were performed by either the principal investigator (K.A.B.) or coinvestigator (K.E.S.). The study protocol was reviewed and approved by the Animal Care and Use Committee of The Ohio State University (2010A00000157).

Study Design

The study was a prospective, randomized, double-blind, active-control single dose study. After echocardiographic phenotyping, animals were randomly assigned and divided into 2 groups: 1 group received a single dose of the active-control drug atenolol[a] (target dose 2 mg/kg PO) and the other group received a single dose of the study drug ivabradine[b] (target dose 0.3 mg/kg PO, selected based on results of previous studies of this drug in cats).[12] To ensure that an acceptable number of cats received the study drug, randomization was performed in a 2 : 1 manner in favor of ivabradine. To assure blinding of the investigators and objectivity of the data, assignment of drug was randomized by 1 investigator not involved in the data acquisition process with the help of a random numbers generator. Moreover, both drugs were placed in identical opaque capsules. All cats were assessed at baseline and after drug administration by physical examination, indirect SBP measurement,[c] and echocardiography by a single investigator (K.A.B.). Auscultation was performed at rest, immediately after lifting the cat up and down 5–8 times, and immediately after inhalation of amyl nitrite to assess for any changes in heart rate and murmur intensity induced by such stressors.[d, 18] The latter 2 activities were performed in random order as chosen by a 3rd party, a registered veterinary technician not involved in the study, though the investigator was not blinded as to the order of these stressors. Amyl nitrite administration was performed as follows:[19] a single glass capsule containing 0.3 mL of 98% amyl nitrite liquid (294 mg) was crushed between the fingertips, with the liquid immediately transforming into a vapor. The crushed capsule was held in front of the cat's nasal planum over 1 minute so that several inhalations were allowed.

After a 10-minute rest period, an echocardiographic examination was performed, followed by DE measurement of LVOT V_{max} during artificial noise intended to invoke stress on the cats (Doppler audio signal maximized for 10–30 seconds; referred to as "noise stress"). After an additional 5-minute rest period, SBP was measured. Cats were then randomized to receive the active control or the study drug. Three hours after administration of either drug, the above-mentioned procedures were repeated. Cats were housed in a quiet, cat-only ward between examinations.

Echocardiography

Cats were gently restrained in right and left lateral recumbency without the use of sedation and imaged from underneath. All echocardiographic studies were performed by 1 investigator (K.A.B.) using a digital high-end ultrasound system[e] with 10 MHz and 7 MHz nominal frequency transducers preset for optimal feline imaging and DE studies. Two-dimensional images were recorded at >80 frames/s. Simultaneous ECG and Doppler images were recorded at 150 mm/s sweep speed. Doppler flow recordings were guided by 2D color-coded DE imaging with appropriate settings to observe low velocity signals. Assessments, measurements, and calculations were performed off-line from digitized still images or cine loops as an average of 3 cardiac cycles, irrespective of the phase of respiration, using the embedded software and calculation packages[f] by a single investigator (K.A.B.) blinded to treatment group.

Echocardiographic variables included: From the right parasternal long-axis view, short-axis view, and long-axis view optimized

for the LV outflow tract—subjective assessment of the presence of dynamic obstruction of the LVOT based on 2D, M-mode, and color flow Doppler; pattern of LV hypertrophy (symmetrical or asymmetrical); dimensions of the IVS and left ventricular posterior wall (LVPW) at end-diastole from both long- and short-axis 2D images; assessment of LV hypertrophy severity using arbitrarily determined categories based on maximum diastolic wall thickness measurements (mild: 6.0–6.9 mm; moderate: 7.0–7.9 mm; severe: >8.0 mm); distance of the anterior mitral valve leaflet (AMVL) coaptation point to the IVS at end-systole and end-diastole; the presence, direction, and subjective severity[20] of MR based on color flow Doppler; the maximum LA cranial-caudal dimension from the long-axis 4 chamber view (LAD);[21] and the maximum LV internal dimensions at end-systole (LVIDs) and end-diastole (LVIDd) from a short-axis image. From the left parasternal apical 3 or 4 chamber and LV outflow views—peak systolic velocity of the lateral mitral annulus (S_a); LV pre-ejection period (PEP); LV ejection time (ET); the ratio of PEP to ET (PEP : ET); LVOT V_{max} using CW Doppler; mid-LV V_{max} using CW Doppler; the maximum flow velocity at the level of the aortic valve (Ao V_{max}) using pulsed wave (PW) Doppler; and the maximum MR velocity using CW Doppler. The echocardiographic variables measured during "noise stress" were LVOT V_{max} and Ao V_{max} using both PW and CW Doppler from the left apical 3 or 5 chamber view. LV shortening fraction (SF) was calculated as $\{(LVIDd - LVIDs)/LVIDd \times 100\}$, and the maximum LA area in systole (LA_{area} s) was determined by planimetry along the endocardial borders of the LA, excluding the pulmonary veins, from the right parasternal long-axis view.

