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Acute echocardiographic effects of sotalol on ventricular systolic function in dogs with ventricular arrhythmias

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Background: Sotalol is a commonly used antiarrhythmic drug that may alter ventricular function.

Objective: To determine the effect of sotalol on echocardiographic indices of ventricular systolic function in dogs with ventricular arrhythmias.

Animals: Thirty-five client-owned dogs with ventricular arrhythmias.

Methods: Dogs with ventricular arrhythmias (n = 27) had an echocardiogram and 5-minute ECG performed at baseline and 2-4 hours post-sotalol (2-2.5 mg/kg PO once). Eight additional dogs underwent the same protocol but did not receive sotalol (within-day variability controls). Left ventricular (LV) internal dimension at end-systole normalized to bodyweight (LVIDs_N), LV ejection fraction (LV EF), LV shortening area, LV fractional shortening, tricuspid annular plane systolic excursion (TAPSE), and right ventricular systolic myocardial velocity were evaluated as indices of systolic function.

Results: All indices except TAPSE had mild decreases in systolic function post-sotalol (all $P \leq .0007$) compared with baseline but only the percent change in LVIDs_N and LV EF were significantly ($P \leq .0079$) different from the percent change of the same indices in control dogs. Sinus heart rate, ventricular premature complexes/5-minutes, and arrhythmia grade also were decreased post-sotalol (all $P \leq .01$) compared with baseline when assessed by a 5-minutes ECG. No dog experienced an adverse event post-sotalol, including dogs with systolic dysfunction or atrial enlargement.

Conclusions and Clinical Importance: A single dose of sotalol may cause a mild decrease in LV systolic function in dogs with ventricular arrhythmias. Sotalol appears to be well tolerated, even in dogs with atrial enlargement or systolic dysfunction.

KEYWORDS
beta-blocker, canine, echocardiography, inotropy, tachyarrhythmia

Abbreviations: 2D, two-dimensional; DCM, dilated cardiomyopathy; LA/Ao, left atrial to aortic root ratio; LV, left ventricle/ventricular; LVAd, left ventricular area at end-diastole; LVAs, left ventricular area at end-systole; LV FS, left ventricular fractional shortening; LVIDd, left ventricular internal dimension at end-diastole; LVIDs, left ventricular internal dimension at end-systole; LVIDs_N, left ventricular internal dimension at end-systole normalized to bodyweight; LV SA, left ventricular shortening area; LVVd, left ventricular volume at end-diastole; LVVs, left ventricular volume at end-systole; RV, right ventricle/ventricular; RV S', peak systolic RV myocardial velocity at the lateral tricuspid annulus; TAPSE_N, tricuspid annular plane systolic excursion normalized to bodyweight; VPC, ventricular premature complex.

1 | INTRODUCTION

Sotalol is a class III antiarrhythmic drug that combines potassium channel-blocking properties (thereby prolonging action potential duration) with nonselective β–adrenergic receptor blocking properties. Sotalol is a commonly used PO antiarrhythmic drug for chronic management of ventricular arrhythmias in dogs. Orally administered sotalol also may be used to acutely terminate arrhythmias in dogs that are hemodynamically stable because of its rapid absorption, with peak plasma concentration likely to occur within 2–4 hours postpill.[1] Sotalol appears to be a well-tolerated and an effective treatment of ventricular arrhythmias in Boxers with familial ventricular arrhythmias,[2] and clinical experience suggests this is also true for other breeds.

Clinicians may hesitate to use sotalol in some situations. As with all β–adrenergic receptor antagonists, sotalol has negative inotropic properties, which raises concern over its use in dogs with systolic dysfunction or congestive heart failure. Systolic dysfunction may be present in dogs affected with ventricular arrhythmias secondary to, for example, arrhythmogenic right ventricular (RV) cardiomyopathy, dilated cardiomyopathy (DCM), tachycardia-induced cardiomyopathy, ischemia, or myocarditis. However, in dogs, the negative inotropic effect of sotalol (because of β–blockade) appears to be modest (ie, approximately one-fifth the negative inotropic effect of propranolol).[3] Also, 2 independent studies in healthy anesthetized dogs using invasive indices of left ventricular (LV) systolic function (+dP/dt) demonstrated that the negative inotropic effect of sotalol is attenuated or balanced by enhanced contractility secondary to prolonged action potential duration and hence, prolonged time for calcium entry.[4,5] Based on these studies, the clinical impact of sotalol administration on systolic function in dogs with ventricular arrhythmias may be negligible, but has not yet been investigated.

Clinical experience suggests systolic dysfunction may be a common finding in dogs with ventricular arrhythmias. Systolic dysfunction may be secondary to primary cardiac disease or a tachyarrhythmia, as is the case with tachycardia-induced cardiomyopathy.[6] In primary cardiomyopathies such as preclinical DCM and arrhythmogenic RV cardiomyopathy, echocardiographic identification of LV or RV systolic dysfunction provides important diagnostic and prognostic information.[7–14] Dogs affected by these diseases are also commonly affected by ventricular arrhythmias that may be managed with sotalol. Therefore, understanding the echocardiographic effects of sotalol on systolic function in dogs with ventricular arrhythmias could provide clinically useful information.

