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Effects of 0.5% Timolol Maleate Ophthalmic Solution on Heart Rate and Selected Echocardiographic Indices in Apparently Healthy Cats

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Background: Echocardiographic assessment of diastolic function is challenging in cats, partially because of transmitral flow pattern fusion associated with high heart rates. With heart rate (HR) reduction, transmitral flow waveforms separate, allowing identification of diastolic dysfunction. Timolol, an ophthalmic, nonselective beta-blocker used in glaucoma is safe and transiently decreases HR in clinical trials.

Hypothesis: Administration of timolol ophthalmic solution decreases HR and facilitates echocardiographic assessment of diastolic function in cats without inducing clinically relevant adverse effects.

Animals: Twenty-five apparently healthy cats.

Methods: Electrocardiograms and echocardiograms including transmitral flow patterns were evaluated before and 20 minutes after ocular administration of 1 drop of timolol 0.5% solution. Twenty cats underwent treatment with timolol, and 5 different cats served as untreated controls to evaluate the effects of acclimation to the hospital environment on HR.

Results: Acclimation to the hospital had no effect on HR in control cats. After timolol administration, a significant median HR reduction of 25 bpm was observed ($P < .0001$). Timolol had no effect on E/A ratio in cats without E/A fusion (7/20, $P = .44$). Of the 13 cats with E and A waves that were fused before timolol application, separation of these waves was identified in 8 cats (62%) after timolol treatment. No bradyarrhythmias were noted after timolol administration, but 2 cats had first-degree atrioventricular block. Timolol resulted in resolution of dynamic outflow tract obstruction in 6 of 6 cats.

Conclusions and clinical importance: Ocular administration of timolol safely decreases HR in cats and could facilitate assessment of diastolic function.

Key words: Cardiomyopathy; Doppler; Echocardiography; Feline.

Hypertrophic cardiomyopathy (HCM) is the most commonly diagnosed cardiac disease in cats.[1–4] The diagnosis of HCM is made when the left ventricular septum or free wall measurement is >6 mm at the end diastole and no metabolic or cardiovascular causes of hypertrophy are identified.[2] However, HCM is heterogeneous in its presentation and progression, and there is no consensus regarding the classification of cats with equivocal echocardiographic findings (ie, left ventricular [LV] wall thickness 5.0–5.9 mm or segmental hypertrophy).[a] These factors makes early diagnosis of HCM a clinical challenge. The pathophysiology of HCM is due in part to diastolic dysfunction secondary to a hypertrophied LV.[4] Diastolic dysfunction also is implicated in other cardiomyopathies of cats such as restrictive cardiomyopathy.[5] Doppler echocardiographic identification of impaired relaxation has been suggested as a possible means for detection of occult cardiomyopathy in cats.[6–13] One of the techniques used to assess diastolic function is echocardiographic evaluation of transmitral flow patterns. Because transmitral flow can be affected by ventricular loading conditions, age, and heart rate, among other factors, its assessment should be interpreted in conjunction with other echocardiographic and clinical variables such as case history or genetic testing to increase suspicion for occult cardiomyopathy. Normal transmitral flow patterns consist of a peak in early diastole that corresponds with early

Abbreviations:

ADRB1	beta-1 adrenergic receptor gene
A vel	velocity of late diastolic transmitral flow
DRVOTO	dynamic right ventricular outflow tract obstruction
E vel	velocity of early diastolic transmitral flow
E/A	ratio of E vel and A vel
FS	fractional shortening
HCM	hypertrophic cardiomyopathy
HOCM	hypertrophic obstructive cardiomyopathy
HR	heart rate
IVSd	interventricular septum in diastole
LVIDd	left ventricular internal dimension during diastole
LVIDs	left ventricular internal dimension during systole
LVPWd	left ventricular free wall in diastole
LVOT	left ventricular outflow tract
OD	right eye
P277Q	missense mutation changing a proline to glutamine at the 277th amino acid
UCD-VMTH	University of California, Davis William R. Pritchard Veterinary Medical Teaching Hospital

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left ventricular filling (E wave), and a second peak (A wave) that corresponds with atrial systole.[14] In humans, dogs, and cats with impaired relaxation, an alteration in this pattern is noted. This change is characterized by a decrease in E velocity, prolonged E deceleration time, and an increase in atrial contribution to left ventricular filling, manifested as an increase in A velocity.[6,14,15] Therefore, an E/A ratio <1.0 suggests impaired relaxation.[14,16] The high heart rates encountered in cats exposed to the clinical situation can lead to E and A wave fusion.[9,10] When fusion is present, evaluation of the E and A velocities is not possible and therefore diastolic dysfunction could go undetected.

