Journal of Veterinary Cardiology (2019) **25**, 14—24

ELSEVIER

Journal of Veterinary Cardiology
ESVC

www.elsevier.com/locate/jvc

Inotropic and chronotropic effects of sotalol in healthy dogs☆

J.R. Treseder, DVM, MS[a], N.L. LeBlanc, DVM, MS*, K.F. Scollan, DVM

Oregon State University, Carlson College of Veterinary Medicine, Department of Clinical Sciences, 105 Magruder Hall, 700 SW 30th Street, Corvallis, Oregon, 97331, USA

Received 25 September 2018; received in revised form 9 July 2019; accepted 16 July 2019

KEYWORDS
Beta-blocker;
Systolic function;
Echocardiography;
Canine

Abstract *Introduction:* Sotalol is an anti-arrhythmic drug commonly used for the treatment of pathologic tachyarrhythmias in dogs. The β-adrenergic blockade associated with sotalol administration may result in reduced myocardial contractility, which is clinically relevant for treating dogs with arrhythmias and concurrent myocardial dysfunction. The inotropic properties of sotalol are not well characterized in dogs.

Animals, Materials, and Methods: Ten healthy, adult, large breed dogs were prospectively enrolled. All dogs underwent physical examination, blood pressure measurement, electrocardiography, 24-h Holter monitoring, and echocardiography including three-dimensional left ventricular volume measurements. Dogs were subsequently administered sotalol (1—2 mg/kg) orally twice daily for 12—16 days, and the same diagnostic tests were performed. Paired statistical analysis was used to compare parameters at baseline and after treatment with sotalol.

Results: Standard echocardiographic parameters of systolic function were reduced on sotalol compared to baseline, including ejection fraction via Simpson's method of disks which was 5.8% (95% confidence interval [CI]: 2.77—8.83%, $p = 0.002$) lower post-treatment. Maximum heart rate on Holter monitor was 17 bpm (95% CI: 9—37 bpm, $p = 0.002$) lower post-treatment than at baseline.

Data presented as an oral abstract at ACVIM Forum 2018 in Seattle, WA.

☆ A unique aspect of the Journal of Veterinary Cardiology is the emphasis of additional web-based materials permitting the detailing of procedures and diagnostics. These materials can be viewed (by those readers with subscription access) by going to http://www.sciencedirect.com/science/journal/17602734. The issue to be viewed is clicked and the available PDF and image downloading is available via the Summary Plus link. The supplementary material for a given article appears at the end of the page. To view the material is to go to http://www.doi.org and enter the doi number unique to this paper which is indicated at the end of the manuscript.

* Corresponding author.
E-mail address: Nicole.leblanc@oregonstate.edu (N.L. LeBlanc).
[a] Current address of Dr. Treseder: Central Hospital for Veterinary Medicine, 4 Devine Street, North Haven, Connecticut 06511, USA.

https://doi.org/10.1016/j.jvc.2019.07.001

Conclusions: Sotalol has a mild negative inotropic effect in healthy dogs based on standard echocardiographic measurements. There is also a negative chronotropic effect at higher heart rates based on 24-h Holter monitoring.

Abbreviations

A	peak velocity of late diastolic transmitral flow
A′	peak velocity of late diastolic mitral annular motion as defined by pulsed wave Doppler
AECG	ambulatory electrocardiography
BPM	beats per minute
BP	blood pressure
CHF	congestive heart failure
E	peak velocity of early diastolic transmitral flow
E′	peak velocity of late diastolic mitral annular motion as defined by pulsed wave Doppler
ECG	electrocardiography
EDV	end-diastolic volume
EF	ejection fraction
ESV	end-systolic volume
FS	fractional shortening
IQR	interquartile range
IVSd	interventricular septum thickness at end-diastole
IVSs	interventricular septum thickness at end-systole
LV	left ventricle
LVIDd	left ventricular internal diameter at end-diastole
LVIDs	left ventricular internal diameter at end-systole
LVPWd	left ventricular posterior wall thickness at end-diastole
LVPWs	left ventricular internal diameter at end-diastole
RPS	right parasternal
RV	right ventricle
S′	peak velocity of systolic mitral annular motion as determined by pulsed wave Doppler
VPC	ventricular premature complex
3D	three-dimensional
3DE	three-dimensional echocardiography
2D	two-dimensional

Introduction

Sotalol is an antiarrhythmic agent commonly used in human and veterinary medicine for control of ventricular and supraventricular arrhythmias. Its antiarrhythmic properties are well established and are largely attributed to potassium channel blockade with concurrent non-selective β-adrenergic blockade, but sotalol's inotropic effects are not well-characterized. The antiadrenergic effects of sotalol may confer benefit or harm depending on the goals of treatment and the underlying heart disease.