The objective of our study was to determine the effect of a single PO dose of sotalol on several echocardiographic indices of RV and LV systolic function in dogs with ventricular arrhythmias. We hypothesized that a single PO dose of sotalol would minimally decrease echocardiographic indices of ventricular systolic function.

2 | MATERIALS AND METHODS

The Institutional Animal Care and Use Committee at the University of California, Davis (protocol #18482) approved all procedures in our study. Owner consent for participation in the study was obtained for each dog before enrollment.

2.1 | Animals

Study subjects were client-owned dogs that presented to the Cardiology Service at the University of California, Davis Veterinary Medical Teaching Hospital for evaluation of cardiac disease or were referred for the purpose of the study. Dogs were enrolled consecutively over a 30-month period if they were diagnosed with a ventricular arrhythmia and were deemed to be hemodynamically stable, weighed >10 kg (for PO sotalol dosing purposes), and were not currently taking any antiarrhythmic drugs or cardiac medications known to affect ventricular function. Dogs were required to have a hemodynamically stable ventricular arrhythmia, defined for the purpose of our study as a ventricular arrhythmia for which urgent antiarrhythmic treatment was not deemed necessary by the attending board-certified veterinary cardiologist. Dogs were excluded from the study if they required sedation to facilitate echocardiography, or if they were diagnosed with congestive heart failure.

2.2 | Study design

For the purpose of this prospective study, all dogs underwent a cardiovascular examination, a 6-lead ECG of 5 minutes duration, and a baseline echocardiogram. After the echocardiogram, dogs received sotalol 2-2.5 mg/kg PO once, rounded to the nearest one-quarter of an 80 or 120 mg tablet (Sotalol hydrochloride tablets, Apotex Inc, Toronto, Ontario, Canada; sotalol group). Dogs received a single PO dose of sotalol for the purpose of the study and not necessarily because it was clinically indicated (ie, the study served as a pharmacodynamic study and not a therapeutic trial). Two-to-four hours postpill, dogs underwent a 2nd ECG and echocardiogram. This time point was selected because peak absorption of sotalol in dogs has been shown to occur within 2–4 hours after PO administration.[1] Time from sotalol administration to the post-sotalol echocardiogram was recorded. Dogs were monitored after the administration of sotalol until discharged to the client, which concluded the study. Sotalol was continued at the discretion of the attending clinician.

To help determine the clinical relevance of the effects of sotalol on ventricular function and to evaluate the effects of acclimation to the hospital environment on the studied indices of ventricular function, 8 additional dogs were recruited to serve as a within-day variability controls (control group) in which the same study protocol was followed but control dogs did not receive sotalol (ie, each dog underwent an ECG and echocardiogram and 2–4 hours later underwent a 2nd ECG and echocardiogram).

2.3 | Echocardiographic assessment

2.3.1 | Image acquisition

All echocardiographic studies (Philips IE33 or Philips EPIQ 7, Philips Healthcare, Andover, Massachusetts) were performed by a board-certified veterinary cardiologist or a cardiology resident under the

direct supervision of a board-certified veterinary cardiologist. All echocardiographic recordings were made with a simultaneous ECG. A standard echocardiographic imaging protocol was followed for each dog and standard echocardiographic imaging planes were used and optimized for assessment of LV and RV function. An effort was made to have the same sonographer perform the repeat echocardiographic examination within the same dog. Tricuspid annular plane systolic excursion (TAPSE) and peak systolic RV myocardial velocity at the lateral tricuspid annulus (RV S') were acquired from left apical 4-chamber views optimized for the RV using M-mode and pulsed wave tissue Doppler imaging, respectively.[15,16]