Measurement reliability was determined for continuous echocardiographic variables. Previously recorded echocardiograms from 6 cats (3 from each study group) were randomly selected to undergo repeated analyses 3 times by 1 observer (K.A.B.) to determine intraobserver measurement variability. The same studies were analyzed once by a 2nd independent observer (K.E.S.) to determine interobserver measurement variability. Both investigators were blinded to the results of the prior echocardiographic analyses.

Assessment of Obstruction and Systolic Function

Dynamic LVOT obstruction was assessed using (1) loudness of the systolic murmur (Grades I-VI/VI), (2) presence of SAM or mid-LV obstruction from 2DE and color Doppler images, (3) severity of MR (+, ++, +++),[20] and (4) LVOT V_{max}, which included peak velocity of mid-LV obstruction if SAM was not present. LV systolic function was assessed using SF, S_a, and PEP : ET.

Statistical Analysis

Statistical analyses were performed with commercially available software.[g] All data were graphed and visually inspected and tested for normality (Kolmogorov–Smirnov test) and equal variance (*F*-test), and transformed if necessary to normal distribution using logarithmic transformation. Descriptive statistics were calculated for all clinical and echocardiographic variables; these are presented as mean ± standard deviation (SD) except for data that failed tests for normality, which are presented as median and range (minimum to maximum). The main statistical procedures included a paired *t*-test to assess the effect of treatment on variables within each treatment group, repeated measures analysis of variance to study the effects of drugs and maneuvers on HR, and analysis of covariance (ANCOVA) to assess differences in response pattern (change scores) between treatment groups, with posttreatment measurement serving as the outcome variable and both treatment group and baseline measurements serving as covariates. Differences in baseline measurements between treatment groups were also compared using an unpaired *t*-test if normally distributed. Data that were not normally distributed were analyzed using a Mann–Whitney rank sum test. Statistical significance was determined at alpha = 0.05. Measurement variability was calculated using the formula: Coefficient of variation (CV) = mean difference between measurements/average of measurements × 100 and expressed in percent.

Results

Forty-two cats with heart murmurs suggestive of dynamic LVOT obstruction were screened, of which 28 met the inclusion criteria. Reasons for noninclusion were too low of a pressure gradient, poor animal compliance, a diagnosis of cardiac disease other than HCM, the presence of mild congestive heart failure, and the discovery of concurrent disease after the time of screening.

No major adverse effects were detected during the study. Four cats had ptyalism during inhalation of amyl nitrite, which rapidly resolved in all cats after withdrawal of the ampule. Inhalation of amyl nitrite could not be performed in 1 cat because of a temporary lack of drug availability.

Demographic data, results of physical examination under all 3 auscultation conditions, and categorical echocardiographic findings, both before and after treatment, are summarized in Table 1. All cats with SAM during the baseline echocardiogram had color flow Doppler evidence of MR, but none of the cats with only mid-LV obstruction. MR was directly caudally in all cats.

Baseline Variables

A comparison of physical examination findings, echocardiographic measurements, and blood pressure measurements at baseline between groups is shown in Table 2. There was a significant difference between groups for Doppler SBP, with baseline SBP being higher in the atenolol group ($P < .0001$). In addition, the AMVL was longer in the ivabradine group ($P = .03$). For all other variables, there was no significant difference between groups at baseline.

Effects of Treatment on Variables

The effects of the 2 treatments on HR, SBP, flow velocities, and echocardiographic variables are summarized in Tables 3 and 4.

Effects on Heart Rate. Ivabradine lowered HR at rest (Fig 1) and HR response to up and down lifting and inhalation of amyl nitrite (all $P < .0001$). Similarly, atenolol lowered HR under all 3 conditions (all $P < .0001$). When comparing treatment-induced change scores of resting HR between treatment groups, there was no difference between the 2 treatments ($P = .61$).

