

Effects of pimobendan on left atrial transport function in cats

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Abstract

Background: Arterial thromboembolism is a sequela of hypertrophic cardiomyopathy (HCM) in cats related to left atrial (LA) enlargement and dysfunction.

Hypothesis: Pimobendan improves LA transport function in cats.

Animals: Twenty-two client-owned cats with HCM and 11 healthy cats.

Methods: Prospective, double-blind, randomized, placebo-controlled clinical cohort study. Cats were randomized to receive either pimobendan (0.25 mg/kg PO q12h) or placebo for 4 to 7 days. Nineteen echocardiographic variables of LA size and function were evaluated. Statistical comparisons included t tests, analysis of variance, and multivariable analyses.

Results: Peak velocity of left auricular appendage flow (LAapp peak; mean \pm SD, 0.85 ± 0.20 vs 0.71 ± 0.22 m/s; $P = .01$), maximum LA volume ($P = .03$), LA total emptying volume ($P = .03$), peak velocity of late diastolic transmitral flow (A peak velocity; 0.77 ± 0.12 vs 0.62 ± 0.17 m/s; $P = .05$), and A velocity time integral (A VTI; 3.05 ± 0.69 vs 3.37 ± 0.49 ; $P = .05$) were increased after pimobendan. Mean change after pimobendan was larger in cats with HCM compared to healthy cats for LA fractional shortening (2.1% vs -2.1% ; $P = .05$), A VTI (0.58 vs 0.01 cm; $P = .01$), LAapp peak (0.20 vs 0.02 m/s; $P = .02$), LA kinetic energy (3.51 vs -0.10 kdynes-cm; $P = .05$), and LA ejection force (1.93 vs -0.07 kdynes; $P = .01$) in the multivariable model. The stronger effect of pimobendan in cats with HCM was independent of LA size.

Conclusions and Clinical Importance: We identified positive, albeit minor, effects of pimobendan on LA function in cats with HCM. Whether or not treatment with pimobendan decreases the risk of cardiogenic embolism deserves further study.

Abbreviations: 2-D, 2-dimensional; A dur, duration of the transmitral A wave; A peak, peak velocity of late diastolic transmitral flow; A VTI, velocity time integral of the transmitral A wave; ABP, arterial blood pressure; ANOVA, analysis of variance; AR dur, duration of the pulmonary vein flow reversal at atrial contraction; AR peak, peak velocity of the pulmonary vein flow reversal at atrial contraction; ATE, arterial thromboembolism; CHF, congestive heart failure; EF, ejection fraction; FAC, fractional area change; FS, fractional shortening; HCM, hypertrophic cardiomyopathy; IVSd, interventricular septum thickness in diastole; LA, left atrial; LA FAC, left atrial fractional area change; LA FS, left atrial fractional shortening; LA : Ao, left atrial dimension to aorta ratio; LA Amax, maximum left atrial area; LA Amin, minimum left atrial area; LAapp peak, peak velocity of left auricular appendage flow; LAapp' peak, peak velocity of left auricular appendage wall motion; LADmax, maximum left atrial cranial-caudal dimension; LADmin, minimum left atrial cranial-caudal dimension; LAVmax, maximum left atrial volume; LAVmin, minimum left atrial volume; LV, left ventricular; LVIDd, left ventricular internal dimension in diastole; LVIDs, left ventricular internal dimension in systole; LVOT, left ventricular outflow tract; LVPWD, left ventricular caudal wall thickness in diastole; QoL, quality of life; SEC, spontaneous echocardiographic contrast; SV, stroke volume; Vmax, maximum velocity.

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KEYWORDS

arterial thromboembolism, echocardiography, feline, hypertrophic cardiomyopathy, Vetmedin

1 | INTRODUCTION

Arterial thromboembolic disease caused by cardiomyopathy is a common and often fatal clinical disorder in the cat.¹⁻¹³ Cardiac embolism occurs when thrombi formed in the left heart travel in the arterial circulation and lead to obstruction of blood flow causing ischemia, infarction, and necrosis.^{1-4,7-12} Thrombus formation is a complex process, with all factors of Virchow's triad contributing to a variable extent. In cats, the source of the thrombus is most often the left auricular appendage (LAapp).^{1-4,7,8,11}

Studies suggest an incidence of myocardial disease in cats of between 8% and 27% in the general population depending on age, with hypertrophic cardiomyopathy (HCM) comprising >90% of cases.^{5,6,13-15} Any cat with myocardial disease and left atrial (LA) enlargement is at increased risk for arterial thromboembolism (ATE), particularly if LA systolic function is impaired and blood stasis is present.^{2,5,8,11} Long-term prognosis of cats that survive the initial ATE episode is generally poor, with <3% cats with ATE still alive 1 year after the event.^{2-4,11,13}

Hypertrophic cardiomyopathy is a condition associated with left ventricular (LV) diastolic dysfunction leading to LA enlargement and ultimately LA dysfunction in most cats.^{5,6,10,13,16} Conceptually, LA function can be divided into 3 major phases.^{10,17-22} A reservoir phase with volume expansion of the left atrium during ventricular systole is followed by a conduit phase during early ventricular diastole in which blood flows directly from the pulmonary veins via the left atrium into the left ventricle, and lastly an active contractile component occurs in late diastole ("LA booster pump" function) that optimizes LV filling in end-diastole²³ and assures proper LV stroke volume.^{10,17-22} It is presumed that LA and LAapp dilatation as well as poor LA contractile function contribute to local blood stasis and intracardiac thrombus formation in affected cats.^{2,8,11,12,24}

Echocardiography has been used to identify cats at risk of developing ATE.^{2,5,6,8,9,11,20,25,26} Several echocardiographic markers of blood stasis indicative of prothrombotic risk in cats have been identified including LA enlargement, impaired LA systolic function, low LAapp flow velocity, and presence of spontaneous echocardiographic contrast (SEC).^{2,8,11-13,18,20}

Pimobendan is a benzimidazole-pyridazinone derivative that acts as a calcium sensitizer and phosphodiesterase III inhibitor causing mixed vasodilatation and increased inotropy.^{10,27-33} The drug is rapidly absorbed in cats with maximum plasma concentrations occurring 0.9 hours after PO administration.³² Based on pharmacokinetic studies in healthy cats^{27,32} twice daily dosing has been recommended.^{27,32} Data on the positive inotropic effect to the left ventricle have been well-established in dogs³⁴⁻³⁷ but rarely studied in cats,³⁸ and limited data are available on its effect on LA function in cats with cardiomyopathy.^{10,31,33,39}

Our primary hypothesis was that pimobendan would improve LA transport function as determined by echocardiography in apparently

healthy cats and cats with HCM. Secondary objectives were to compare effect size of pimobendan on LA function in cats with HCM vs healthy cats and to determine whether or not the effect of pimobendan on LA function in cats with LA enlargement differs from that in cats with normal LA size.