2.3.2 | Echocardiographic measurements

Echocardiographic measurements and calculations were performed by a single investigator at a digital off-cart workstation (JLK; Syngo Dynamic Workplace, Version 10.0.01_HF04_Rev5 [Build 2884], Siemens Medical Solutions, Malvern, Pennsylvania). This investigator was blinded to drug status and order of the echocardiographic studies. Values for each echocardiographic variable consisted of the average of 3 measurements obtained during sinus rhythm only. To avoid post-extrasystolic potentiation and its effects on ventricular function, measurements were not obtained from cardiac cycles immediately after a ventricular premature complex (VPC). Left ventricular internal dimension from the same cardiac cycle was measured at end-diastole (LVIDd) and end-systole (LVIDs) at the level of the papillary muscles from the right parasternal short axis view using M-mode echocardiography. Left atrial-to-aortic root dimension (LA/Ao) was measured in a standard fashion from a right parasternal short axis view using 2D echocardiography.[17] A ratio >1.5 was used to indicate left atrial enlargement. Left ventricular internal dimension at end-systole was normalized to body weight (LVIDs_N) using the following formula: LVIDs_N = LVIDs (cm) ÷ (body weight$^{0.315}$).[18] Left ventricular fractional shortening (LV FS) was calculated as ([LVIDd − LVIDs]/LVIDd) × 100. From the same short axis view and using 2D echocardiography, LV area was determined by planimetry by manually tracing the internal border of the lumen of the LV at end-diastole (LVAd) and end-systole (LVAs) while excluding the papillary muscles. Left ventricular shortening area (LV SA; also known as fractional area change) was calculated as ([LVAd – LVAs]/LVAd) × 100. From the right parasternal long axis 4-chamber view and left apical 4-chamber view optimized for the LV, LV volume was estimated from 2D echocardiography using Simpson's method of discs as previously described[19] at end-diastole (LVVd) and end-systole (LVVs). Left ventricular ejection fraction (LV EF) was calculated as ([LVVd – LVVs]/LVVd) × 100. For the purpose of our study, LV systolic dysfunction was defined as a LV FS <25%.[18] However, breed-specific reference values for LVVs indexed to body surface area were utilized to diagnose systolic dysfunction in Boxers (>50 mL/m^2),[20] Doberman Pinschers (>55 mL/m^2),[19] and Great Danes (47 mL/m^2).[21] Body weight-specific reference values for TAPSE were used to determine if RV systolic dysfunction was present, and TAPSE was normalized to body weight (TAPSE_N) according to the following formula: TAPSE_N = TASPE (cm) ÷ (body weight$^{0.297}$).[16]

2.4 | Electrocardiographic assessment

All dogs had a 6-lead ECG (Philips PageWriter TC70 Cardiograph, Philips Healthcare, Andover, Massachusetts) recorded while in right lateral recumbency. All ECGs were reviewed, assessed and measured by a single investigator (LCV) blinded to sotalol status. Average heart rate while in sinus rhythm and number of VPCs were quantified during the 5-minutes ECG recording. Ventricular arrhythmia severity was graded according to the following scale adapted from a previous study[22]: 0 = no VPCs, 1 = single VPCs, 2 = ventricular bigeminy or trigeminy, 3 = accelerated idioventricular rhythm, 4 = ventricular couplets or triplets, and 5 = ventricular tachycardia or R-on-T phenomenon. The highest grade observed was the grade assigned.

2.5 | Statistical analysis

Statistical analyses were performed using a commercial software package (Prism 7 for Mac OS X, Version 7.0c, GraphPad Software, Inc, La Jolla, California). A power calculation based on previously published echocardiographic reproducibility and measurement variability data in dogs[23] determined that a sample size of 22 would provide 80% power for detecting a 20% change in echocardiographic indices of LV systolic function. A sample size of 27 was used in the study to ensure adequate power was achieved. Descriptive statistics were generated and normality testing with the D'Agostino-Pearson test was performed for all continuous data. Data are reported as mean (standard deviation [SD]) unless otherwise stated. Differences in paired (baseline versus post-sotalol) data were determined by a paired *t*-test or a Wilcoxon matched-pairs signed rank test (if non-normally distributed). Differences in unpaired data (control versus sotalol group) were determined by an unpaired *t*-test with Welch's correction or Mann-Whitney rank-sum test (if non-normally distributed). Ordinal data (arrhythmia grade) was compared with a Wilcoxon matched-pairs signed rank test. A Chi-squared test was used to compare proportions. Within-day variability of the echocardiographic indices in the control dogs was quantified with the coefficient of variation ([SD ÷ average] × 100). When determining the statistical significance of the 6 echocardiographic indices of systolic function, *P* values were corrected using Bonferroni's method of multiple comparisons. That is, a $P < .05 \div 6$ or $P < .008$ denotes statistical significance for these comparisons. Otherwise, $P < .05$ was considered statistically significant.

3 | RESULTS

A total of 35 dogs were enrolled in our study, 27 in the sotalol group and 8 in the control group. Within the sotalol group, mean (SD) age was 9.4 (3.4) years and body weight was 31.5 (8.8) kg with 19 (70%) dogs being female. The sotalol group consisted of 8 Boxers, 5 each were Doberman Pinchers and mixed breeds, and other breeds were each represented once (Labrador Retriever, Great Dane, Saint Bernard, Portuguese Water Spaniel, Golden Retriever, Vizsla, Weimaraner, and English Pointer). Clinical and echocardiographic diagnoses consisted of the following: echocardiographically unremarkable in 9 dogs,

TABLE 1 Electrocardiographic and echocardiographic ventricular function data of dogs (n = 27) at baseline and post-sotalol