The antiadrenergic properties of sotalol present a salient concern for exacerbation of underlying systolic dysfunction. The label recommendation for human use advises caution when initiated in patients with left ventricular (LV) dysfunction or congestive heart failure (CHF) based on a 1-year incidence of new or worsened CHF of 3% in patients without a prior history and 10% in those with a prior history of CHF [1]. In veterinary patients with systolic dysfunction with or without the presence of CHF, the safety of sotalol is based on anecdote and expert opinion rather than empirical evidence. Among veterinary cardiologists, there is a lack of consensus in general on the therapeutic or detrimental effects of β-adrenergic blockade in patients with structural heart disease.

The theoretical benefit of β-adrenergic blockade relates to negative inotropic and chronotropic effects which reduce myocardial oxygen demand [2—4], as well as the antiarrhythmic potential of β-blockers to reduce the risk for sudden death [5]. This has led to frequent use of β-blockers for diseases that cause concentric myocardial hypertrophy such as subaortic stenosis. However, there are few studies on long-term outcomes of these diseases and even fewer which evaluate the efficacy of medical therapy; those that have been published have failed to show a survival benefit with β-blockers [6—9]. Sotalol, by virtue of its prolongation of the action potential duration, has the potential to confer benefit beyond traditional β-adrenergic blocker therapy with a more potent antiarrhythmic effect.

The emergence of three-dimensional echocardiography (3DE) may allow for more accurate measurement of systolic function. In veterinary medicine, the use of 3DE is limited primarily to research institutions and is rarely used in clinical practice. Initial verification of LV volumetric data using 3DE has showed underestimation compared with volumetric gold standard imaging modalities such as cardiac magnetic resonance and multidetector row computed tomography, similar to humans [10—12]. However, 3DE can be performed as an extension of a standard echocardiographic study, without sedation or radiation exposure. Therefore, it may become more routinely used and allow detection of subtle functional changes such as those associated with mild β-adrenergic blockade.

There is widespread use of sotalol in veterinary medicine, primarily to suppress malignant ventricular arrhythmias. A recently published study showed that a single dose of oral sotalol causes a mild decrease in LV systolic function in dogs with ventricular arrhythmias [13]. However, there remains a paucity of literature evaluating sotalol's effect on ventricular function in the clinical setting, especially after chronic use. The objective of this study was to characterize the inotropic and chronotropic effects of sotalol in a population of healthy dogs. We hypothesized that echocardiographic indices of systolic function would decrease following oral sotalol and a negative chronotropic effect would be demonstrated as well.

Animals, materials, and methods

Healthy adult (1—6 years old), large-breed (>20 kg) dogs were prospectively recruited from the veterinary community at the Oregon State University College of Veterinary Medicine. This study was approved by the Institutional Animal Care and Use Committee at Oregon State University; all dog owners provided written consent before enrollment into the study (protocols 4777, 4779, 4902, 4910). Dogs with a history of a murmur, arrhythmia, or clinical signs of cardiopulmonary disease were excluded. Dogs were also excluded if they were currently being administered any medications, with the exception of monthly preventative drugs for ectoparasites and endoparasites.

Dogs were screened for study inclusion with a complete physical examination, oscillometric blood pressure (BP), 10-lead electrocardiography (ECG), and standard echocardiogram. Dogs were excluded from the study if there was evidence of clinically important systemic or cardiovascular disease upon initial assessment. Dogs were eligible for inclusion if there was evidence of trivial degenerative valve disease, i.e. if there were characteristic lesions of the mitral valve and/or trivial mitral regurgitation on echocardiogram in the absence of a murmur, cardiac chamber enlargement, or evidence of systolic dysfunction.