2 | MATERIALS AND METHODS

The study was approved by the local oversight committees (Clinical Research Committee of the Veterinary Medical Center, protocol #: 2017-19 and the Institutional Animal Care and Use Committee, protocol #: 2017A00000111). Written consent authorizing participation of cats in the study was obtained from all owners.

2.1 | Study population

Between January 2018 and December 2019, 22 cats with evidence of HCM based on global or segmental end-diastolic LV wall thickness ≥ 6 mm⁶ in the absence of any other condition that could cause a similar amount of LV wall thickening and 11 apparently healthy cats were recruited prospectively. Cats were owned by staff, students, and clients of The Ohio State University Veterinary Medical Center. Cats were allocated randomly to receive either pimobendan or placebo. Randomization and drug preparation were carried out by an independent third party (in-house pharmacy) unaware of any patient information other than group assignment (HCM vs healthy). Randomization was performed independently for HCM vs healthy cats to assure equal distribution of pimobendan recipients in both groups.

All cats underwent physical examination and 2-dimensional (2-D), M-mode, and Doppler echocardiography (Vivid E9 with EchoPac software package BT13 version 113.1.3, GE Medical Systems, Waukesha, Wisconsin), systolic arterial blood pressure (ABP) measurement using the Doppler method (Ultrasonic Doppler flow detector, Model 811-B, Parks Medical Electronics Inc, Aloha, Oregon), and had PCV and total solids concentration measured. In cats >6 years of age, plasma total thyroxine concentration (TT4) as well as renal function tests were analyzed. Repeated ABP measurement >160 mm Hg, TT4 > 3.0 $\mu\text{g}/\text{dL}$ (laboratory reference range, 1.0-3.0 $\mu\text{g}/\text{dL}$), and blood urea nitrogen concentration > 50 mg/dL and serum creatinine concentration > 2.8 mg/dL were used to diagnose systemic hypertension,⁴⁰ hyperthyroidism, and advanced renal disease,⁴¹ respectively.

Inclusion categories were subclinical HCM, HCM with recent but not current congestive heart failure (CHF), or apparently healthy cats. Ongoing treatments were permitted but dose changes during the study period and 1 week before enrollment were not allowed.

Exclusion criteria were CHF; dynamic LV outflow tract (LVOT) obstruction with a maximum velocity (LVOT Vmax) >3.5 m/s; systemic hypotension (ABP < 100 mm Hg) or hypertension; renal failure more advanced than International Renal Interest Society stage 2; current treatment with pimobendan, atenolol, or diltiazem; hyperthyroidism; systemic disease; anemia with PCV <25%; thrombi in the left atrium; and client or cat noncompliance.

2.2 | Study design

At baseline (exam 1), cats were enrolled based upon results of history; physical examination findings; 2-D, M-mode, and Doppler echocardiography; blood chemistry results; and ABP results. Thoracic radiography (digital radiography system EDR-6, Sound-Eklin, Carlsbad, California) was performed if clinically indicated. All cats were sedated using butorphanol (0.25 mg/kg IM) before echocardiography.⁴² Additional sedation with acepromazine (0.02-0.1 mg/kg IM)⁴² and gabapentin (50-150 mg PO before presentation to the hospital) was permitted as needed to avoid overt sympathetic stimulation associated with stress.

Cats were enrolled as either diseased (HCM) or apparently healthy and assigned randomly to receive either pimobendan or placebo as described. Target dose of pimobendan (Vetmedin, Boehringer Ingelheim Vetmedica Inc, St. Joseph, Kansas) was 0.25 mg/kg^{27,31,32} PO (range, 0.22-0.28 mg/kg equating to 0.94-1.88 mg/cat q12h) with crushed commercially available 1.25 mg tablets placed into an opaque gelatin capsule. For placebo, identical capsules were used, and filled with lactose powder. Clients were instructed to administer the medication PO, q12h for a minimum of 4 and a maximum of 7 days dependent upon the day of the week of enrollment and owner availability. On the final day of the study (exam 2), clients were instructed to not administer the last dose so that it could be administered in hospital by the principal investigator and the echocardiographic examination performed 90 to 120 minutes after drug administration. On this day, cats received a physical examination, ABP measurement, and echocardiogram. In addition, clients completed a quality of life (QoL) form (modified Cats' Assessment Tool for Cardiac Health⁴³ [mCATCH] questionnaire) once at completion of the study containing 15 questions reflecting on the treatment period and pertaining to the potential impact of the drug on the cat's QoL on a scale of 0 to 5, with 0 being no change and 5 being maximum negative effect (see Supplement 1).

2.3 | Echocardiography

2.3.1 | Image acquisition

Transthoracic echocardiographic examinations were performed in all cats by a single operator (S. L. K.) with the cats gently restrained in lateral recumbency using a commercially available ultrasound machine and phased-array transducers with a nominal frequency of 6.0 or 12.0 MHz. Sweep speed during the recording of the echocardiogram was 50 to 150 mm/s. Right and left long- and short-axis views were used for data acquisition. Two-dimensional cine loops, M-mode, and

Doppler tracings were stored on the internal hard drive of the echocardiography machine and were analyzed offline using a dedicated analysis system (EchoPac, GE Medical Ultrasound, Waukesha, Wisconsin) in a randomized and blinded fashion performed en bloc at the end of the enrollment period (December 2019) without knowledge of cat and drug. Unblinding was only done after all data had been quantified. In all instances, a simultaneous 1-lead ECG was recorded. Measurements were obtained using raw data and digital still images as an average of 3 to 5 cardiac cycles, regardless of respiratory phase.

2.3.2 | Assessment of LA size and function

Two-dimensional echocardiographic variables of LA size were obtained from a right parasternal long-axis 4-chamber view. The maximum LA cranial-caudal dimension (LADmax) was measured at end-ventricular systole in the echocardiographic frame immediately before mitral valve opening.^{18,20,44} Minimum LA diameter (LADmin) was measured from the smallest LA dimension at the conclusion of active atrial contraction. Maximum and minimum LA area (LAAmax, LAAmin) and volume (LAVmax, LAVmin) were obtained during the same time periods as dimensional measurements using planimetry of the LA endocardial borders without inclusion of the pulmonary veins or LAapp and extending from the hinge points of the mitral valve leaflets excluding the coaptation point of the valve leaflets and the modified single plane Simpson's method of disks, respectively. Calculated parameters of global LA mechanical function included LA shortening fraction (LA FS = [(LADmax – LADmin)/LADmax] × 100%), LA fractional area change (LA FAC = [(LAAmax – LAAmin)/LAAmax] × 100%), and LA ejection fraction (LA EF = [(LAVmax – LAVmin)/LAVmax] × 100%).^{18,20,44}