Effects on Peak Blood Flow Velocity. Both ivabradine and atenolol lowered LVOT V_{max}, including V_{max} associated with mid-LV obstruction in cats without

Table 1. Demographic data, results of physical examination, and selected echocardiographic variables in 28 cats with hypertrophic obstructive cardiomyopathy at baseline (before) and 3 hours after (after) oral administration of a single dose of ivabradine (n = 18) or atenolol (n = 10). Age and body weight presented as mean (± SD).

	Ivabradine		Atenolol	
	before	after	before	after
Age (years)	5.9 ± 3.6	–	6.8 ± 3.8	–
Breed	17 DSH 1 Maine Coon	–	9 DSH 1 Persian	–
Sex	17 MC 1 MI	–	7 MC 3 FS	–
Body weight (kg)	5.52 ± 0.97	–	5.27 ± 1.25	–
Murmur—at rest (0–6/6)				
0	0	0	0	4
1	0	1	0	1
2	2	4	0	5
3	8	11	9	0
4	8	2	1	0
5	0	0	0	0
6	0	0	0	0
Gallop—at rest (n)	3/18	3/18	0/10	0/10
Systolic anterior motion (n)	16/18	16/18	9/10	5/10
Mid-LV obstruction (n)	2/18	2/18	1/10	1/10
Pattern of LV hypertrophy	13/18 symmetric 5/18 asymmetric	–	7/10 symmetric 3/10 asymmetric	–
Severity of LV hypertrophy	7 mild 5 mod 6 sev	–	6 mild 2 mod 2 sev	–
Mitral regurgitation (n)	16/18	15/18	9/10	4/10
Severity of MR (0–3/3)				
0	2	3	1	6
1	3	2	3	3
2	13	13	6	1
3	0	0	0	0

MC, male castrated; MI, male intact; FS, female spayed. See Abbreviations for remainder of key.

Table 2. Comparison of baseline measurements between cats before oral administration of either ivabradine (n = 18) or atenolol (n = 10). Variables are expressed as mean (± SD) unless stated otherwise.

Variable	Ivabradine	Atenolol	*P*
Age (years)	5.9 ± 3.6	6.8 ± 3.8	.52
BW (kg)	5.52 ± 0.97	5.27 ± 1.25	.56
HR at rest (bpm)	200 (170–260)[a]	212 ± 27	.89
HR after lifting (bpm)	226 ± 26	227 ± 29	.89
HR after amyl nitrite (bpm)	218 ± 27	220 ± 34	.81
LVPWd—Lax (mm)	6.61 ± 1.01	6.15 (5.61–7.82)[a]	.31
IVSd—Lax (mm)	7.31 ± 0.85	6.83 ± 0.71	.14
LVPWd—Sax (mm)	6.60 ± 1.02	6.20 ± 0.90	.31
IVSd—Sax (mm)	7.02 ± 0.88	6.62 ± 0.85	.26
AMVL to IVS systole (mm)	3.80 (2.51–4.22)[a]	3.76 ± 0.63	.41
AMVL to IVS diastole (mm)	7.44 ± 1.38	7.98 ± 1.48	.34
$LA_{area}s$ (cm^2)	2.46 (1.58–4.99)[a]	2.46 ± 0.74	.42
LAD_s (mm)	16.25 (13.11–24.80)[a]	15.80 ± 2.96	.36
LVIDs (mm)	4.69 ± 1.05	4.68 ± 1.09	.98
LVIDd (mm)	14.30 ± 1.95	15.55 ± 1.81	.11
Length of AMVL (mm)	12.29 ± 1.02	11.30 ± 1.26	.03
SF (%)	66 ± 8	70 ± 6	.17
S_a (cm/s)	7.17 ± 2.36	8.19 ± 1.92	.26
PEP : ET	0.26 ± 0.04	0.25 ± 0.03	.51
Ao V_{max} (m/s)	1.13 ± 0.25	1.16 ± 0.17	.71
LVOT V_{max} (m/s)[b]	4.22 ± 0.99	4.22 ± 0.98	.99
Ao V_{max} during noise (m/s)	1.15 ± 0.24	1.20 ± 0.18	.58
LVOT V_{max} during noise (m/s)	4.18 ± 1.38	4.05 ± 1.33	.80
SBP (mmHg)	110 ± 8	127 ± 10	<.0001

Unadjusted univariate *P*-values based on Student's *t*-test or Mann–Whitney rank sum test.