Upon inclusion in the study, baseline evaluation consisted of BP measurement, ECG, standard two-dimensional (2D), M-mode, and Doppler echocardiography, 3DE, and a 24-h Holter monitor. Sotalol was then prescribed at 1—2 mg/kg orally twice daily. Post-treatment evaluation occurred 12—16 days after initiation of sotalol administration and included the same diagnostic tests. This was considered adequate time for the drug to reach steady state based on a half-life of ~5 h [14], and a clinically relevant period at which dogs are often reassessed after initiation of antiarrhythmic therapy. Each dog then underwent a short tapering protocol consisting of a reduction in dose frequency to once daily administration for 3 days, after which sotalol was discontinued.

Blood pressure measurement

Oscillometric blood pressure measurement[b] was performed by an experienced technician before other diagnostic testing to minimize stress from handling and restraint. Dogs were unsedated and gently restrained in right lateral recumbency. Each dog was fitted with a blood pressure cuff estimated to be 30—40% of the limb's circumference, and the cuff was applied to the mid-metatarsal region of the left hindlimb. Five consecutive measurements of systolic, diastolic, and mean arterial pressure were recorded; measurements associated with the highest and lowest mean arterial pressure or obvious outliers of systolic or diastolic blood pressure were discarded. The mean of the remaining three measurements of systolic, diastolic, and mean arterial pressures were recorded.

Electrocardiography

A 10-lead ECG[c] was performed in unsedated dogs restrained in right lateral recumbency. Electrocardiography was performed according to standard technique, and electrical activity was recorded for

[b] CARDELL Veterinary Monitor 9401, Midmark, Tampa FL, USA.
[c] MAC 5500, GE Healthcare, Freiburg, Germany.

15—30 s [15]. The underlying heart rhythm and presence of pathologic arrhythmias was noted.

Echocardiography

Dogs were unsedated and restrained in right and left lateral recumbency. All dogs underwent M-mode, 2D, Doppler, and 3DE imaging with simultaneous ECG recording.[d] Two-dimensional imaging was obtained with an 8-3 MHz phased array or X5-1 MHz matrix transducer, and all 3D imaging was obtained with an X5-1 MHz matrix transducer. All 2D echocardiograms were performed by the same cardiology resident (JT) under the supervision of a board-certified cardiologist; 3DE images were obtained by at least two echocardiographers, a cardiology resident, and a board-certified cardiologist (JT and NL or KS). Measurements were performed for three consecutive cardiac cycles except in rare cases where image quality was considered inadequate, in which case non-consecutive cardiac cycles with at least two cardiac cycles were measured. All measurements were obtained during sinus rhythm, and the mean value was recorded. The authors were not formally blinded to treatment status, though measurements were performed in a single batch several months after data acquisition.

M-mode images of the LV were obtained from the right parasternal (RPS) short axis view at the level of the papillary muscles. Left ventricular free-wall thickness at end diastole (LVPWd) and end systole (LVPWs), interventricular septal wall thickness at end diastole (IVSd) and end systole (IVSs), LV internal diameter at end diastole (LVIDd), and LV internal diameter at end systole (LVIDs) were measured with wall thicknesses measured from leading edge to leading edge. Fractional shortening (FS) was calculated according to the formula (LVIDd-LVIDs)/LVIDd $\times$ 100. M-mode images of the LV at the level of the mitral valve were also obtained from the RPS short axis view, and E-point-to-septal separation was measured. M-mode images from the left apical four-chamber view optimized for the right heart were obtained with the cursor parallel to the RV free wall. These images were used to measure tricuspid annular plane systolic excursion as previously described [16,17].

Standard 2D imaging planes were obtained in each dog [18]. The LVPWd, LVPWs, IVSs, IVSd, LVIDd, and LVIDs were measured from the RPS short-axis view at the level of the papillary muscles with wall thicknesses measured from leading edge to trailing edge. Fractional shortening was calculated according to the same formula used to calculate M-mode FS. The ratio of the left atrial to aortic root diameter was measured from the RPS short-axis basilar view as previously described [19]. Left ventricular end-systolic and end-diastolic volumes were measured using monoplane Simpson's method of disks from the RPS long axis four-chamber view [20]. End-diastolic volume (EDV) was measured when the mitral valve was closed, and the LV volume was at its largest, selected from frames at the onset of the QRS complex. The frame used to measure end-systolic volume (ESV) was the last frame before mitral valve opening. Left ventricular end-diastolic and end-systolic volumes were recorded and used to calculate ejection fraction (EF) according to the formula (EDV-ESV)/EDV $\times$ 100. Left apical four-chamber views optimized for the right heart were obtained as previously described and used to measure right ventricular (RV) fractional area change [16]. Right ventricular end-diastolic area was measured with the tricuspid valve closed and the RV area at its largest, and RV end-systolic area was measured at the last frame before tricuspid valve opening with the RV area at its smallest. Right ventricular fractional area change was calculated according to the formula (RV end-diastolic area — RV end-systolic area)/RV end-diastolic area $\times$ 100.