Doppler-derived LAapp flow velocity as a marker of left auricular contractile function was acquired from a tilted left cranial imaging view.^{8,24,45} The LAapp was visualized, and pulsed wave Doppler with a 2 to 3 mm sample volume placed in the midportion of the auricle with the low velocity reject filter set at zero was used to obtain maximum LAapp flow velocity (LAapp peak).^{8,9} Peak velocity of lateral wall motion of the LAapp (LAapp' peak) was determined in the same image plane using pulsed wave tissue Doppler imaging with a 2 to 3 mm sample volume placed in the center of the lateral wall of the LAapp.⁴⁶

Pulmonary venous flow was recorded from a right parasternal short-axis heart base view with a 3 to 4 mm sample volume placed at least 5 mm into the vein.¹⁶ Peak flow velocity (AR peak) and duration at atrial contraction (AR dur) were measured.^{16,25,47}

Left atrial systolic function also was assessed by LA ejection force, LA kinetic energy, and LA total emptying volume.^{17,19,21,22} The LA ejection force is the force developed by the left atrium during atrial systole to push blood into the left ventricle. Using Newton's law, force equals mass × acceleration with mass being the product of the density and volume of blood passing through the mitral annulus during atrial contraction. Left atrial ejection force subsequently was calculated as (0.5 × 1.06 g/cm² × mitral orifice area × peak A wave velocity²) with 1.06 g/cm² being the estimated density of blood and mitral orifice area calculated from the radius of the mitral valve using πr^2 .^{21,48} The mitral valve radius was measured from a right parasternal long axis

4-chamber view using an early diastolic frame. Left atrial kinetic energy is the product of blood mass and velocity squared ($0.5 \times 1.06 \text{ g/cm}^2 \times \text{LA stroke volume} \times \text{peak A wave velocity}^2$) where LA stroke volume is calculated from the velocity time integral (VTI) of the A wave \times mitral valve orifice area.^{17,19,21,22,49} Left atrial total emptying volume (including the sum of passive and active LA emptying volume) was determined as the largest LA volume minus the smallest LA volume from a right parasternal long axis 4-chamber view. This calculation was performed for volumetric measurements as LAVmax minus LAVmin.²¹

2.3.3 | Assessment of LV size and function

Left ventricular size and systolic function were assessed by analyzing 2-D recordings obtained from right parasternal long- and short-axis imaging views. Thickness of the caudal wall (LVPWd) and the interventricular septum (IVSd) as well as LV chamber internal dimensions were measured at end-diastole (LVIDd) and end-systole (LVIDs), and LV FS was calculated from right parasternal long-axis images.^{6,50}

From a left apical 4- or 5-chamber view, LVOT Vmax, transmitral flow patterns, and motion of the lateral mitral annulus were obtained and measured as previously described.^{6,16,47,51,52} Transmitral flow was determined to be separated only if E wave velocity was $<20 \text{ cm/s}$ at the onset of the A wave as described previously.⁵³

2.4 | Observer measurement variation

Interobserver and intraobserver measurement variability was determined for selected echocardiographic variables of LA function. For intraobserver measurement variability, 1 observer (S. L. K.) measured variables of 8 randomly selected cats from each group (5 HCM, 3 healthy). Each variable was measured 3 times and results averaged. This process was repeated on 3 separate occasions. Interobserver variability was determined by 2 observers (S. L. K. and K. E. S.) blinded to each other's measurements of the same variables from the same 8 cats mentioned above. The coefficient of variation (CV) was calculated for each variable.

2.5 | Statistical analysis

Statistical analyses were performed using commercial software (Statistical Analysis Software, version 9.4, SAS Institute Inc, Cary, North Carolina and GraphPad Prism, version 8, GraphPad Software, Inc, San Diego, Carolina). Sample size necessary to identify a significant treatment effect was estimated using an online sample size calculator (ClinCalc.com), pilot data from 60 healthy cats, and 3 echocardiographic variables of LA function: anticipated mean and SD of LAapp peak, LA FS, and LA FAC ($0.38 \pm .25 \text{ m/s}$, $21\% \pm 9\%$, and $33\% \pm 15\%$, respectively), type 1 and 2 error ($\alpha = 0.05$, power 0.80), a defined clinically relevant effect size and the SD of this change (0.25 m/s , 12%, and 14%, respectively), and summated measurement and recording variability (between 4% and 9%). Considering a low

number of incomplete data sets ($<10\%$) at the conclusion of the study and a low drop-out rate of cats between exam 1 and exam 2, a required number between 21 and 27 cats treated with pimobendan was deemed necessary. Descriptive statistics are reported as mean and SD for normally distributed variables and median (interquartile range) for non-normally distributed variables. Variables were tested for normality using the Shapiro-Wilk test and by visual inspection. Logarithmic transformation was applied for some variables because of violation of the normality assumption of residuals. Baseline differences between the 2 treatment groups (pimobendan vs placebo) were assessed using an unpaired *t* test or the Mann-Whitney *U* test, depending on distribution of data. Differences between and within outcome variables obtained at exam 1 and exam 2 for each individual treatment group first were evaluated by repeated measures analysis of variance (ANOVA). This analysis was followed by a 1-way ANOVA to identify differences between groups (pimobendan vs placebo) regarding size of the treatment effect on individual variables (exam 2 minus exam 1). To identify possible associations between disease status (HCM vs apparently healthy cats) and treatment effect, a 2-way ANOVA model was constructed including the change from baseline (exam 2 minus exam 1) as the dependent variable and the covariates "drug" and "disease" as independent variables (model: $\Delta Y = ax_1 + bx_2$, where *Y* is the dependent variable, *x*₁ is drug, and *x*₂ is disease). The latter analysis was repeated for pimobendan-treated cats to answer the question whether or not the effect of pimobendan is affected by disease status. Last, multivariable analysis using a 3-factor ANOVA model and including treatment (pimobendan), disease status (HCM vs apparently healthy cats), and the dichotomous variable LA enlargement (Yes/No), based on a diagnostic cut-off of LADmax $>16 \text{ mm}$ defining LA enlargement,⁸ was performed to determine whether or not presence of LA enlargement had an independent influence on the size of the pimobendan effect (exam 2 minus exam 1). A *P* value of $<.05$ was considered significant, with Bonferroni correction (adjusted *P* values) performed to conserve the overall type I error when multiple comparisons were conducted. For multivariable modeling, only unadjusted *P* values are reported, considering the small number of observations and the exploratory character of these analyses.