Timolol is a nonselective beta-blocker, commonly used in dogs and cats for the treatment of glaucoma.[17,18] In 1 study, instillation of 1 drop of 0.5% timolol ophthalmic solution twice daily decreased heart rate (HR) in healthy cats by a mean of 17 bpm.[19] Ophthalmic administration of timolol has been reported to decrease HR in healthy beagle dogs by 10%.[20]

The aims of this study were to (i) evaluate the clinical effectiveness of topical timolol ophthalmic solution in HR reduction and (ii) identify its effects on selected echocardiographic parameters in clinically healthy cats. We hypothesized that the administration of timolol ophthalmic solution would decrease HR and facilitate echocardiographic assessment of selected diastolic function parameters without clinically relevant adverse effects in cats.

Materials and methods

The study protocol was reviewed and approved by the University of California, Davis Animal Care and Use Committee protocol #18093. Signed consent was obtained from each owner before enrollment in the study.

Animals

Apparently healthy cats with and without heart murmurs were recruited from referring veterinarians, veterinary students and staff, and clinical cases presenting to the University of California Davis William R. Pritchard Veterinary Medical Teaching Hospital (UCD-VMTH). Cats with ocular disease, history of respiratory disease or cough, documented arrhythmia, or clinical signs of congestive heart failure were excluded. Cats receiving medications considered to have cardiovascular effects were excluded. Cats with a disposition that prevented safe handling for an echocardiogram without sedation also were excluded.

Study Design

A physical examination, 6-lead electrocardiogram (ECG), venous blood sampling, and full echocardiographic study including transmitral flow velocities were performed in that order.[21] One drop of 0.5% timolol maleate ophthalmic solution[b] was instilled into the right eye and the cats were returned to their hospital cage or carrier. Twenty minutes later, a 6-lead ECG and repeated echocardiogram were performed. The right eye then was irrigated with saline solution to remove any residual timolol and cats were discharged to their owners. The owners were contacted the next day to document any adverse signs after discharge from the hospital.

Five cats were selected from the clinical case load to serve as a control group in order to evaluate the effect of acclimation to the hospital environment on HR. This group received a full physical examination, a lead II ECG, and a complete echocardiogram. They then were placed into a cage within the UCD-VMTH cardiology treatment room for 20 minutes. No timolol intervention was provided. A reevaluation lead II ECG was performed.

Electrocardiography

Six-lead and lead II ECGs were obtained in right lateral recumbency.[c] Recordings were made at 50 mm/s with an amplitude of 20 mm/mV. A 10-second ECG was recorded and saved for manual measurement by 1 of the authors (CGH). Heart rate, PR interval, QRS interval, and QT interval were measured for all 6-lead ECGs, and HR was measured for each lead II ECG. All intervals were measured and recorded as an average of 3 consecutive complexes.

Echocardiography

All echocardiograms were performed by 1 of 2 investigators (JAS or CGH) using an 12-4 mHz sector array transducer.[d] Each cat was manually restrained in right, then left lateral recumbency; no sedatives were employed. Two-dimensional, M-mode, color Doppler, and spectral Doppler echocardiographic measurements were obtained. Transmitral flow velocities were obtained from the left parasternal apical view as previously described.[6,22] Sample volume was set at 1.5 mm with a sweep speed of 150 mm/s. Left auricular flow velocity was obtained from an oblique left apical parasternal long-axis view as previously described.[23] All measurements were performed by 1 observer (CGH) using an offline work station.[e] The average value for 3 consecutive cardiac cycles was obtained for each measurement whenever possible. Left ventricular wall measurements (interventricular septum ([VS] and left ventricular free wall [LVPW]) were obtained in diastole at the level of the chordae tendineae and measured leading edge-to-leading edge from an M-mode recording. Two-dimensional maximal diastolic dimension of LVPW and IVS also were obtained in right parasternal short- and long-axis imaging planes during the initial echocardiogram for each cat. Left atrial size was measured in 2 dimensions (2D) on the right parasternal short-axis view and indexed to aortic root diameter. The aortic diameter was measured parallel to the commissure of the noncoronary and right coronary aortic valve cusps. The left atrial dimension was measured parallel to the commissure of the left coronary and noncoronary aortic valve cusps as previously described.[24] The E and A wave fusion on the transmitral flow pattern was defined as either complete summation of the E and A waves (no overlap) or partial summation where the initiation of the A wave overlap was >0.20 m/s relative to the E wave peak velocity. E and A wave separation was defined as a transmitral E and A wave pattern where the initiation of the A wave began at a point <0.20 m/s of the peak E wave velocity.[25]