	Baseline	Postsotalol	Percent change (%)	*P*-value (baseline vs. post-sotalol)
Electrocardiographic variables				
Sinus heart rate (min^{-1})	120 (29)	97 (22)	−17.6 (14.7)	**<.0001**
VPCs/5-min[a]	18 (9–32)	4 (0–17)	–	**<.0001**
Arrhythmia severity grade[a]	1 (1–4)	1 (0–1)	–	**.014**
Echocardiographic variables				
LVIDs_N	1.0 (0.17)	1.1 (0.17)	11.0 (10.0)	**<.0001**
LV FS (%)	29.2 (6.0)	24.7 (6.2)	−13.5 (11.3)	**<.0001**
LV SA (%)	44.7 (12.0)	40 (11.5)	−9.6 (12.0)	**.0002**
LV EF (%)	50.3 (10.9)	43.3 (9.1)	−11.7 (15.6)	**.0005**
TAPSE_N	0.54 (0.13)	0.51 (0.11)	−4.9 (14.5)	.041
RV S' (cm/s)	16.8 (5.8)	12.7 (3.0)	−18.8 (23.9)	**.0007**

Normally distributed data presented as mean (SD).
[a]Non-normally distributed data presented as median (interquartile range).
Abbreviations: LVIDs_N, left ventricular internal dimension at end-systole normalized to bodyweight; LV EF, left ventricular ejection fraction; LV FS, left ventricular shortening fraction; LV SA, left ventricular shortening area; RV S', peak systolic RV myocardial velocity at the lateral tricuspid annulus; TAPSE_N, tricuspid annular plane systolic excursion normalized to bodyweight; VPC, ventricular premature complex.
Bolded *P*-values denote statistical significance (Bonferroni corrected $P < .008$).

arrhythmogenic RV cardiomyopathy in 7 dogs, preclinical DCM in 5 dogs, myxomatous mitral valve disease in 4 dogs, and mild subaortic stenosis and suspected myocarditis of unknown etiology (cardiac troponin I = 28.5 ng/mL) in 1 dog each. Mean (SD) dose of sotalol received was 2.5 (0.2) mg/kg. Time from sotalol administration to the post-sotalol echocardiogram was 2.9 (0.4) hours. A summary of the baseline and post-sotalol ECG and echocardiographic ventricular systolic function data are presented in Table 1 and Figure 1. All ventricular systolic function indices (LVIDs_N, LV FS, LV SA, LV EF, TAPSE_N, and RV S') documented decreased systolic function post-sotalol compared to baseline (all Bonferroni corrected $P < .008$) with the exception of TAPSE_N. Figure 1 allows visualization of the response of individual dogs, and it should be noted that not all dogs' indices of systolic function were decreased post-sotalol. For example, 5 dogs had a measured increase in LV EF post-sotalol (Figure 1D). Additionally, sinus heart rate, number of VPCs/5 min, and arrhythmia grade all were significantly (all $P \leq .014$) decreased post-sotalol. At their baseline assessment, 9 dogs (33%) in the sotalol group had LV systolic dysfunction. Seven dogs (26%) had RV systolic dysfunction, 3 of which also had LV systolic dysfunction. Eight dogs (30%) had LA enlargement, 5 of which also had LV systolic dysfunction. None of the dogs experienced any adverse events including respiratory difficulty, syncope, collapse, lethargy, or weakness after the single dose of sotalol.

Eight dogs were enrolled in the control group, and a summary of their electrocardiographic and echocardiographic data is presented in Table 2. Mean (SD) age was 10.4 (1.9) years. Body weight was 29.7 (10.1) kg. Three dogs (38%) were female. The control group consisted of 2 Labrador Retrievers, a Weimaraner, Bull Terrier, mixed breed dog, Bulldog, and a Boxer. Echocardiographic diagnoses of dogs in the control group included the following: echocardiographically unremarkable in 3 dogs, myxomatous mitral valve disease and a heart base mass in 2 dogs each, and DCM in 1 dog. Two dogs (25%) in the control group were diagnosed with LV systolic dysfunction and 1 dog (13%) was diagnosed with RV systolic dysfunction. Two dogs (25%) had LA enlargement. No statistically significant differences were identified between the control and sotalol group for body weight ($P = .61$), age ($P = .42$), proportion of female dogs ($P = .10$), sinus heart rate ($P = .51$), number of VPCs/5 min ($P = .72$), arrhythmia grade ($P = .24$), proportion of dogs with LV systolic dysfunction ($P = .66$), proportion of dogs with RV systolic dysfunction ($P = .44$), and proportion of dogs with LA enlargement ($P = .80$).

Percent change in ventricular function indices in the control versus sotalol groups are presented in Figure 2. Percent change of LV FS (–13.5 [11.3]%), LV SA (–9.6 [12.0]%), TAPSE_N (–4.9 [14.5]%), and RV S' (–18.8 [23.9]%) post-sotalol were not significantly different (all $P \geq .06$) when compared with the percent change of controls (–4.3 [15.6]%, 0.6 [12.3]%, −9.4 [17.9]%, −9.9 [20.9]%, respectively). However, percent change of LVIDs_N (11.0 [10.0]%) and LV EF post-sotalol (–11.7 [15.6]%) were significantly different ($P \leq .0079$) compared with the percent change of the same indices in control dogs (2.1 [4.8]%, 0.4 [8.0]%, respectively).