Observer variability of echocardiographic measurements was calculated by $[\text{SD}/\text{average of measurements}] \times 100$ and expressed as the CV in percentage and also as an absolute value.⁵⁴

3 | RESULTS

Thirty-three cats were enrolled and completed the study. Population characteristics for both groups are summarized in Table 1. Relevant LVOT obstruction, arbitrarily defined as LVOT Vmax $>2.7 \text{ m/s}$ by continuous wave Doppler with a late-peaking Doppler flow profile, while avoiding contamination of the outflow signal by mitral regurgitation, was found with similar frequency in both treatment groups (cats with LVOT Vmax $>3.5 \text{ m/s}$ were not enrolled because of safety concerns). All cats were sedated using butorphanol approximately 10 minutes before echocardiography. In 8 cats with HCM and 7 healthy cats,

acepromazine was administered in the hospital, and in 11 cats gabapentin was administered by the clients at home before transportation of the cats to the hospital for additional sedation. The sedation protocol utilized remained constant between both examinations for all cats except 2–1 of which in the placebo group required acepromazine at exam 2 only and another in the pimobendan group that required gabapentin at exam 2 only. Six cats were receiving concurrent medications including clopidogrel ($n = 4$), amitriptyline ($n = 1$), apixaban ($n = 1$), enalapril ($n = 1$), and levetiracetam ($n = 1$). No baseline differences of variables of LA size and function were found between treatment groups (all $P > .05$). Results of ABP, QoL, heart rate, and echocardiographic data are summarized in Table 2. Heart rate, LVOT Vmax, LV FS, and 8 variables of LA size and function were different after pimobendan whereas only 1 variable of LA function was different after placebo. Comparing effect size after treatment with pimobendan and placebo, heart rate, 2 variables of LA size, and LA total emptying volume were different ($P < .05$) whereas other variables of LA function failed to reach statistical significance (Table 2, Figure 1). The treatment effect of pimobendan was larger in HCM cats as compared to apparently healthy cats for 5 variables of LA function (Figure 2): LA ejection force (mean difference, 1.93 kdynes vs -0.07 kdynes; $P = .01$), A VTI (mean difference, 0.58 cm vs 0.01 cm; $P = .01$), LAapp peak (mean difference, 0.20 m/s vs 0.02 m/s; $P = .02$), LA FS (mean difference, 2.1% vs -2.1% ; $P = .05$), and LA kinetic energy (mean difference, 3.51 kdynes-cm vs -0.1 kdynes-cm; $P = .05$). No difference was found in effect size of pimobendan between cats with and without LA enlargement regardless of disease category (HCM vs apparently healthy;

all P values between .4 and .7). In addition, there was no independent influence of LA enlargement on the effect size of pimobendan on variables of LA function in cats with HCM (all P values between .54 and .76) ruling out possible collinearity between presence of HCM and LA enlargement regarding the effect of pimobendan. Therefore, the differential effect of pimobendan in cats with HCM vs apparently healthy cats could not be explained by differences in LA size.

Two cats in the pimobendan group and 3 cats in the placebo group had dynamic LVOT obstruction before pimobendan. Peak LVOT Vmax changed from 2.8 to 1.4 m/s in 1 pimobendan-treated cat and was similar at both examinations (3.4 vs 3.5 m/s) in another cat on pimobendan. In addition, 2 cats without dynamic LVOT obstruction at exam 1 had obstruction at exam 2 after pimobendan (change of LVOT Vmax from 1.65 to 3.89 m/s and 0.91 to 3.16 m/s). In the placebo group, LVOT Vmax was lower after drug in 2 cats (3.5–3.3 m/s and 3.0–0.8 m/s) and higher in 1 cat (2.7–3.3 m/s). None of the cats treated with placebo had dynamic LVOT obstruction at exam 2 if not already present at exam 1. No differences in client-observed QoL scores were identified between groups (Table 2; $P = .99$). The cat with the highest QoL score of 28 (out of 75 possible) was in the placebo group. In the pimobendan group, the highest score was 16/75, with this cat experiencing inappropriate urinations and lethargy, although it had a known history of feline idiopathic cystitis.

Data on reproducibility are found in Table 3. All CVs evaluated were $<5\%$ for intra- and interobserver measurement variability.

TABLE 1 Baseline characteristics of the cats in each treatment group

Group	Pimobendan	Placebo
n	17	16
HCM/Healthy	11/6	11/5
Domestic shorthair	16	13
Sphinx	1	2
Siamese	0	1
Sex (female/male) ^a	3/14	8/8
Body weight (kg) ^a	5.73 ± 1.29	4.82 ± 1.01
Age (y)	7.0 (4.75–11.25)	6.0 (4.0–9.5)
Dynamic LVOT obstruction	2	3
LA enlargement (HCM/Healthy)	4/3	4/0
Days between exams	6 (5–7)	6.5 (5.5–7)

Note: Values are expressed as mean ± SD for normally distributed data and median with 25th to 75th percentiles for non-normal distribution. LA enlargement was defined as a maximum LA cranial-caudal dimension (LADmax) > 16 mm. Dynamic left ventricular outflow tract (LVOT) obstruction was defined as a dynamic flow profile in the LVOT recorded by continuous wave Doppler and a peak velocity > 2.7 m/s (cats with a flow velocity > 3.5 m/s violated entry criteria and thus were not enrolled). Abbreviations: HCM, hypertrophic cardiomyopathy; LA, left atrial; LVOT, left ventricular outflow tract.

^aStatistically significant differences with $P < .05$.

4 | DISCUSSION

Left atrial size and function are important echocardiographic markers of disease severity, functional status, and prognosis in HCM in cats^{2,4-6,11,13,20} and humans.^{17,55-59} Adverse outcomes such as CHF and ATE are linked to LA enlargement and dysfunction,^{7-9,11,12,20,27,60} with stagnant intracardiac blood flow being an important contributor to the pathogenesis of arterial thromboembolic disease in cats.^{7,9,11,12,60} Our results indicate that pimobendan, a positive inotropic drug, improves LA transport function. Although effect size was small, several echocardiographic variables indicated increased blood flow in the left atrium and left auricle and thus increased LA mechanical function after pimobendan. This effect was more prominent in cats with HCM compared to healthy cats. Moreover, the effect of pimobendan was independent of the presence of LA enlargement.