Pulsed wave Doppler was performed at the level of the pulmonic valve from the RPS short axis-basilar view, and the peak pulmonic outflow velocity was measured. The peak aortic outflow velocity was measured from continuous wave Doppler images obtained from the subcostal or left apical five-chamber view. Pulsed wave Doppler was also performed to assess mitral inflow with interrogation at the level of the open mitral valve leaflet tips from the left apical four-chamber view. The E wave was identified as the first positive wave in early diastole (following the T wave on the ECG), and the A wave was identified as a positive wave after the P wave on the ECG. The maximal E and A wave velocities were measured to calculate the peak E wave to peak A wave ratio.

Pulsed wave tissue Doppler imaging was performed from the left apical four-chamber view at the lateral mitral annulus, septal mitral annulus, and lateral tricuspid annulus, with the latter performed from a left apical view optimized for the right heart [16,21,22]. The E′ and A′ waves were identified as negative waves in early and late diastole, respectively, using the ECG for reference as described for mitral inflow measurements. The S′

[d] iE33, Philips Medical Systems, Andover MA, USA.

wave was identified as the positive wave immediately after the QRS complex. The peak E wave to peak E′ wave ratio was calculated using the maximal E′ wave velocity on tissue Doppler of the lateral mitral annulus. Peak S' was recorded for the lateral and septal mitral annulus and the lateral tricuspid annulus.

Real-time 3DE images of the LV were obtained from the RPS long axis four-chamber view and from the left apical four-chamber view. Real-time 3DE images of the RV were obtained from the left apical four-chamber view optimized for the right heart. Full volume, ECG-gated 3D images were obtained with pyramidal volumes expanded to encompass the chamber of interest. Full volume 3D data sets were acquired from subvolumes of four consecutive cardiac cycles. Each recorded loop contained five full-volume data sets.

The 3DE data were stored digitally and analyzed off-line using commercially available software.[e] End-diastolic and end-systolic frames were automatically identified by the software. Reference points (apex, mitral annulus, and aortic valve for the LV; LV apex, mitral annulus, tricuspid valve, RV apex, and RV septal hinge points for the RV) were manually identified for appropriate chamber orientation on multiple views (four cross—sectional planes for the LV; six planes for the RV), and contour tracing was performed with semiautomatic border detection (Fig. 1). Automatically calculated volume measurements of interest were recorded (Fig. 2): EDV, ESV, stroke volume, and EF. Measurements were performed on a single data set (i.e. one complete heartbeat) within a series of five consecutive cardiac cycles obtained during sinus rhythm.

Holter monitoring

A 24-h ambulatory electrocardiogram (AECG) using a digital, 3-channel transthoracic system[f] was performed. Each dog was sent home after AECG placement to allow recording in the dog's normal environment. Owners were encouraged to maintain the dog's normal activity level and follow a typical routine. The AECG was removed after 24 h, and AECG digital files were analyzed by a cardiology resident (JT) under the supervision of a board-certified cardiologist (NL or KS) with an AECG analysis system.[g] The total number of ventricular premature complexes (VPCs) per 24-h period, and maximum, mean, and minimum heart rate were tabulated. The number of sinus pauses longer than 3 s was also recorded for each Holter. The occurrence of other pathologic arrhythmias was noted, if present.