Coefficients of variation for within-day variability of the echocardiographic indices of ventricular systolic function were as follows: LVIDs_N = 2.7%, LV FS = 8.6%, LV SA = 5.5%, LV EF = 4.2%, TAPSE_N = 12.5%, and RV S' = 16.6%.

4 | DISCUSSION

Results of our study show that, with the exception of TAPSE_N, all studied echocardiographic indices of RV and LV systolic function evaluated after a single PO dose of sotalol were mildly decreased in dogs with ventricular arrhythmias when compared with baseline. To help delineate the clinical relevance of these changes, the percent change of each ventricular systolic function index post-sotalol was compared to the percent change of controls that underwent the same study protocol but were not treated with sotalol (to rule out an effect of within-day variability or acclimation). Only the percent change in LVIDs_N and LV EF post-sotalol were found to demonstrate a mild but significant

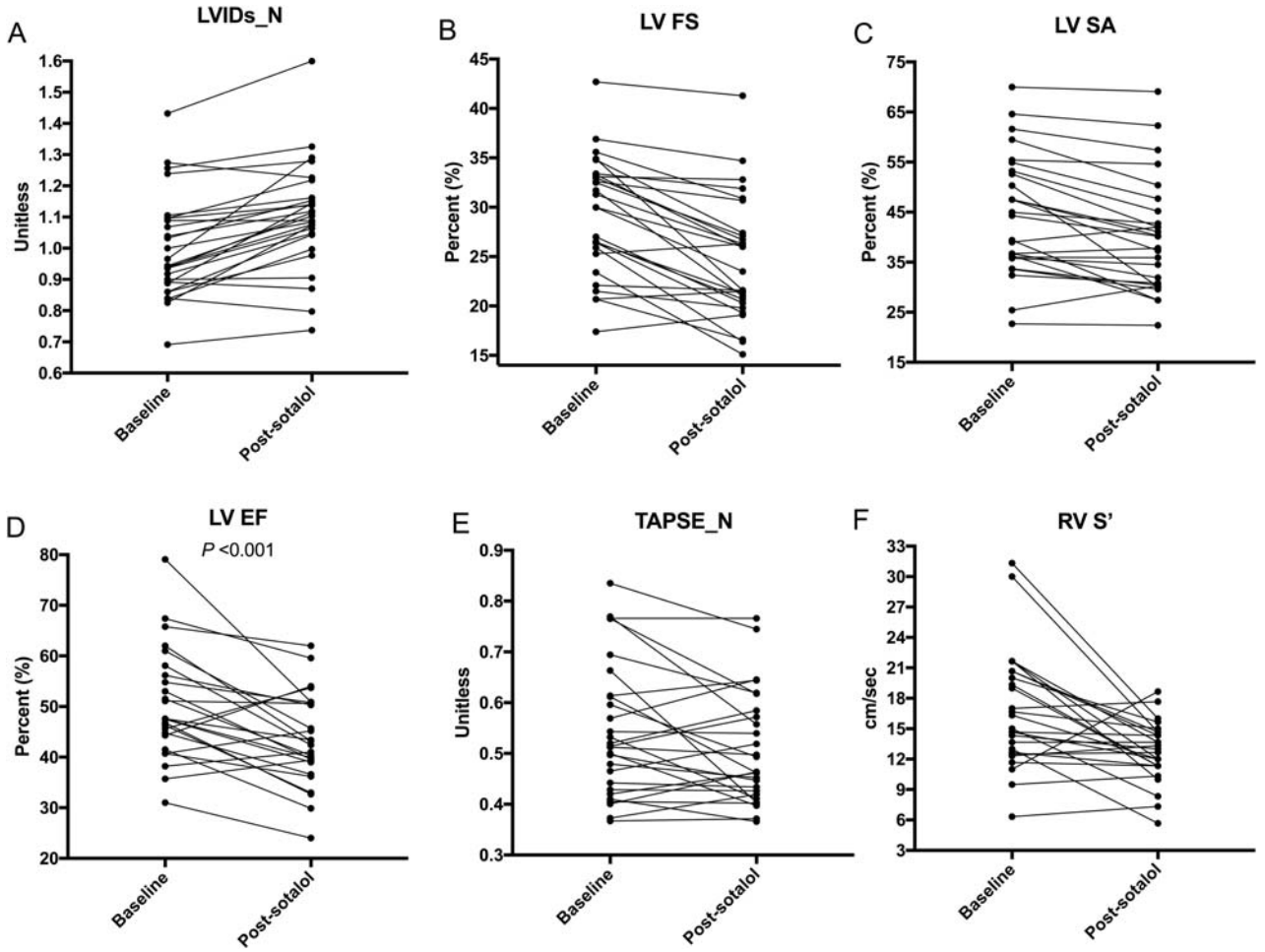

FIGURE 1 Left ventricular internal dimension at end-systole normalized to bodyweight (LVIDs_N) (A), Left ventricular fractional shortening (LV FS) (B), left ventricular shortening area (LV SA) (C), left ventricular ejection fraction (LV EF) (D), TAPSE normalized to bodyweight (TAPSE_N) (E), and peak systolic RV myocardial velocity at the lateral tricuspid annulus (RV S') (F) from 27 dogs at baseline and 2–4 hours post-sotalol 2-2.5 mg/kg PO. Statistical significance was reached for all presotalol and post-sotalol comparisons (Bonferroni corrected $P < .008$) with the exception of TAPSE_N