Although pimobendan has not been licensed for use in cats, data on its positive inotropic effect as determined by cardiac catheterization in healthy anesthetized cats,³⁸ on pharmacokinetic properties,^{27,32} on short- and long-term clinical use in cats with myocardial disease with and without CHF,^{29-31,33} and on safety^{30,31} all have been reported. However, information on the effect of pimobendan on LA transport function in cats is scarce.^{10,33}

Left atrial size was mildly but significantly increased after pimobendan based on LA area and LA volume measurements. This finding is different from previously reported data. In 1 prospective study with purpose-bred healthy cats,¹⁰ minimum (end-diastolic) but not maximum LA dimension

TABLE 2 Clinical and echocardiographic data of treatment groups and between-group comparisons

Variable	Pimobendan			Placebo			Pimobendan vs placebo [*] P value
	Exam 1	Exam 2	P value	Exam 1	Exam 2	P value	
ABP (mm Hg)	132 ± 22	127 ± 17	.28	132 ± 14	133 ± 22	.69	.31
QoL	n.d.	0 (0-3)	n.d.	n.d.	0.5 (0-3)	n.d.	.99
HR (bpm)	180 ± 32	198 ± 33	<.001	181 ± 30	186 ± 23	.07	.02
LADmax (mm)	15.28 ± 1.72	15.20 ± 1.74	.95	15.02 ± 2.32	14.92 ± 2.20	.7	.76
LA : Ao	1.34 ± 0.13	1.27 ± 0.14	.09	1.36 ± 0.22	1.37 ± 0.20	.64	.09
LA FS (%)	28 ± 5	29 ± 5	.67	29 ± 6	30 ± 7	.07	.44
LAAmax (cm ²)	2.23 ± 0.49	2.42 ± 0.54	.02	2.17 ± 0.57	2.07 ± 0.47	.2	.01
LA FAC (%)	48 (46-55)	52 (46-55)	.85	49 ± 8	50 ± 8	.41	.96
LAVmax (mL)	2.35 ± 0.76	2.59 ± 0.84	.03	2.28 ± 1.00	2.11 ± 0.80	.15	.01
LA total emptying volume (mL)	1.48 ± 0.56	1.66 ± 0.57	.03	1.39 ± 0.51	1.30 ± 0.35	.23	.02
LA EF (%)	63 (61-67)	65 (60-69)	.68	63 ± 9	63 ± 9	.5	.76
LA kinetic energy (kdynes-cm)	6.66 ± 7.60 ^a	8.94 ± 6.51 ^a	.19	5.64 ± 2.46 ^b	4.22 ± 2.57 ^b	.69	.25
LA ejection force (kdynes)	1.95 ± 1.48 ^a	2.50 ± 1.14 ^b	.27	1.95 ± 0.72 ^b	1.43 ± 0.67 ^b	.13	.17
A peak (m/s)	0.62 ± 0.17 ^a	0.77 ± 0.12	.05	0.65 ± 0.09 ^b	0.60 ± 0.09	.68	.08
A dur (ms)	66 ± 9 ^a	60 ± 9 ^b	.26	63 ± 9 ^b	65 ± 5 ^b	.87	.37
A VTI (cm)	3.05 ± 0.69 ^a	3.37 ± 0.49	.05	2.82 ± 0.35	2.84 ± 0.48	.92	.28
LA total SV (mL)	2.45 ± 1.12 ^a	2.61 ± 1.12 ^b	.65	2.38 ± 0.63 ^b	2.02 ± 0.65 ^b	.21	.29
AR peak (m/s)	0.35 ± 0.15	0.37 ± 0.20	.69	0.33 (0.28-0.37)	0.30 (0.25-0.34)	.03	.38
AR dur (ms)	56 ± 13	47 ± 11	.002	57 ± 14	53 ± 12	.06	.24
LAapp peak (m/s)	0.71 ± 0.22	0.85 ± 0.20	.009	0.71 ± 0.19	0.76 ± 0.18	.08	.12
LAapp' peak (cm/s)	18.6 ± 6.3	20.2 ± 6.1 ^c	.12	19.9 ± 5.2	20.0 ± 5.6	.17	.79
LVOT Vmax (m/s)	0.91 (0.72-1.12)	0.98 (0.93-1.71)	.009	1.21 (0.93-1.56)	1.04 (0.78-1.79)	.35	.09
LV FS (%)	66 (51-70)	70 (58-76)	.03	63 ± 10	64 ± 8	.31	.43

Note: Values are expressed as mean ± SD for normally distributed data and median with 25th to 75th percentiles for non-normal distribution. Superscript (a) refers to availability of only 10 and superscript (b) of only 8 observations due to summated transmitral flow waves, respectively. Superscript (c) refers to availability of only 16 observations. Exam 1, baseline exam before drug administration; Exam 2, exam after drug administration.

Abbreviations: A dur, duration of the A wave; A peak, peak velocity of late diastolic transmitral flow; ABP, arterial blood pressure; AR dur, duration of the AR wave; AR peak, peak velocity of pulmonary vein flow reversal at atrial contraction; HR, heart rate; LA FAC, left atrial fractional area change; LA FS, left atrial fractional shortening; LA:Ao, left atrial dimension to aorta ratio; LAAmax, maximum left atrial area; LAapp peak, peak velocity of left auricular appendage flow; LAapp' peak, peak velocity of left auricular appendage wall motion; LADmax, maximum left atrial cranial-caudal dimension; LAVmax, maximum left atrial volume; LV FS, left ventricular fractional shortening; LVOT, left ventricular outflow tract; n.d., not determined; QoL, quality of life; SV, stroke volume; Vmax, maximum velocity.

^{*}The P values in the last column refer to comparison of treatment effects (post-treatment value minus baseline value) between treatment groups.

was decreased after 7 days of treatment with pimobendan. In contrast, pimobendan did not change LA size based on LA : Ao in a long-term study (506 days) in healthy cats²⁸ and in a retrospective study in cats with cardiomyopathy and CHF.²⁹ The reason for the increased LA area and volume estimates after pimobendan in our study is not completely understood. Improved LV systolic function as evidenced by increased LV FS, although mild, may have led to increased LV relaxation and untwist and thus LV suction, increasing forward pulmonary venous flow into the left atrium in systole and leading to increased LA size. In addition, a direct effect of pimobendan as a positive inotropic drug on LA relaxation¹⁹ and LA

distensibility,⁶¹ increasing LA reservoir function^{19,55,62} and thus LA size, should be considered. Last, chance alone may have contributed to this difference, but based on our study design (randomized, blinded, and placebo-controlled) this possibility is unlikely. The overall effect of treatment with pimobendan on LA size however was very small, and thus clinically irrelevant.