Pharmacogenetic Analysis

A polymorphism in the feline beta-1 adrenergic receptor gene (ADBR1) has been described as a missense mutation changing proline to glutamine at the 277th amino acid position (P277Q), although a functional effect of this polymorphism has not yet been characterized in cats.[26] To examine a potential pharmacogenetic association between the documented ADRB1 polymorphism and response to ophthalmic timolol in cats of this study, a venous blood sample was obtained from all participating cats. The genotyping methodology was carried out as previously described.[25] Briefly, DNA was extracted from whole blood. Routine polymerase chain reaction (PCR) and Sanger sequencing were

performed to determine the genotype of the P277Q polymorphism. Sequences were aligned to the reference sequence and cats were classified as wild type, heterozygous, or homozygous for this previously described polymorphism.

Statistical Analysis

Data were assessed for normality both visually and with a D'Agostino & Pearson omnibus normality test when the sample size was adequate for testing (N > 6). For sample sizes <6 (control cats), data were treated as nonnormally distributed. All normally distributed data are reported as mean ± SD and nonnormally distributed data are reported as median (interquartile range [IQR]). Differences between pre- and post-timolol ECG and echocardiographic measurements were assessed using a paired *t*-test for normally distributed data and a Wilcoxon matched pairs signed rank test for nonnormally distributed data. Heart rates before and after 20 minutes of hospitalization in untreated cats were compared using Wilcoxon matched pairs signed rank test. Statistical software was used for calculations and analysis.[f] Statistical significance was determined at a *P* value <.05.

Results

A total of 27 cats were recruited and 25 cats were enrolled. No cats were receiving any medications at the time of study enrollment. One cat was excluded because evidence of first-degree atrioventricular block was noted on its initial ECG; the second cat was excluded because its disposition did not allow a complete echocardiogram to be performed without sedation. Five control cats were selected from clinical cases undergoing echocardiography for evaluation of incidentally detected heart murmurs. The remaining 20 cats were enrolled in the timolol portion of the study. For subjects enrolled in the timolol portion of the study, age ranged from 7 months to 17 years with mean age of 6.1 (±4.55) years. Six cats had a heart murmur auscultated on physical examination. Heart rate on initial ECG ranged from 137 to 272 bpm with a median HR of 188 bpm. After timolol application, a significant decrease in HR ($P < .0001$) to a median of 159 bpm (range 137–200 bpm) occurred (Fig 1A). On visual inspection of the data, cats with HR <175 bpm (n = 3) did not have a substantial change in HR after timolol application.

For 5 control cats, age ranged from 5 to 12 years with a median age of 7 years. Baseline HR of control cats was not significantly different from baseline HR of cats that received timolol ($P = .42$). Median HR on initial presentation was 200 bpm (range, 160–233 bpm), and after 20 minutes of acclimation to the hospital environment, no significant difference was detected in HR (median, 214 bpm; range, 151–225; $P = .81$; Fig 1B).

For cats that received timolol, baseline echocardiogram transmitral flow velocity measurement showed E and A wave fusion in 13 of 20 cats, whereas clear E and A wave separation was visualized in the remaining 7 cats. All 13 of the cats with E and A wave fusion had complete fusion with no discernable E and A waves. After timolol administration, 5 of these 13 cats (38%) had E and A waves that remained fused, whereas 8/13 cats (62%) had E and A separation (Fig 2). When all data points were pooled, median HR was significantly higher in cats with E and A wave fusion at 197 bpm (IQR: 190, 203) when compared to those with E and A wave separation (median, 158 bpm; range, 151–163; $P < .0001$). In the 7 cats in which E and A waves were separated at baseline, these waves remained separated, with no significant change in E/A ratio, after timolol administration ($P = .4$). Of those 7 cats, all E/A ratios that were <1.0 remained <1.0 after timolol, and those that were >1.0 remained >1.0 (Fig 3).