[a]Indicates variable expressed as median (min to max).

[b]Indicates inclusion of mid-LV obstruction. BW, body weight; bpm, beats per minute; LVPWd, left ventricular posterior wall in diastole; IVSd, interventricular septum in diastole; Lax, long-axis; Sax, short-axis; $LA_{area}s$, left atrial area in systole; LADs, left atrial diameter in systole. See Abbreviations for remainder of key.

SAM, compared to baseline ($P = .006$ ivabradine; $P < .0001$ atenolol; Fig 2). However, when comparing change scores of LVOT V_{max} between treatment groups, atenolol lowered LVOT V_{max} significantly more ($P < .0001$) compared to ivabradine (Fig 3). The addition of noise stress had no effect on change scores ($P = .0001$). Ivabradine did not change Ao V_{max} both without ($P = .19$) and during ($P = .089$) noise stress. Atenolol lowered Ao V_{max} both without ($P = .002$) and during ($P = .002$) noise stress.

Effects on Indices of LV Systolic Function. Ivabradine did not change LV SF ($P = .41$), whereas atenolol decreased it ($P = .009$). The change score between groups was significantly different ($P = .004$). Ivabradine did not change S_a compared to baseline

Table 3. Mean (± SD) for selected variables in 28 cats at baseline and 3 hours after oral administration of a single dose of ivabradine (n = 18) or atenolol (n = 10).

	Ivabradine			Atenolol		
	before	after	*P*	before	after	*P*
HR—Rest (min^{-1})	200 (170–260)[a]	153 ± 23	<.0001	212 ± 27	156 ± 22	<.0001
HR—Stress (min^{-1})	226 ± 26	167 ± 24	<.0001	227 ± 29	164 ± 21	<.0001
HR—AN (min^{-1})	218 ± 27	159 ± 16	<.0001	220 ± 34	156 ± 20	<.0001
LVOT V_{max} (m/s)	4.22 ± 0.99	3.90 ± 1.19	.006	4.22 ± 0.98	1.68 ± 0.81	<.0001
LVOT V_{max} Noise (m/s)	4.18 ± 1.38	3.70 ± 1.62	.069	4.05 ± 1.33	1.71 ± 0.83	<.0001
Ao V_{max} (m/s)	1.13 ± 0.25	1.10 ± 0.26	.190	1.16 ± 0.17	0.92 ± 0.17	.002
Ao V_{max} Noise (m/s)	1.15 ± 0.24	1.10 ± 0.26	.089	1.20 ± 0.18	0.91 ± 0.17	.002
SF (%)	66 ± 8	67 ± 7	.410	70 ± 6	64 ± 5	.009
S_a (cm/s)	7.17 ± 2.36	6.97 ± 1.77	.240	8.19 ± 1.92	5.43 ± 1.48	.002
PEP (ms)	35 ± 4	36 ± 4	.280	30 ± 4	40 ± 6	.001
ET (ms)	134 ± 15	156 ± 12	<.0001	129 ± 9	146 ± 12	.048
PEP : ET	0.26 ± 0.04	0.23 ± 0.03	.011	0.25 ± 0.03	0.28 ± 0.04	.002
IVS-Coapt syst (mm)	3.80 (2.51–4.22)	3.95 (2.81–4.38)	.025	3.76 ± 0.63	4.05 ± 0.80	.083
IVS-Coapt diast (mm)	7.44 ± 1.38	7.74 ± 1.40	.250	7.98 ± 1.48	7.44 ± 1.08	.270
LADs—Lax (mm)	16.25 (13.11–24.80)	16.82 (13.60–26.00)	.046	15.80 ± 2.96	15.31 ± 2.53	.049
$LA_{area}s$—Lax (cm^2)	2.46 (1.58–4.99)	2.58 (1.89–5.43)	.057	2.46 ± 0.74	2.14 (1.70–3.40)	.130
LVIDs Sax (mm)	4.69 ± 1.05	5.11 ± 1.12	.020	4.68 ± 1.09	5.39 ± 0.81	.020
LVIDd Sax (mm)	14.30 ± 1.95	15.41 ± 1.33	.007	15.55 ± 1.81	15.19 ± 1.29	.220
SBP (mmHg)	110 ± 8	114 ± 13	.300	127 ± 10	120 ± 17	.130

Unadjusted *P*-values for within-treatment group comparisons: Student's *t*-test or Mann–Whitney rank sum test.