Left atrial booster pump function plays a fundamental role in LV filling, particularly in cats with HCM and LV diastolic dysfunction where increased LA contraction is essential for maintenance of LV filling and augmentation of stroke volume.^{55,56,63} It is difficult to assess

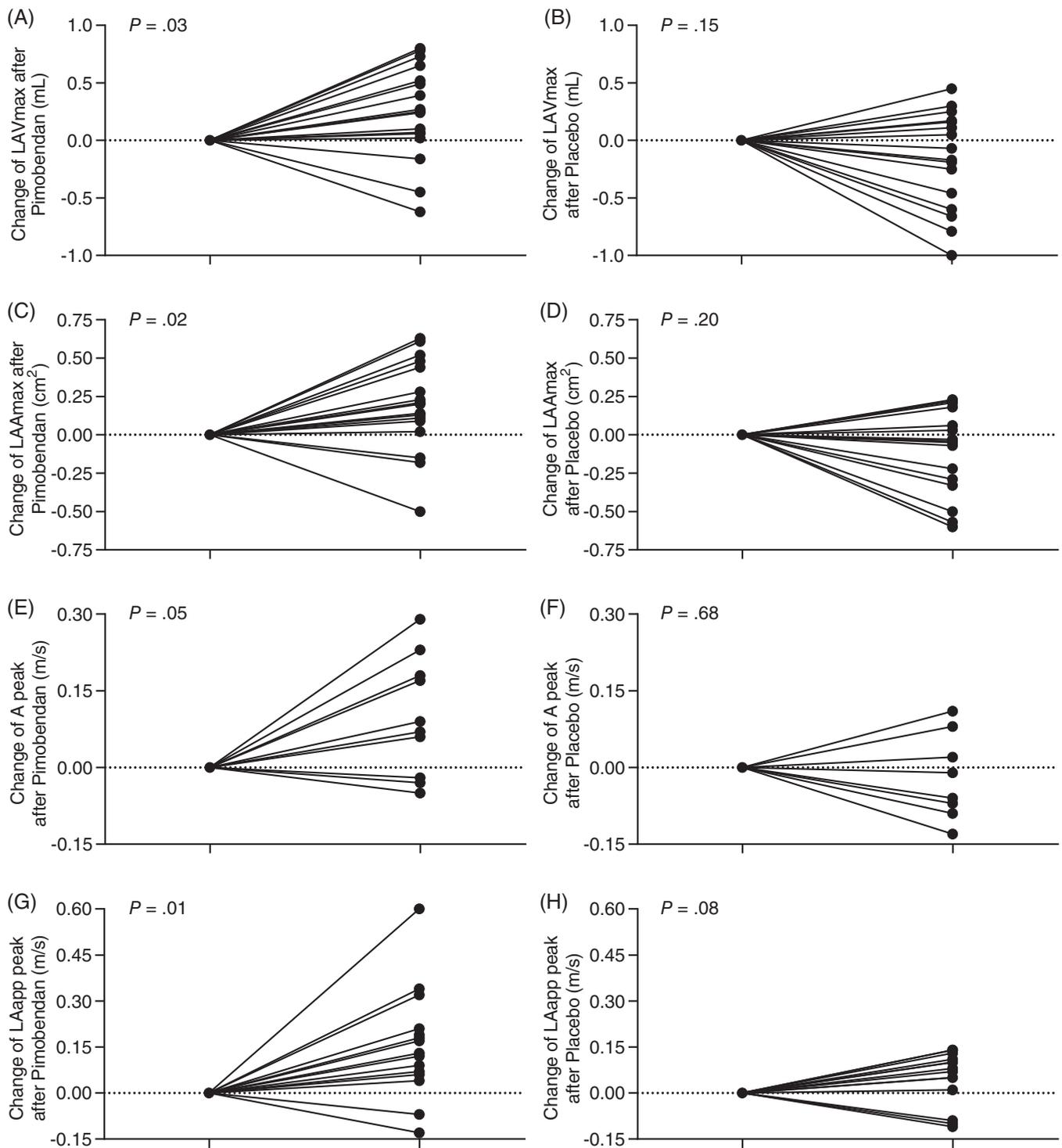


FIGURE 1 Change plots showing the difference between exam 1 and exam 2 of select echocardiographic variables of left atrial (LA) size and function after treatment with Pimobendan (panels A, C, E, G) and Placebo (panels B, D, F, H). A,B, Change of maximum LA volume (LAVmax, n = 17 vs n = 16). C,D, Change of maximum LA area (LAAMax, n = 17 vs n = 16). E,F, Change of peak velocity of late diastolic transmitral flow (A peak, n = 10 vs n = 8). G,H, Change of peak velocity of left auricular appendage flow (LAapp peak, n = 17 vs n = 16)

echocardiographically because of the interplay of myocyte contractility, preload, afterload, atrial geometry, the fact that both the atrium proper as well as the more compliant left auricle contribute to global LA function, and the interdependence of LA and LV function.^{8,17,19,22,56,64} In addition, the phasic nature of LA filling and

ejection with reservoir, conduit, and booster pump function makes determination of single variables characterizing global LA function challenging. The diagnostic gold standard in the evaluation of LA function relates to variables derived from pressure-volume loops such as LA peak rate of change of pressure in early systole (+dP/dtmax) and