Statistical analysis

Statistical analyses were performed with commercial analysis software.[h] Normal distribution of continuous data was assessed with the D'Agostino & Pearson test. Baseline and post-treatment data were compared with paired *t*-tests for normally distributed data and Wilcoxon signed-rank tests for non-normally distributed data. Volumetric measurements performed in 2D were compared with 3D data with Wilcoxon signed-rank tests. A two-sided alpha of $p < 0.05$ was considered significant. No correction was made for multiple comparisons. Normal data are expressed as mean $\pm$ standard deviation or mean (standard deviation), and non-normal data are expressed as median values with interquartile range (IQR). The difference between means is expressed as mean with 95% confidence interval (CI).

Results

Ten dogs were enrolled in the study. The mean age was 3.4 $\pm$ 1.9 years (range 1.1—6.4 years), and mean weight was 26.1 $\pm$ 4.3 kg (range 21.0—35.8 kg). The majority of the study population (eight dogs) consisted of mixed breed dogs, with two purebred dogs (one German Shepherd and one Golden Retriever). At baseline, the mean heart rate was 101 $\pm$ 26 beats per minute (bpm), systolic BP was 127 $\pm$ 11 mmHg, diastolic BP was 69 $\pm$ 14 mmHg, and mean BP was 91 $\pm$ 10 mmHg. The mean sotalol dose administered was 1.56 $\pm$ 0.23 mg/kg.

When comparing parameters at baseline and following treatment with sotalol, the post-treatment heart rate on physical exam was 20 bpm (95% CI 2—38 bpm) lower than at baseline ($p = 0.036$). There was no significant difference between baseline and post-treatment systolic, diastolic, or mean BP.

Salient 2D and M-mode echocardiographic findings are listed in Table 1. All measured indices of LV systolic function on M-mode were significantly different on sotalol than at baseline. These

[e] 4D LV-ANALYSIS, TOMTEC Imaging Systems GMBH, Munich, Germany.
[f] Trillium 5900, Forest Medical, LLC, East Syracuse NY, USA.
[g] Trillium Platinum Holter analysis, Forest Medical LLC, East Syracuse NY, USA.
[h] Prism 7, GraphPad Software, San Diego CA, USA.

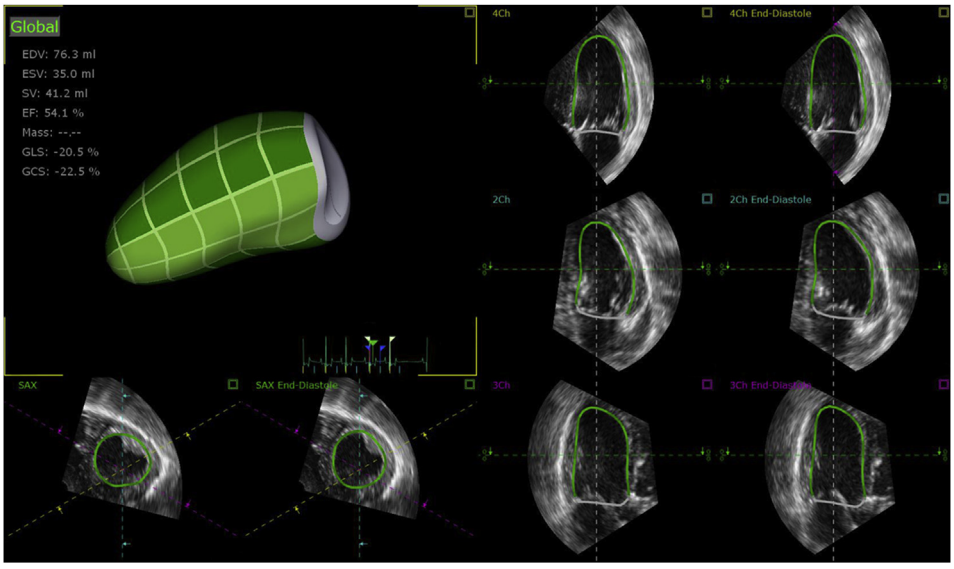

Figure 1 Analysis of real-time three-dimensional echocardiography imaging of left ventricle: Tracking revision following semiautomatic border detection. EDV, end-diastolic volume; EF, ejection fraction; ESV, end-systolic volume; GCS, global circumferential strain; GLS, global longitudinal strain; SV, stroke volume.