[a]Indicates median (min to max) used as data not normally distributed. AN, amyl nitrite; IVS-Coapt, distance of the mitral valve coaptation point to the interventricular septum; syst, systole; diast, diastole. See Abbreviations and Table 2 for remainder of key.

Table 4. Mean change score (pre minus post) for selected variables in 28 cats after oral administration of a single dose of ivabradine (n = 18) or atenolol (n = 10). Both within and between-treatment group comparisons are shown.

Variable	Group	Change	95% CI	*P* (Within Group)	*P* (Between Groups)
HR at rest (bpm)	Iva	59	53, 72	<.0001	–
	Aten	56	41, 68	<.0001	.61
Heart murmur grade	Iva	1	0.23, 1.02	.16	–
	Aten	2	1.18, 2.32	<.0001	<.0001
IVS-Coapt dias (mm)	Iva	−0.31	−0.79, 0.19	.25	–
	Aten	0.24	−0.51, 0.89	.27	.23
IVS-Coapt sys (mm)	Iva	−0.23	−0.29, 0.01	.025	–
	Aten	−0.29	−0.41, 0.01	.083	.43
$LA_{area}s$ (cm^2)	Iva	−0.20	−0.24, 0.08	.057	–
	Aten	0.15	−0.09, 0.36	.13	.020
LADs (mm)	Iva	−0.42	−0.61, 0.10	.046	–
	Aten	0.52	−0.10, 0.40	.049	.006
LVIDs Sax	Iva	−0.42	−0.40, 0.64	.020	–
	Aten	−0.71	−2.10, 0.54	.020	.30
SF (%)	Iva	−1.0	−2.7, 2.1	.41	–
	Aten	6.0	1.7, 8.4	.009	.004
PEP : ET	Iva	0.03	0.01, 0.04	.011	–
	Aten	−0.03	−0.05, 0.00	.002	.0001
LVOT V_{max} (m/s)[a]	Iva	0.32	−0.04, 0.71	.006	–
	Aten	2.53	2.07, 3.13	<.0001	<.0001
LVOT V_{max} Noise (m/s)[a]	Iva	0.35	0.01, 1.01	.069	–
	Aten	2.09	1.83, 3.25	<.0001	.0001
SBP (mmHg)	Iva	−4.0	−10.2, 5.4	.30	–
	Aten	7.0	−7.7, 16.4	.13	.045

[a]Indicates inclusion of mid-LV obstruction. See Abbreviations and Tables 2 and 3 for key.

($P = .24$), whereas atenolol lowered it ($P = .002$). Ivabradine had no effect on PEP ($P = .28$), whereas atenolol prolonged it ($P = .001$). Both ivabradine ($P < .0001$) and atenolol ($P = .048$) increased ET. Ivabradine decreased LV PEP : ET compared to baseline ($P = .011$), whereas atenolol increased it ($P = .002$),

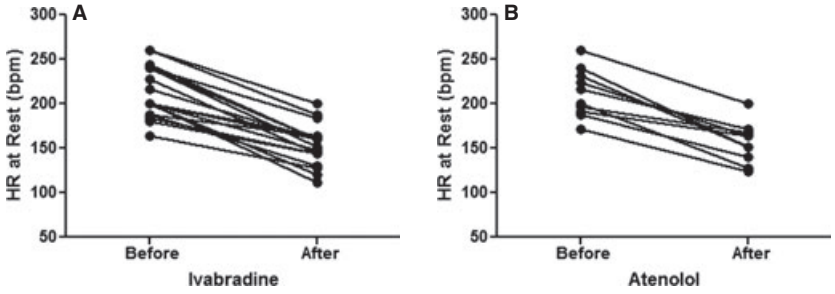

Fig 1. Resting heart rate (HR) before (before) and 3 hours after (after) oral administration of a single dose of ivabradine (panel A, n = 18) or atenolol (panel B, n = 10) in 28 cats with hypertrophic cardiomyopathy.