Two-dimensional and M-mode-derived echocardiographic measurements are summarized in Table 1.

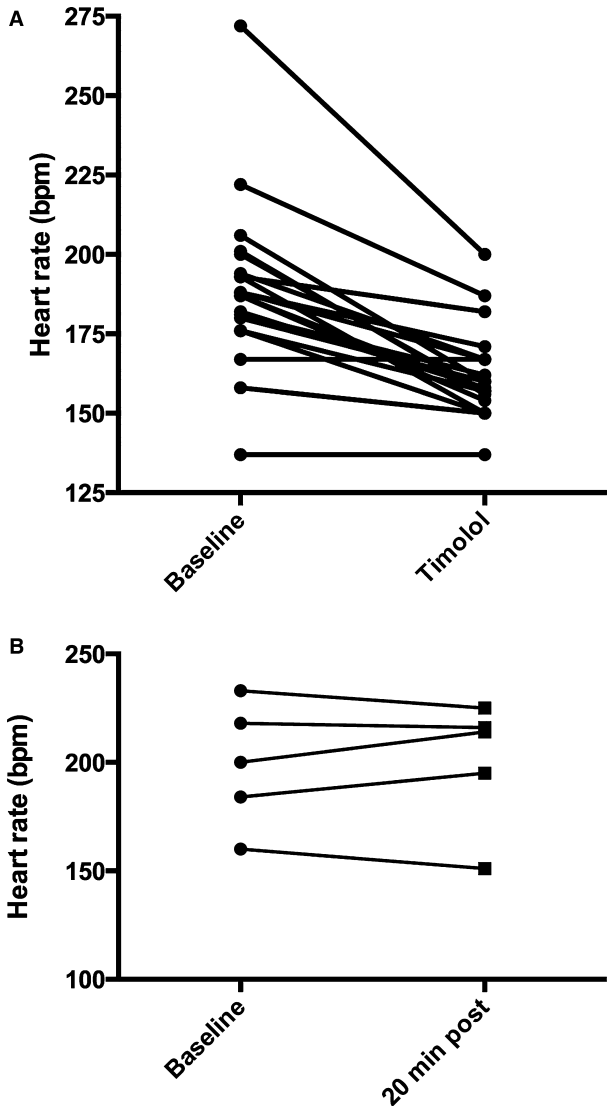

Fig. 1. (**A**) Heart rate (HR; *y*-axis) at baseline and after timolol time points (*x*-axis) for 20 cats. After timolol administration, there was a significant decrease in HR ($P < .0001$), with no substantial change appreciated in cats with an initial HR <176 bpm. (**B**) Heart rate (HR; *y*-axis) at baseline and 20 minutes after acclimation (*x*-axis) for 5 control cats that did not receive timolol. There was no significant difference between HR at baseline or after acclimation in these cats ($P = .8$)

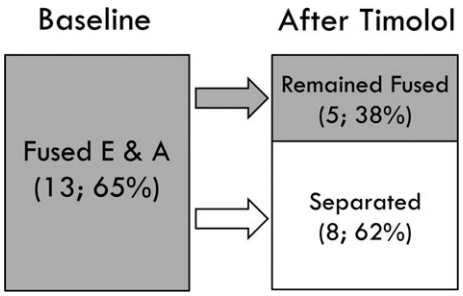

Fig. 2. Graphical depiction of cats with transmitral flow E and A wave fusion or separation at baseline (left) and after timolol administration (right). At baseline time point 13 of 20 cats (65%) had E and A fusion, whereas 7 of 20 cats (35%) had separation. After ophthalmic administration of timolol 62% of previously fused waves became separated, whereas the waves in 5 of 13 cats (38%) remained fused. All 7 of 7 initially separated profiles, remained separated. E- peak early diastolic flow velocity; A- peak late diastolic flow velocity.