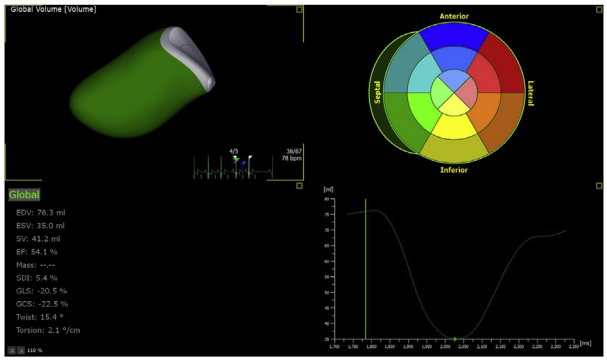

Figure 2 Analysis of real-time three dimensional echocardiography imaging of left ventricle: Global volume. EDV, end-diastolic volume; EF, ejection fraction; ESV, end-systolic volume; GCS, global circumferential strain; GLS, global longitudinal strain; SDI, systolic dyssynchrony index; SV, stroke volume.

included a reduction in FS (Fig. 3) and an increase in LVIDs and E-point-to-septal separation. Post-treatment LVPWs was significantly lower than baseline by a median of 0.95 mm ($p = 0.004$). There was no significant difference between baseline and post-treatment LVPWd, IVSd, IVSs, LVIDd, or tricuspid annular plane systolic excursion on M-mode measurements.

All measured indices of LV systolic function using 2D were significantly different on sotalol than at baseline. These included a reduction in FS (Fig. 3) and EF (Fig. 4) and an increase in LVIDs and ESV. Post-treatment LPWs was significantly lower than baseline by a mean of 1.35 mm (95% CI 0.57—2.13, $p = 0.003$). Left ventricular internal diameter at end-diastole was significantly increased by 1.93 mm (95% CI 0.38—3.48, $p = 0.020$) compared with baseline. There was no significant difference between baseline and post-treatment LVPWd, IVSd, IVSs, EDV, ratio of the left atrial to aortic root diameter, or RV fractional area change on 2D measurements.

Peak pulmonic and aortic outflow velocities were both significantly ($p = 0.004$, 0.002, respectively) lower on sotalol (pulmonic: 0.77 m/s $\pm$ 0.11; aortic: 1.28 m/s $\pm$ 0.18) than at baseline (pulmonic: 0.92 m/s $\pm$ 0.13; aortic: 1.53 m/s, IQR 1.21—1.62). The ratio of E to A was significantly ($p = 0.016$) higher on sotalol (1.81 $\pm$ 0.47) than at baseline (1.46 $\pm$ 0.32).

For tissue Doppler imaging, S′ measured at the septal mitral annulus was significantly lower on sotalol than at baseline. There was no significant difference in S′ measured at the lateral mitral annulus or lateral tricuspid annulus before and after treatment. There was also no significant difference in the ratio of E to E' (lateral mitral annulus) before and after treatment.

Baseline and post-treatment studies from 7/10 dogs were available for 3DE analysis because of technical issues with the picture archiving and communication system. Review of the acquired 3D LV volume sets revealed poor image quality from the left apical view in most dogs, and border detection was considered inaccurate and incomplete despite manual adjustment. Therefore, only images from the RPS four-chamber view were included for analysis of LV function.

Table 1 Two-dimensional and M-mode echocardiographic indices of left ventricular systolic function at baseline and after treatment with sotalol in 10 normal dogs; data are presented as mean (standard deviation) for normally distributed data and median (interquartile range) for non-normally distributed data.

Echocardiographic parameter	Baseline	Post-treatment	Mean or median of differences	95% CI of mean/median of differences	*p*-value
MM FS (%)	32.5 (2.6)	24.9 (5.7)	7.64	3.17—12.11	**0.004**
2D FS (%)	30.7 (28.7—33.8)	27.4 (4.0)	3.39	0.05—9.23	**0.010**
MM LVIDs (mm)	25.5 (2.4)	28.7 (3.2)	3.22	0.96—5.48	**0.010**
2D LVIDs (mm)	25.2 (2.9)	28.3 (2.0)	3.11	1.63—4.59	**0.001**
ESV (SMOD) (mm^3)	26.0 (4.6)	30.0 (4.6)	3.95	1.28—6.62	**0.009**
EF (SMOD) (%)	53.8 (4.4)	48.0 (6.8)	5.80	2.77—8.83	**0.002**
MM EPSS (mm)	3.08 (0.92)	3.99 (0.97)	0.91	0.25—1.57	**0.012**
Peak S' (lateral) (mm)	0.14 (0.02)	0.13 (0.02)	0.01	−0.02—0.01	0.235
Peak S' (septal) (mm)	0.11 (0.02)	0.09 (0.01)	0.02	0.01—0.03	**0.003**