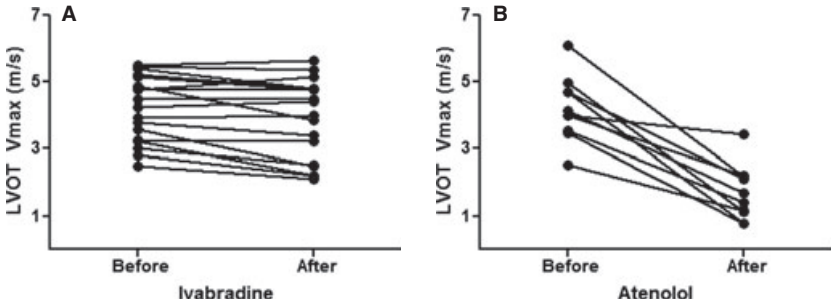

Fig 2. Peak velocity in the left ventricular outflow tract (LVOT V_{max}), including mid-LV obstruction in cats without SAM, before (before) and 3 hours after (after) a single oral administration of ivabradine (panel A, n = 18) or atenolol (panel B, n = 10).

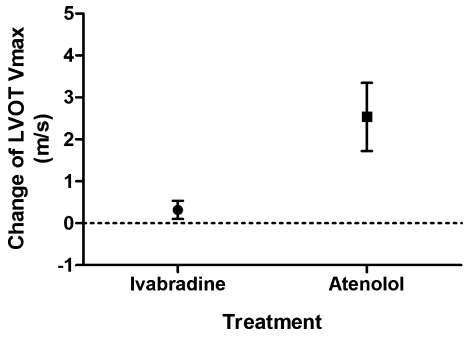

Fig 3. Mean change in peak velocity in the left ventricular outflow tract, including peak velocity of mid-LV obstruction if SAM was not present (LVOT V_{max}; baseline value minus 3-hour post-drug value) with 95% confidence intervals of the mean change in 28 cats with hypertrophic cardiomyopathy after a single dose of ivabradine (n = 18) or atenolol (n = 10).

with a significant difference ($P = .0001$) between treatments.

Effects on 2-D Measurements. Ivabradine increased the distance from the mitral valve coaptation point to the IVS compared to baseline in systole ($P = .025$), whereas atenolol had no effect ($P = .083$). Neither treatment had an effect on the distance from the mitral valve coaptation point to the IVS in diastole ($P = .25$ ivabradine; $P = .27$ atenolol). When comparing the change scores between treatment groups, there was no difference for the distance of the mitral valve coaptation point to the IVS in both systole ($P = .43$) and diastole ($P = .23$). Ivabradine ($P = .046$) increased LAD compared to baseline whereas atenolol ($P = .049$) decreased it, with significant differences in change scores between treatment groups ($P = .006$). Both ivabradine ($P = .37$) and atenolol ($P = .11$) did not change LA_{area} s compared to baseline, though the difference of change scores between treatments was significant ($P = .020$) with atenolol decreased as compared to ivabradine. Both ivabradine ($P = .036$) and atenolol ($P = .045$) increased the short-axis LVIDs compared to baseline, with no difference in change scores between treatment groups ($P = .30$). Ivabradine increased the short-axis LVIDd compared to baseline ($P = .007$), whereas atenolol had no effect on LVIDd ($P = .22$).

Effects on Doppler Systolic Blood Pressure. Both ivabradine ($P = .30$) and atenolol ($P = .13$) did not affect the mean Doppler SBP measurement; however, there was a difference between change scores ($P = .045$), with atenolol lowering SBP relative to ivabradine.

Repeatability Studies

For all variables, the CV for inter- and intraobserver measurement variability was less than 10%.

Discussion

The results of this study indicate that a single dose of oral ivabradine sufficient to significantly reduce HR exerts a statistically significant, but clinically negligible,

effect on dynamic LVOT obstruction in cats with preclinical HCM. This finding was in contrast to the active-control atenolol, which consistently reduced, and in some cases relieved, obstruction while producing similar reductions in HR. Furthermore, there was no evidence that ivabradine aggravates obstruction in any of the cats. Additional findings support the conclusions of other recent studies, notably that ivabradine predictably lowers HR, while having minimal effects on LV systolic function and SBP.[9,10,12] Lastly, there was a counterdirectional change in LA size between the 2 treatments, with a decrease after atenolol administration and an increase after ivabradine administration, although these were small in magnitude.