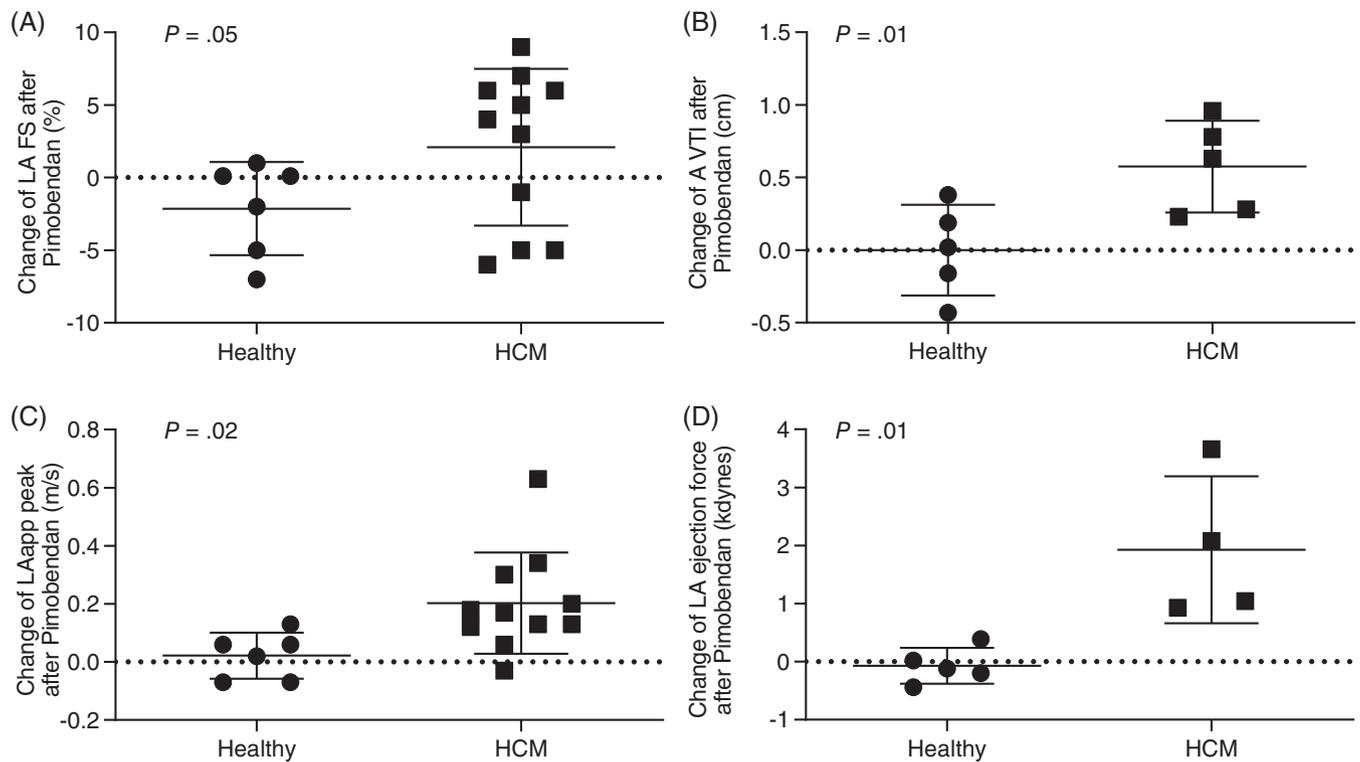


FIGURE 2 Dot plots demonstrating the difference (mean ± SD) between exam 1 and exam 2 of select echocardiographic variables of left atrial (LA) function between apparently healthy cats and cats with hypertrophic cardiomyopathy (HCM) after treatment with Pimobendan. A, Change of LA fractional shortening (LA FS; healthy, n = 6, $-2.1\% \pm 1.3\%$ vs HCM, n = 11, $2.1\% \pm 1.6\%$). B, Change of velocity time integral of the transmitral A wave (A VTI; healthy, n = 5, $0.01 \text{ cm} \pm 0.15$ vs HCM, n = 5, $0.58 \text{ cm} \pm 0.14$). C, Change of peak velocity of left auricular appendage flow (LAapp peak; healthy, n = 6, $0.02 \text{ m/s} \pm 0.03$ vs HCM, n = 11, $0.20 \text{ m/s} \pm 0.05$). D, Change of LA ejection force (healthy, n = 5, $-0.07 \text{ kdynes} \pm 0.14$ vs HCM, n = 4, $1.93 \text{ kdynes} \pm 0.63$). Incomplete data sets in panels B and D are related to missing data due summation of transmitral flow waves making quantification of the A wave impossible

TABLE 3 Data on intra- and interobserver measurement variability of selected echocardiographic variables of LA function derived from 8 cats

Variable	Intraobserver variability		Interobserver variability	
	Absolute difference	CV % (±SD)	Absolute difference	CV % (±SD)
LADmax (mm)	0.10	0.56 ± 0.35	0.19	1.28 ± 0.98
LA FS (%)	0.66	2.47 ± 1.74	1.41	4.83 ± 3.36
LAAmax (cm ²)	0.02	1.02 ± 0.49	0.08	3.33 ± 2.80
LAVmax (mL)	0.04	1.47 ± 0.79	0.12	4.58 ± 4.97
A peak (m/s)	0.01	0.21 ± 0.40	0.01	1.46 ± 1.97
AR dur (ms)	0.64	1.15 ± 0.70	2.07	3.97 ± 4.32
LAapp peak (m/s)	0.01	0.35 ± 0.66	0.01	1.35 ± 1.60

Note: The absolute difference is presented as SD between measurements for intraobserver variability and difference between observer measurements for interobserver variability. The coefficient of variation (CV %) is presented as mean value ± SD. For abbreviations, see Table 2.

LA elastance,^{17,55,65} both of which are not clinically feasible in client-owned cats. In our study, 5 echocardiographic variables of LA function suggested improved LA systole after pimobendan using univariate analysis (LA total emptying volume, A peak, A VTI, AR dur, and LAapp peak).

The transmitral A wave (both A peak and A VTI) represents forward blood flow in late diastole secondary to atrial contraction. It is determined by a multitude of factors of which LA contractile function,

LA preload, heart rate, PQ interval, and LA afterload (mainly characterized by LV compliance) are most important.^{20,21,63,66} Increased LA booster pump function is a hallmark of subclinical HCM^{17,57} secondary to delayed LV relaxation, and decreased LV compliance related to myocyte hypertrophy, fibrosis, and small vessel disease with ischemia.^{10,19,21} Therefore, decreased LA function may lead to LA afterload mismatch^{55,66} in the setting of HCM, a phenomenon describing the inverse relationship between increased impedance to LV filling caused

by increased ventricular stiffness and the ability of LA pump function to adequately fill the LV in diastole.⁶³ Therefore, decreased LA function, often combined with LA afterload mismatch^{55,66} as documented in people with symptomatic HCM,^{55,63} will lead to decreased A peak. Similar findings have been observed in cats with HCM and CHF.²⁰ Thus, a higher A peak, as found in our study in cats after pimobendan (and also increased A VTI and total atrial emptying volume), likely indicates increased LA systolic function. In this context, improvement of afterload mismatch of LA booster pump function with dobutamine, a different positive inotropic agent, has been observed in experimental dogs.⁶⁶ Whether or not improved LV compliance with decreased LA afterload secondary to the inotropic and vasodilatory effects of pimobendan also increased A peak remains unknown. However, the latter hypothesis is supported by the finding of decreased pulmonary venous AR dur^{47,51,67} after pimobendan.

Decreased LAapp flow velocity is related to low LAapp contractile function and local blood stasis.^{8,19,68} It is closely related to SEC, a known precursor of thromboembolism in cats.^{1,8,11,60} Left auricular appendage function as determined by LAapp Vmax increased after pimobendan but not after placebo. This effect was more prominent in cats with HCM compared to apparently healthy cats. Although the effect was relatively mild, normal (as opposed to decreased) LAapp peak, present in all cats before pimobendan, must be taken into consideration to fully appreciate this finding. Whether or not the effect size of pimobendan on left auricular appendage flow would have been larger in cats with auricular dysfunction and decreased LAapp peak at baseline cannot be answered by our results, but could be a target for future investigations. In contrast, in a recent study of 13 cats with HCM,³³ LAapp peak was not increased after a single dose of pimobendan. Reasons for the discrepancy between the 2 studies may be related to lower sample size (13 vs 17 cats), single vs multiple doses of pimobendan, and higher sympathetic tone of the cats in the previous study,³³ as evidenced by higher heart rate (mean 231 vs 198 bpm) making identification of additional positive inotropic effects beyond the effect of sympathetic stimulation more difficult. Controlled long-term studies are needed to determine if improved LAapp flow observed after pimobendan leads to thromboembolic risk reduction in cats with cardiomyopathy.