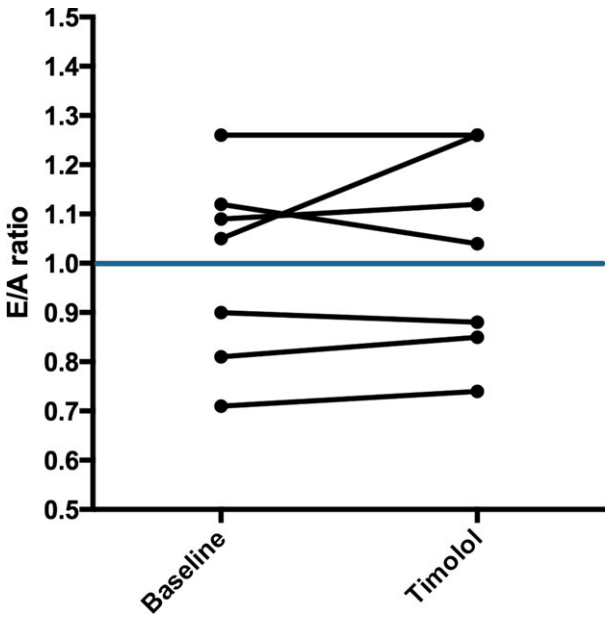

Fig. 3. E/A ratio at baseline and after timolol time points in the 7 cats that had E and A wave separation at baseline. The blue line denotes an E/A ratio of 1.0. Below the line, or an E/A ratio <1.0 is consistent with impaired relaxation, whereas above the line is considered normal. All cats that had evidence of impaired relaxation (n = 3) at the baseline time point, remained impaired after timolol administration. The 4 cats with a normal E/A ratio before timolol remained normal after timolol. E/A- ratio of peak E to peak A velocity.

There was no significant difference in septal or left ventricular free wall measurements in diastole after timolol application ($P = .91$ and $P = .18$, respectively). An example of the effects of timolol on transmitral flow pattern is shown in Fig 4. Comparison of baseline and posttimolol measurements identified a significant decrease in left ventricular systolic function, assessed by fractional shortening (FS)% ($P < .0001$) and left ventricular internal dimension in systole (LVIDs; $P < .0001$). After timolol application there was no significant change in LA/Ao ($P = .36$) or left auricular flow velocity ($P = .117$).

On baseline echocardiogram, 1 cat was diagnosed with hypertrophic obstructive cardiomyopathy with systolic cranial motion of the mitral valve and a peak left ventricular outflow tract (LVOT) velocity of 3.4 m/s; the interventricular septum measured 7.1 mm in diastole with a free wall measurement of 5.6 mm. After timolol application, no evidence of obstruction was noted on color flow Doppler and peak left ventricular outflow tract (LVOT) velocity was decreased to 1.3 m/s. The remaining cats in the study did not have structural cardiac disease. Five cats had dynamic right ventricular outflow tract obstruction (DRVOTO) noted on initial echocardiogram based on color Doppler and spectral Doppler assessment. After timolol application, DRVOTO was no longer noted in any of these cats.

Ptyalism was noted immediately after timolol was applied in 2/20 cats (10%) and lasted <5 minutes. Anisocoria with miosis OD (the treated eye) was reported in 11 cats (55%) after timolol application but was temporary. Most owners noted return to normal pupil size within 24 hours. In 1 cat, miosis lasted 48 hours.

No hemodynamically relevant arrhythmias were identified after application of timolol but 2 cats (10%) developed mild first-degree atrioventricular block with PR intervals of 95 and 100 ms. No significant difference in QRS duration or QT interval was observed before and after timolol application ($P = .80$ and $P = .08$, respectively).

No genotypic differences were identified in this population and all cats (25/25) were found to be wild type (matching the reference sequence) for the P277Q ADRB1 polymorphism.