TABLE 2 Electrocardiographic and echocardiographic ventricular function data at baseline (exam 1) and 2–4 hours later (exam 2) of control dogs (n = 8)

	Exam 1	Exam 2	Percent change (%)	*P*-value (Exam 1 vs. exam 2)
Electrocardiographic variables				
Sinus heart rate (min^{-1})	112 (22)	114 (23)	−17.6 (14.7)	.61
VPCs/5-min[a]	14.5 (6–39)	17.5 (4.75-24.3)	–	.46
Arrhythmia severity grade[a]	1 (0.25-2)	1 (0–1.75)	–	.38
Echocardiographic variables				
LVIDs_N	1.0 (0.21)	1.0 (0.19)	2.1 (4.8)	.34
LV FS (%)	29.9 (9.8)	28.9 (8.8)	−4.3 (16)	.59
LV SA (%)	52.8 (9.4)	53.8 (11.2)	0.6 (12.3)	.66
LV EF (%)	55.4 (10.0)	55.9 (10.7)	0.4 (7.9)	.70
TAPSE_N	0.54 (0.06)	0.49 (0.12)	−9.4 (17.9)	.20
RV S' (cm/s)	15.5 (4.6)	13.5 (3.1)	−9.9 (20.9)	.11

Normally distributed data presented as mean (SD).
[a]Non-normally distributed data presented as median (interquartile range).
Abbreviations: LVIDs_N, left ventricular internal dimension at end-systole normalized to bodyweight; LV EF, left ventricular ejection fraction; LV FS, left ventricular shortening fraction; LV SA, left ventricular shortening area; RV S', peak systolic RV myocardial velocity at the lateral tricuspid annulus; TAPSE_N, tricuspid annular plane systolic excursion normalized to bodyweight; VPC, ventricular premature complex.