Hypertrophic cardiomyopathy is understood not only as a myocardial disease of the left ventricle but as a cardiomyopathic process affecting all 4 cardiac chambers.^{57,69,70} In this context, the differential effect of pimobendan on LA function observed in our study warrants discussion. Multivariate analysis identified a stronger effect of pimobendan on variables of LA function in cats with HCM compared to apparently healthy cats considering 5 echocardiographic indices: LA FS, A VTI, LAapp peak, LA kinetic energy, and LA ejection force. Similar to previously reported data,^{33,39} an increase in LA FS occurred after pimobendan in cats with HCM, with LA FS used as an important functional marker of LA function as reported elsewhere.^{11,20,27} Decreased LA FS has been identified as an independent predictor of prognosis²⁷ and, more specifically, 2-year mortality risk associated with ATE,¹¹ in cats with HCM. Moreover, LA FS was decreased in cats with subclinical HCM and HCM with CHF compared to healthy cats,²⁰ making LA systolic function assessed by LA FS a potential treatment target for cats with HCM. However, comparability of LA FS data

between our study and previously reported results^{11,27,33} is hampered by the fact that different methods were used to determine LA FS. Whereas LA FS was acquired from 2-D right parasternal long-axis images using LADmax and LADmin²⁰ in our study, right parasternal short-axis heart base views were used to determine the LA : Ao ratio and M-mode in other studies.^{11,27,33} There are concerns that LA FS as determined in the previous studies is not only influenced by LA contractile function but also by LV systolic performance. Aortic root motion is an index of LV stroke volume.⁷¹ Increased LV stroke volume leads to increased aortic root motion.⁷² Therefore, LA FS determined from M-mode short-axis measurements should be interpreted as a summary measure of LA and LV systolic function, and thus LA FS calculated using 2-D measurements from long-axis images is preferred for isolated evaluation of LA function independent of LV function.

In addition to LA FS, A VTI, and LAapp peak, pimobendan had a stronger effect on LA kinetic energy and LA ejection force^{48,49,73-76} in cats with HCM compared to healthy cats. To our knowledge, LA kinetic energy and LA ejection force have not been used to characterize LA systolic function in cats. Both variables are considered less load dependent than other echocardiographic variables of LA function.^{48,49} Left atrial ejection force is defined as the vigor exerted by the left atrium in accelerating blood into the left ventricle during atrial systole by combining dimensional (mitral valve orifice area) and velocity (A peak) echocardiographic measures.^{17,48} Left atrial kinetic energy is similar to ejection force but adds volume (LA stroke volume) to area and velocity measurements.^{17,76} Both variables provide reasonable estimates of atrial workload during LA contraction.^{48,73,76} Significantly increased LA ejection force and kinetic energy as found in our study suggest pimobendan may enhance LA systolic function in cats with HCM, thus confirming conclusions regarding the effect of pimobendan derived from other echocardiographic variables of LA systolic function.

Based on hemodynamic assumptions,^{76,77} positive inotropic agents have been regarded as contraindicated in people with HCM and in particular HCM with dynamic LVOT obstruction.^{78,79} However, limited data support the notion that the positive inotropic effect of pimobendan will exacerbate obstruction and increase morbidity.²⁹ Although evaluation of the effect of pimobendan on dynamic LVOT obstruction was not an objective of our study and cats with an LVOT Vmax >3.5 m/s were not enrolled for safety reasons, pimobendan was associated with minor effects on LVOT obstruction in cats with LVOT Vmax ≤3.5 m/s. Two cats without LVOT obstruction at baseline developed mild obstruction after pimobendan and 2 cats with obstruction at baseline either did not experience a change in LVOT Vmax or had decreased LVOT Vmax after pimobendan. This observation is in agreement with recent reports in cats with HCM in which worsening of obstruction was not observed after pimobendan administration.^{31,33} Further study on the impact of pimobendan on LVOT obstruction is necessary.

Pimobendan's hemodynamic effects have been assessed in various animal models including pigs and dogs, where a dose-related increase in heart rate has been observed. Increased heart rate also has been reported in studies of humans IV administration of pimobendan.⁸⁰ Although cardiac output and blood pressure were not simultaneously measured in our cats, a possible explanation for the mild but significant increase in heart rate after pimobendan may be a

compensatory response to decreased systemic vascular resistance. In addition, the possibility of increased sympathetic tone on exam 2 also should be considered. Cats in the placebo group also experienced an increase in heart rate (181 ± 30 vs 186 ± 23 , $P = .07$) but this increase was not statistically significant.

Our study had several limitations. Variables used for evaluation of LA function have not been validated against a gold standard in cats. The low number of cats enrolled negatively impacted the power of the statistical analysis to detect significant differences between groups. A population of healthy cats was included to address the primary objective of the study. However, given their normal LA size and function, this population may have limited our ability to identify treatment effects of pimobendan. Cats with HCM had a larger effect size after pimobendan. Mixing healthy cats and cats with HCM in the 2 treatment groups may have diluted significant changes after pimobendan. Therefore, the results discussed should be interpreted with caution. It would have been desirable to study a population of cats with HCM and LA enlargement and dysfunction, the true target population that may benefit from treatment with an inodilator. Summation of transmitral flow waves because of tachycardia limited the number of quantifiable A and AR waves and related variables. Blood concentrations of pimobendan and its active metabolite were not obtained, and pharmacokinetic data on pimobendan administered PO in cats with HCM have not been reported. The number of echocardiographic variables describing LA systolic function did not include motion of the mitral annulus in late diastole⁸¹ and acceleration of the A wave.⁶⁵ Therefore, we may have missed effects of pimobendan on LA function. Three apparently healthy cats had LA enlargement based on a LADmax cut-off of 16 mm and visual assessment of LA size. Allometric scaling may have been a better modality to determine presence of LA enlargement in these cats given their higher body weights (6.7, 7.1, and 8.4 kg).^{82,83} However, presence of occult cardiomyopathy cannot be completely ruled out in these cats. Use of sedation may have influenced the results of our study, although the drugs chosen had minimal known effects on cardiac size and performance. Last, a cross-over design may have been preferable.

In conclusion, various echocardiographic variables indicated improvement of LA systolic function after short-term treatment with pimobendan. This effect was particularly clear in cats with HCM, but effect size was small. Further randomized controlled trials focusing on the effect of pimobendan in cats with LA enlargement and dysfunction are needed to confirm or extend the results of our study. It remains to be determined whether or not treatment with pimobendan decreases the risk of ATE in cats with cardiomyopathy.

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CONFLICT OF INTEREST DECLARATION

Authors declare no conflict of interest.

OFF-LABEL ANTIMICROBIAL DECLARATION

Authors declare no off-label use of antimicrobials.

INSTITUTIONAL ANIMAL CARE AND USE COMMITTEE (IACUC) OR OTHER APPROVAL DECLARATION

Study was approved by the local authorities: Clinical Research Committee of the Veterinary Medical Center, protocol # 2017-19 and the IACUC, protocol # 2017A00000111.

HUMAN ETHICS APPROVAL DECLARATION

Authors declare human ethics approval was not needed for this study.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of this article.

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