Ivabradine is a negative chronotropic agent that decreases HR response to sympathetic stimulation, resulting in an increase in diastolic filling time. As SAM seemingly results from altered hydrodynamic forces on the mitral valve leaflets secondary to abnormal geometry of the valve apparatus and the LVOT,[14,22–25] it is reasonable to speculate that ivabradine might be able to reduce obstruction as a result of its negative chronotropically mediated effect on such forces. In addition, the increase in diastolic filling time achieved with ivabradine results in better LV filling, thus increasing the distance between the AMVL and the LVOT at the onset of systole. Furthermore, the negative chronotropic effect of ivabradine should result in a negative Bowditch effect, in which myocardial contractility decreases with decreasing HR.

However, as ivabradine lacks more potent negative inotropic effects, its failure to reduce obstruction in this study suggests that a substantial negative inotropic effect is required to alter the mitral valve outflow tract spatial relationship sufficiently to limit the formation of SAM. A proposed explanation of pressure gradient development in patients with SAM states that an amplifying feedback loop is generated, as early mitral-septal contact induced by rapid LV ejection acceleration creates a narrowed orifice, resulting in a pressure difference, which further forces the leaflet against the septum, decreasing the orifice size and further increasing the pressure difference.[26] Negative inotropic agents such as beta-blockers, by decreasing the ejection acceleration, decrease the force on the mitral valve leaflets in early systole, which delays the development of SAM. Mitral-septal contact occurs later during the ejection period, leaving less time for the aforementioned feedback loop to narrow the orifice, reducing the final pressure difference.[26] In addition, delaying the trigger to SAM could allow more time for papillary muscle shortening to increase chordal tension, which might completely prevent SAM from developing.[25,27] HR reduction alone, as evidenced by ivabradine, does not decrease LV ejection acceleration and, thus, is unable to decrease the force on the mitral valve leaflets that promote SAM. We speculate that the minor reduction in LVOT velocity achieved in this study with ivabradine is likely because of the increased distance between the AMVL and the LVOT measured at the beginning of systole; this could develop secondary to prolongation of diastolic filling or from a negative Bowditch effect.

To evaluate the effect of ivabradine under stress, provocative maneuvers intended to induce dynamic obstruction were performed. Amyl nitrite is a peripheral and coronary venous and arterial vasodilator in humans that also acts to decrease venous return, results in afterload reduction, reflex tachycardia, and a secondary positive inotropic response.[19] The combination of these effects leads to a small but consistent increase in Doppler LVOT V_{max}, which is why amyl nitrite has been used in human patients to identify HCM patients with latent LVOT obstruction.[18] Amyl nitrite has a rapid onset and offset of action after inhalation because of rapid absorption through the pulmonary alveoli and rapid metabolism, probably by hydrolytic denitration.[19] Drug effect should be present within 30 seconds to 1 minute and should last no more than 3–5 minutes. There is no known drug interaction between amyl nitrite and ivabradine or atenolol. This study failed to show any effect of amyl nitrite on heart rate or murmur intensity. A likely explanation of this is the fact that virtually all cats turned their head or backed away from the amyl nitrite capsules, as the inhalant form has an unpleasant odor, and possibly did not inhale a dose sufficient to induce relevant hemodynamic effects. In humans, additional provocative maneuvers such as treadmill exercise, the Valsalva maneuver, and dobutamine infusion are used to induce latent obstruction.[28] These provocative maneuvers aggravate obstruction via activation of the sympathetic nervous system, with an associated increase in the inotropic state. Moreover, human patients who have their provoked gradients reduced or abolished by medications most often exhibit relief or at least a reduction in their clinical signs, thus proposing another argument in support of obstruction relief in these patients.[29]

Lifting of cats up and down and introduction of noise seem to be useful provocations because they reproduce the symptomatic state of a fight-or-flight situation. In this study, HR was reduced by both ivabradine and atenolol at rest and in response to both provocative maneuvers. However, whereas both drugs had a similar effect on HR reduction, only atenolol reduced murmur intensity under both stress conditions. This difference can likely be attributed to greater reduction in LVOT V_{max} and MR achieved with atenolol.