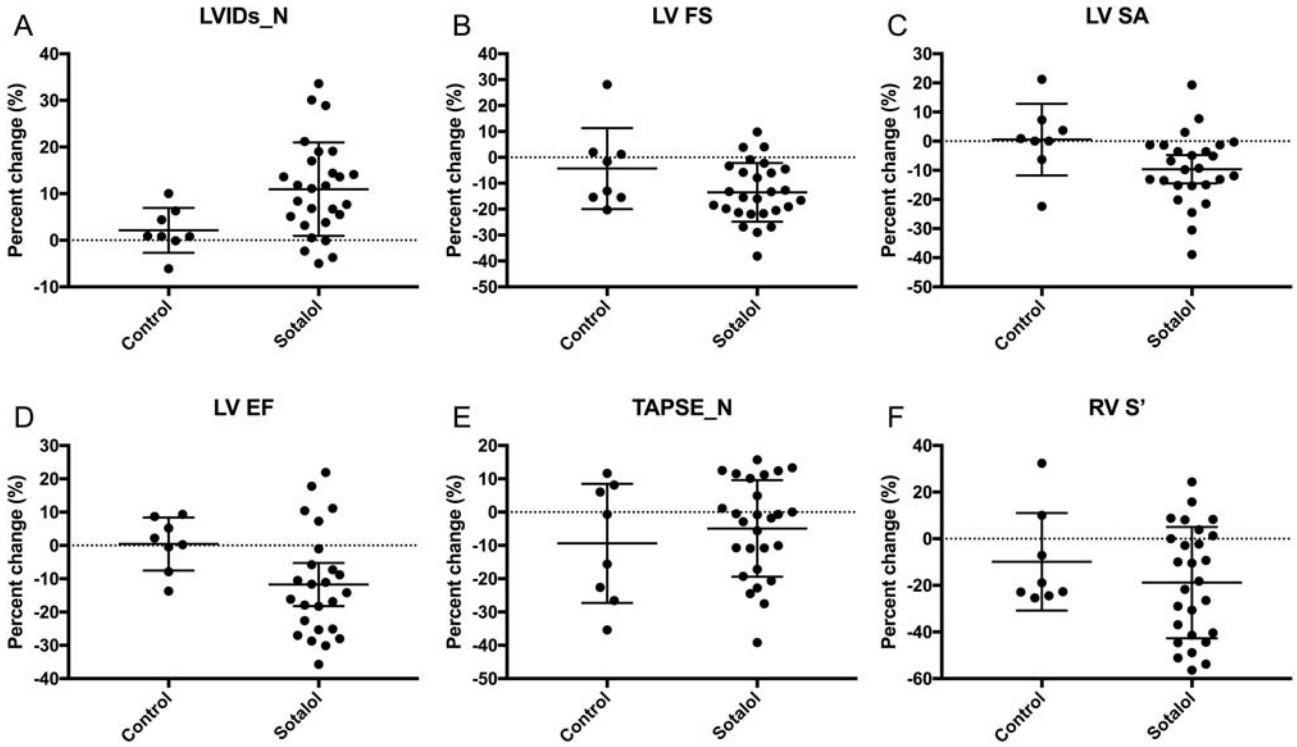

FIGURE 2 Scatter dot plots of LV internal dimension at end-systole normalized to bodyweight (LVIDs_N) (A), left ventricular fractional shortening (LV FS) (B), left ventricular shortening area (LV SA) (C), left ventricular ejection fraction (LV EF) (D), TAPSE normalized to bodyweight (TAPSE_N) (E), and peak systolic RV myocardial velocity at the lateral tricuspid annulus (RV S') (F) comparing the percent change in ventricular function of dogs in the control group (n = 8) verses dogs that received sotalol (n = 27). For each group, horizontal lines and error bars represent mean and SD. Statistically significant differences (Bonferroni corrected $P < .008$) were identified when comparing the percent change of LVIDs_N ($P = .002$) and LV EF ($P = .0079$) post-sotalol to the percent change of the same indices in control dogs. Statistically significant differences were not identified for the other indices of ventricular systolic function

decrease in LV systolic function compared to the percent change of controls whereas the other 4 indices (2 of LV systolic function and 2 of RV systolic function) were not significantly different from controls. These findings suggest the documented changes in LVIDs_N and LV EF were likely caused by sotalol and not secondary to variability of the echocardiographic indices or acclimation to the hospital environment, as may be the case for the other studied indices of systolic function (LV FS, LV SA, TAPSE_N, and RV S'). Clinically, the single dose of sotalol was well tolerated, even in dogs with systolic dysfunction or left atrial enlargement, and no adverse effects occurred during the monitoring period.

Our study was designed to determine the acute echocardiographic effects of sotalol on RV and LV systolic function in a clinically relevant manner. The results should be considered to provide pharmacodynamics data and not as a therapeutic trial. Previous studies in dogs[4,5] evaluating the inotropic effect of sotalol have used a more precise method of evaluating systolic function, LV +dP/dt, under experimental conditions in a more controlled and invasive manner while the dogs were under general anesthesia. These studies found that sotalol at a dose of 2 mg/kg did not significantly decrease LV systolic function compared to baseline. Unlike the pure β–blocker esmolol, sotalol attenuated the decrease in systolic function noted with esmolol.[4] Our study found that 2 systolic function indices (LVIDs_N and LV EF) indicated a mild decrease in LV systolic function post-sotalol beyond within-day variability controls. Differences in study design (anesthetized healthy dogs versus awake dogs with ventricular arrhythmias) and methods of quantifying systolic function (use of an invasive gold standard versus echocardiography) are important considerations when comparing studies. Despite the advantage of more accurately quantifying systolic function, these studies were performed in a smaller number of healthy anesthetized dogs. By not studying this effect in awake dogs with ventricular arrhythmias (ie, the most likely patient population to be managed with sotalol), the general clinical extrapolation of their results is limited. In addition, the β–blocker effects and thus inotropic effects of sotalol likely will have different effects in awake versus anesthetized dogs, because awake dogs likely have higher sympathetic tone susceptible to β–blockade. Lastly, differences in drug formulation also potentially could help explain how our results differed. Because of the unavailability of sotalol for parenteral use in the United States, we evaluated the more clinically relevant effects of PO sotalol (versus IV) on systolic function.

Four of 6 echocardiographic indices of systolic function failed to show a statistically significant difference in percent change post-sotalol compared with percent change of controls. The percent change post-sotalol for LVIDs_N and LV EF identified were considered mild with an 11%-12% changed noted. A likely explanation for the significant

difference between LVIDs_N and LV EF and their respective controls might be because these indices were found to have the lowest within-day variability coefficients of variation (LVIDs_N = 2.7% and LV EF = 4.2%) compared with the other indices and are therefore more sensitive at detecting smaller changes beyond within-day variability. It is also possible LVIDs_N and LV EF are more accurate indices of systolic function, but this was not assessed in our study.