Discussion

In this study, ophthalmic application of timolol decreased HR and facilitated visualization of separated E and A waves on transmitral flow in the majority of cats in which the waves initially were fused. Assessment of diastolic function is a routine portion of the echocardiographic examination when evaluating cats for cardiomyopathies. Spectral Doppler assessment of transmitral flow patterns is a common tool used to diagnose diastolic dysfunction, and it has been proposed that this technique may help identify occult cardiomyopathy when interpreted as part of the complete clinical evaluation.[25] Although these data are useful in cats, the high HR of cats in the clinic and subsequent E and A wave fusion on spectral Doppler assessment make transmitral flow patterns impossible to assess in some subjects. Previous investigators have reported success in separating E and A waves with vagal maneuvers, but in our experience, the response is exceedingly transient and not as robust as previously reported.[25] Additionally, cat demeanor often precludes application of ocular or nasal planum pressure, which is reported to

Table 1. Echocardiographic measurements for baseline time point and after timolol administration in 20 cats

Variable	Baseline	Posttimolol	% change	*P* value
HR (bpm)	188 (177, 199)	159 (155, 167)	−13.6 (−9.4, 20.5)	<.0001
IVSd (cm)	0.46 (0.41, 0.50)	0.45 (0.41, 0.51)	0.98 (−10.6, 9.3)	.91
LVPWd (cm)	0.48 (0.44, 0.53)	0.50 (0.42, 0.53)	−3.8 (−7.1, 2.8)	.18
LVIDd (cm)	1.50 (1.37, 1.69)	1.60 (1.42, 1.69)	3.1 (−6.9, 9.4)	.53
LVIDs (cm)	0.67 (0.13)	0.87 (0.15)	30.9 (20.7)	<.0001
FS%	55.86 (7.69)	44.14 (7.60)	−20.4 (12.1)	<.0001
LA (cm)	1.18 (0.14)	1.25 (0.14)	7.0 (14.3)	.10
LA/Ao	1.22 (0.11)	1.26 (0.18)	4.3 (15.6)	.36
LAA Flow Vel (cm/s)	49.68 (17.25)	45.37 (13.07)	−4.6 (24.2)	.117

Normally distributed data are presented with mean (SD). For nonnormally distributed data median (IQR) is listed. HR, heart rate; IVS, interventricular septum; LVPW, left ventricular free wall; LVID, left ventricular internal dimension; d, measured in end-diastole; s, measured at end-systole; FS%, left ventricular shortening fraction; LA, 2-dimensional left atrial diameter; LA/Ao, left atrial diameter indexed to aortic diameter; LAA Flow Vel, left auricular appendage flow velocity.

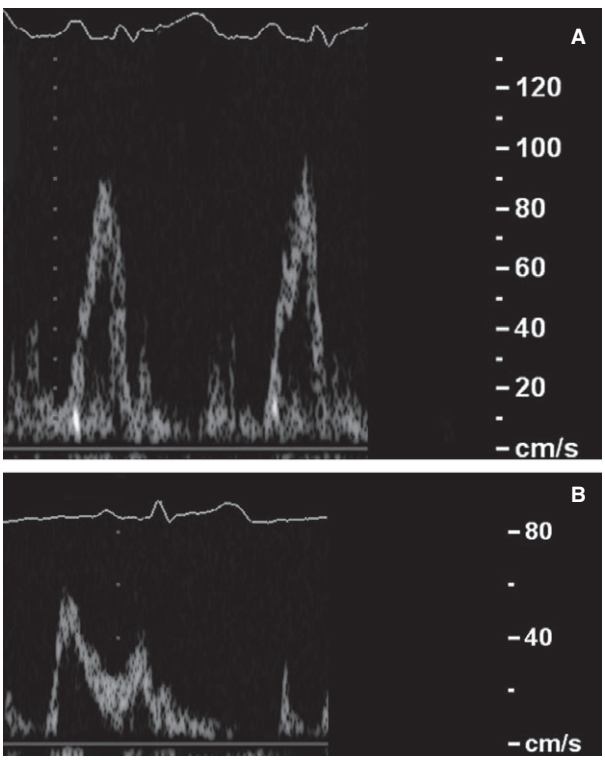

Fig. 4. Transmitral flow from a 3-year-old cat enrolled in the timolol portion of this study. Heart rate at baseline (**A**) was 210 bpm, and 182 bpm after timolol administration (**B**). E and A fusion noted at baseline, with clear separation appreciated after timolol administration. Sweep speed is 150 mm/s, lead II timing lead is also depicted. MC-male castrated; DSH- domestic shorthair.

be most successful at increasing vagal tone in cats undergoing echocardiography.[25] A potential alternate solution is the identification of a safe, effective, and temporary pharmacologic intervention that decreases HR and facilitates diastolic function testing without altering the ultimate assessment.