Importantly, this study showed no evidence that a single dose of ivabradine worsens the severity of obstruction, indicating that ivabradine could potentially be safe for use in cats with the obstructive form of HCM. Whereas this study showed no effect of ivabradine on LV SF or S_a in cats with HCM, it did demonstrate that ivabradine reduced LV PEP : ET, suggesting a possible improvement of LV systolic function that, theoretically, could further enhance dynamic outflow obstruction. However, similar to a previous study in healthy cats,[10] this study demonstrated a significant increase in both LV systolic and diastolic

dimensions after the administration of ivabradine, which might prevent worsening of an already present obstruction. As LVIDs is relatively preload independent compared to other echocardiographic variables used in the estimation of LV systolic function, it stands to reason that an increase in LVIDs is suggestive of a decrease in LV systolic function, a finding consistent with that previously found via measurement of the peak rate of LV pressure increase ($+dP/dt_{max}$) in anesthetized cats with HCM.[9] Moreover, the reduction in LV PEP : ET achieved in this study was due solely to ivabradine's effect on LV ET, an expected consequence of heart rate reduction, and might not be indicative of a direct effect on LV systolic function.

Atenolol decreased LA size when compared to ivabradine, which increased it. This finding, whereas modest, differs from previous observations in normal cats, in which there was no significant difference between the response to atenolol and ivabradine after 4 weeks of treatment, both of which resulted in no significant change in LA size.[10] Whereas the difference in treatment period between these 2 studies might, in part, explain this discrepancy, a compelling argument could be made that in HCM cats with obstruction, as opposed to normal cats, by reducing dynamic LVOT obstruction, forward flow is increased, resulting in less MR, which could result in a decrease in LA volume. Indeed, in this study, 5 of 9 cats with baseline MR in the atenolol group had no MR after drug administration, with 3 of the 4 remaining having only mild MR; to the contrary, only 1 of 16 cats with baseline MR in the ivabradine group had no MR after drug administration, with 13 of the cats considered to have moderate MR and only 2 cats having mild MR after treatment.

This study has several limitations. The sample size is relatively small, rendering the study underpowered to fully appreciate the effect of ivabradine on outflow tract obstruction. The lack of a cross-over design did not allow for the evaluation of the effect each drug would have had on each individual cat, which would have eliminated between-subject variability and thus strengthened these results. The dosage of each drug used was based on clinical experience for atenolol and experimental data for ivabradine. Whether these dosages are equivalent with regard to their intrinsic effects in feline HCM remains unknown. All cats enrolled in this study were presumed to be affected with HCM; however, in the absence of definitive genetic or histopathologic confirmation, it is possible that some of the cats could have been affected with mitral valve dysplasia or a secondary cardiomyopathy and should not have been included in the study. Only a single before drug and single after drug echocardiogram was performed on each cat. As dynamic LVOT obstruction is a labile process, the lack of multiple examinations that could confirm reproducibility of these data could potentially lead to the erroneous conclusion that ivabradine significantly reduces the degree of dynamic LVOT obstruction, when in fact, the reduction achieved in this study might solely be because of random variability. Finally, as only a single dose of the study medications was given in this study, these results cannot be extrapolated to assume that chronic usage of either drug would achieve results similar to those achieved in this study.

In conclusion, this study indicates that a single oral dose of ivabradine, while significantly decreasing HR, is ineffective at reducing dynamic LVOT obstruction to a clinically relevant degree in cats with preclinical HCM. In this regard, it was inferior to the "standard therapy" of atenolol. Ivabradine does not appear to aggravate obstruction in this population of cats, and therefore, appears safe to administer, although safety assessment would require clinical studies involving many more cats. Whether ivabradine can be an effective long-term treatment in cats with preclinical HCM because of its ability to reduce HR and its minimal influence on cardiac function requires further study.

Footnotes

[a] Atenolol, Mallinckrodt Inc, St. Louis, MO
[b] Procoralan, Les Laboratoires Servier, 22 Rue Garnier, 92200 Neuilly-sur-Seine, France
[c] Ultrasonic Doppler Flow Detector, Model 811-B, Parks Medical Electronics Inc, Aloha, OR
[d] Amyl Nitrite Inhalants USP, X-Gen Pharmaceuticals Inc, Northport, NY
[e] Vivid 7 Dimension, GE Medical Systems, Milwaukee, WI
[f] EchoPac software package, Version BT06, GE Medical Systems
[g] SAS version 9.1, SAS Institute, Cary, NC

Acknowledgment

Funding: This study was supported by a Cardiology Research Fund at The Ohio State University.

Conflict of Interest: Authors disclose no conflict of interest.

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