In humans, considerable clinical evidence documents PO sotalol's lack of effect on systolic function (LV EF determined by radionuclide angiography) in the majority of cases.[24–27] However, most of these studies evaluated LV EF after more long-term treatment, which could explain the differences in our findings. Interestingly, one of the previously mentioned invasive studies in dogs[5] noted a similar significant decrease in systolic function (LV +dP/dt) after the 1st dose of sotalol when compared with baseline. After repeated dosing, however, systolic function increased and was not significantly different from baseline. The authors attributed this initial effect to sotalol's β–blocking properties and the later increase in systolic function to an increase in intracellular calcium concentration.[5] Given these findings and the results of our study, dose titration of sotalol may be ideal, particularly in dogs with decreased systolic function, as has been advocated by some.[28]

Several of the dogs in our study were diagnosed with systolic dysfunction, including 9 (33%) with LV systolic dysfunction (5 of which had LA enlargement), 7 (26%) with RV systolic dysfunction, and 3 (11%) with both. None of the dogs in our study experienced any adverse effects, including overt signs of low cardiac output or congestion, secondary to sotalol administration during the monitoring period. However, the short-term nature of our study design and lack of objective monitoring criteria (eg, heart rate with continuous ECG, respiratory rate, blood pressure) should be emphasized, and these results should be interpreted with caution. One study evaluating sotalol's antiarrhythmic effect in Boxers with ventricular arrhythmias showed that sotalol was well tolerated when administered for 21–28 days.[2] However, results of systolic function assessment were not reported.

Our study showed that a single PO dose of sotalol significantly decreases sinus heart rate, number of VPCs/5-minutes, and arrhythmia severity grade 2–4 hours post-sotalol as assessed by a 5-minutes ECG. A proarrhythmic effect of sotalol was not identified by the 5-minutes ECG post-sotalol. These results agree with a study[2] evaluating the more long-term antiarrhythmic effects of sotalol in Boxers with ventricular arrhythmias using 24-hours Holter monitor analysis in which a lack of a proarrhythmic effect and decreases in average heart rate, VPCs/24 hours, and arrhythmia grade also were documented. However, because of the relative insensitivity of 5-minutes ECGs,[29] a more robust ECG assessment (ie, 24-hours ambulatory ECG) is necessary to confirm our findings and more accurately judge the effectiveness of sotalol on ventricular ectopy in our patient population.

Our study had several limitations, including the relatively few number of dogs in our control group, a lack of a gold standard to assess systolic function (also discussed above) and the short-term nature of our study design based on a single PO dose of sotalol. In addition, the dogs that made up our study sample were affected by a variety of diseases (known or unknown) associated with ventricular arrhythmias. This represents a limitation of our study design insomuch as our results cannot be directly translated to a single disease entity such as preclinical DCM of the Doberman pinscher. Our findings cannot necessarily be extrapolated to dogs being treated with sotalol chronically or when the drug has reached steady state. Our study design mandated that the post-sotalol evaluations were performed during a narrow range of time (2–4 hours postpill). Drug concentrations of sotalol were not measured to evaluate differences in drug absorption or patient metabolism. In addition, we did not determine if the dogs in our study were affected by a β–adrenergic receptor polymorphism.[30] These polymorphisms have been shown to impact heart rate response to atenolol in healthy dogs, and, as such, their possible role in our patient population is unknown.[31] These limitations are certainly potential explanations for the variability of an individual dog's response to sotalol depicted for each of the echocardiographic indices in Figure 1. We were unable to identify common characteristics such as breed or type or severity of structural cardiac disease in the minority of dogs that did not show a mild decrease in systolic function post-sotalol (ie, the 5 dogs in which LV EF increased post-sotalol). Other potential explanations for the individual variability noted for both control dogs and dogs that received sotalol would be flaws or lack of precision or accuracy in the echocardiographic indices used, measurement variability, or the occurrence of human error on some of the measurements. Demonstration of drug absorption coupled with evaluation of systolic function by a gold standard index would have been ideal to document the true pharmacologic response or lack thereof in each dog. We also did not monitor the dogs' cardiac rhythm throughout the study period and consider the 5-minutes ECG assessment (versus more prolonged or thorough ECG monitoring) a limitation of our study. For example, frequent ventricular ectopy before the post-sotalol echocardiographic examination could have been a primary reason for decreased systolic function (because of myocardial stunning) noted in some dogs. Lastly, we acknowledge that having multiple sonographers with varying levels of experience perform the echocardiographic examinations represents a limitation. It would have been ideal for all of the echocardiographic studies to have been performed by the same sonographer. However, doing so often is impractical. In our opinion, the most important comparison in our study is the change noted within each individual dog, and the same sonographer performed repeat echocardiographic examinations in most of the cases (in all but 3 dogs). Despite these limitations, our study results provide clinicians with valuable information on the acute echocardiographic effects of sotalol on ventricular function in dogs with ventricular arrhythmias.

In conclusion, our study shows that a single PO dose of sotalol may cause a mild decrease in LV systolic function in dogs with ventricular arrhythmias when assessed by LVIDs_N and LV EF. Significant differences beyond the percent change of control dogs were not documented when assessed by 4 other echocardiographic indices of ventricular systolic function (LV FS, LV SA, TAPSE_N, and RV S'). Despite the possibility of a mild decrease in ventricular systolic function, a single PO dose of sotalol appears to be well tolerated, even in dogs with left atrial enlargement or systolic dysfunction because no adverse effects were noted during the study period. Additional longer-

term studies with a larger number of controls would be ideal to confirm our findings.

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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

The IACUC at the University of California, Davis (protocol #18482) approved all procedures in our study.

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