Timolol, a nonselective topically-applied ophthalmic beta-blocker, significantly decreased HR in cats undergoing echocardiographic examination. The greatest effect on HR was noted in tachycardic cats. This observation is consistent with the expectation that increased HR in these cats was secondary to increased sympathetic tone,[27] and that sympathetic drive was ameliorated by a single ophthalmic dose of timolol in some cats. A similar effect previously has been reported in human patients in whom a single topical dose of timolol created statistically significant cardiovascular effects at rest and after exercise, as well as a decrease in cardiac sympathetic tone.[28] Data from the control group of cats supports the conclusion that acclimation to the hospital environment was not solely responsible for the decreased HR observed in our study, and leads to the conclusion that the effects noted in our study are a result of beta-blockade from systemic absorption of timolol.

Ophthalmic dosing of timolol effectively separated transmitral flow patterns (E and A wave separation) in 62% of the cats in which the waves initially were fused, thereby allowing diastolic function assessment in these individuals. Importantly, the effect of beta-blockade by timolol did not have an adverse effect on our ability to interpret E and A profiles because the profiles that were separated at baseline did not significantly change after timolol administration. This finding supports the notion that opthalmically administered timolol can aid in assessment of myocardial relaxation, a common component of screening for occult cardiomyopathy.

Transmitral flow profiles can be affected by HR, Doppler angle, loading conditions, left atrial function, and age.[6,10,29] In our study, each cat acted as its own baseline control, ruling out an effect of age on the results obtained. In the absence of E and A wave fusion, HR has minimal effect on the interpretation of E/A ratio.[29] In our study, changes in left ventricular loading conditions were seen between baseline and posttimolol time points, as demonstrated by increased left ventricular systolic dimensions and decreased FS. However, the effect of these alterations on transmitral flow pattern was not statistically significant or clinically relevant based on our data. Ours was a pilot study and a larger patient population and more extensive diastolic function assessment were not included.

The variable response in E and A wave separation noted could be related to individual variability in sympathetic tone and excitement. Other considerations for variable response to timolol include variable ocular absorption, variable drug metabolism, or perhaps other pharmacogenetic factors such as beta receptor polymorphisms beyond those already identified in cats.[26]

Left atrial size did not change significantly between baseline and posttimolol application, but our study may have been underpowered to detect a difference given the small variation in left atrial size recorded among cats. One measure of left atrial function, left auricular flow velocity, was not significantly different from baseline, therefore the effect of timolol on atrial contribution to left ventricular filling is thought to be negligible. Additional assessments of left atrial function (eg, LA ejection fraction, shortening fraction) may represent an area of future investigation. Given the effect of timolol on left ventricular function and the theoretical effect on left atrial size, caution should be observed with respect to the ocular application of timolol in cats with clinical signs of congestive heart failure, left atrial enlargement, or impaired systolic function. The effects of timolol on systolic function highlight the importance of obtaining systolic function assessments before application of timolol, as performed in this study. For instance, a clinical strategy could be to perform a complete echocardiogram, then if E and A fusion was noted on transmitral flow, administer ophthalmic timolol, wait 20 minutes and then reassess transmitral flow profiles. In our study, timolol was evaluated as a tool to facilitate assessment of 1 measure of diastolic function in an effort to identify cats with occult cardiomyopathy. Therefore, the utility of this medication in cats with clear evidence of hemodynamically relevant heart disease is beyond the scope of our study.

In our study, timolol resulted in significant decrease in both measures of systolic function measured. This observation is consistent with the negative inotropic effects expected with beta-blockade. Therefore, ophthalmic application of timolol may help elucidate a patient's response to beta-blockade and could be particularly useful in cats with obstructive cardiomyopathy, although further study is needed to investigate this hypothesis. In our study, all cats (6 total) with evidence of dynamic obstruction (DRVOTO or hypertrophic obstructive cardiomyopathy (HOCM)) on baseline echocardiogram had relief of that obstruction after timolol administration. Although it has yet to be proven effective, treatment for cats with occult hypertrophic cardiomyopathy might include beta-blockade.[30–33] The ability to understand an individual's response to beta-blockade at the time of initial evaluation could represent a benefit of ophthalmic timolol application.

Pharmacogenetics and individualized medicine are growing fields. In humans, genetic polymorphisms that result in variable response to beta-blocker treatment could alter therapeutic choices.[34] This pharmacogenetic effect on medication administration also has been demonstrated in dogs.[35] Although the functional effects of feline beta receptor polymorphism are not well documented, this remains an area of interest for future investigation. In our study, an influence of the documented P277Q ADRB1 polymorphism was not responsible for the variable response to timolol. Because all of the cats in our study had the wild type genotype we cannot accurately assess the functional relevance of this polymorphism. Obviously, the role of polymorphisms that have yet to be reported cannot be predicted. Practically, topical application of timolol in the clinic might help determine if a cat will respond as expected to systemic beta-blocker treatment, although further investigation is necessary.

No clinically relevant adverse effects were noted after timolol administration. As previously reported, miosis was observed in the treated eye.[17,36] Miosis occurred secondary to inhibition of beta-adrenergic fibers of the iris sphincter muscle,[18,37] which is reported to be transient in nature.[17] Although miosis induced by timolol may be disturbing to an owner, it is not considered clinical relevant to the animal.[37] First-degree AV block was noted in a small proportion of the cats treated with timolol (10%). This occurrence was not considered pathologic or dangerous, but caution should be employed when administering timolol to cats with a previously documented conduction disturbance or arrhythmia. A history respiratory disease or current cough were exclusion criteria for our study and as such the safety data generated cannot be applied to cats in which respiratory disease is a concern.

Based on our findings, systemic absorption of timolol after ophthalmic administration occurs in cats as has been documented in human patients.[38] In humans, approximately 80% of the topically administered medication drains through the nasolacrimal duct and thereby is systemically absorbed.[39] Fewer cardiovascular effects are noted in people when the 0.1% hydrogel formulation is used as compared to the 0.5% aqueous solution used in our study.[38]

Our study had several limitations. Because of the marked and obvious effects of beta-blockade on HR and left ventricular systolic function, no attempt at blinding was made. Ours was a pilot study that aimed to include both healthy cats and those with occult cardiomyopathy, but only 1 subject with a diagnosis of hypertrophic obstructive cardiomyopathy was enrolled. Furthermore, the sample size of patients with E and A wave separation at baseline was small, and small alterations in E and A velocity after timolol may not be have been appreciated. Although a significant decrease in HR was noted in treated cats and not in control cats, the control group does not necessarily rule out the possibility of individual variation in hospital acclimation. A future direction to address this limitation could include a single-blinded, placebo-controlled study using a cross-over design to confirm that alteration in HR was not caused by individual variation in acclimation. A final limitation is that the study design included evaluation only at a 20-minute time period and effects beyond this time frame are unknown.

Several assessments were outside the scope of this investigation and worth consideration in future investigations. Although the majority of cats included in this study had a HR that returned to normal before hospital discharge (generally within 1–2 hours), this information was not recorded for all cats and long term HR data were not collected for this study. Therefore, the duration of action of timolol and its effects on HR after a single dose are not fully understood at this time. Additionally, our study did not aim to determine the optimal effective dose. A single dose of 1 drop of 0.5% solution was applied based on a previous study,[36] but a similar HR response might be noted with a lower dose or could be marked with higher doses.

In conclusion, ophthalmic timolol application in cats safely decreased HR, generated changes in echocardiographic parameters and facilitated diastolic function assessment in cats in our study. Thus, the ophthalmically administered timolol may facilitate echocardiographic assessment of cats and warrants further investigation.

Footnotes

[a] Wilkie L, Fuentes VL, Rishniw M. Online survey to assess inter- and intraobserver agreement on echocardiographic classification of cardiomyopathy in cats (abstract). J Vet Intern Med 2015; 29: 1263.

[b] Timolol Maleate Ophthalmic Solution, USP 0.5%. Akorn, Inc. Lake Forest, IL.

[c] Mac 5500 Electrocardiogram, GE Healthcare, Waukesha, WI.

[d] Philips iE33 Ultrasound, Philips Heathcare, Andover, MA.

[e] syngo Dynamics, Siemens Medical Solutions, Malvern, PA.

[f] Prism 6.0, Graph Pad Software, La Jolla, CA.

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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.

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