CI, confidence interval; EF, ejection fraction; EPSS, E point to septal separation; ESV, end-systolic volume; FS, fractional shortening; LVIDs, left ventricular internal diameter at end-systole; MM, M-mode; 2D, two-dimensional; SMOD, Simpson's method of discs.
The bolded p-values represent statistically significant variables.

Real-time 3DE measurements included LV EDV, ESV, stroke volume, and EF, none of which was significantly different before and after treatment with sotalol (Table 2). Baseline and post-treatment 3D ESV, EDV, and EF were compared to the corresponding 2D volumetric measurements using Simpson's method of disks. There was no significant difference between the 2D and 3D measurements.

Holter data

There was a median of 1.5 VPCs (IQR 0—3.5) and three pauses greater than 3 s (IQR 0—13) on baseline Holter. The baseline minimum heart rate was 34 ± 2 bpm, average heart rate was 64 bpm (IQR 61—68 bpm), and maximum heart rate was 218 bpm (IQR 211—224 bpm); only the maximum heart rate was significantly different post-treatment at 195 ± 14 bpm ($p = 0.002$; Fig. 5). There was no significant difference in the total number of VPCs post-treatment (median 0, IQR 0—3) nor in the number of pauses (median 4, IQR 0—14.75; $p = 0.375$ and 0.844, respectively). One dog (case 9) had 150 single VPCs and 54 single atrial premature complexes on baseline Holter and 126 VPCs and 64 atrial premature complexes post-treatment, although only sinus rhythm was noted on baseline ECG and during the echocardiogram.

Discussion

Sotalol is an antiarrhythmic drug used frequently in dogs with structural heart disease; however, the

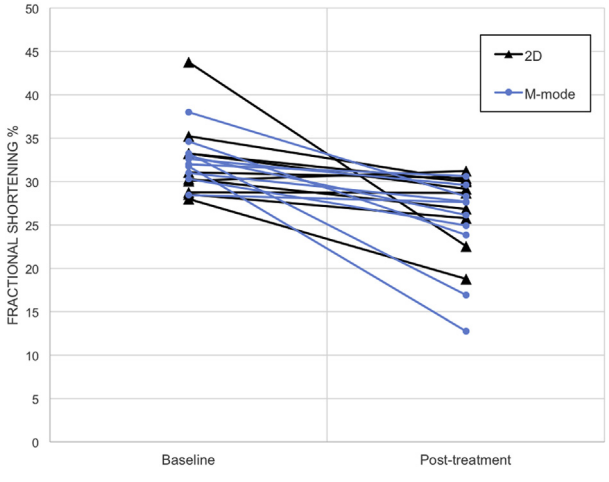

Figure 3 Fractional shortening with two-dimensional and M-mode measurements at baseline and after treatment with sotalol in 10 normal dogs. 2D, two-dimensional.

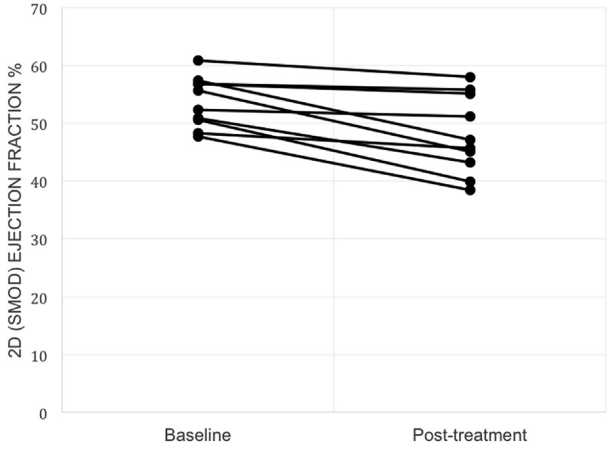

Figure 4 Ejection fraction measured on two-dimensional images using Simpson's method of discs at baseline and after treatment. 2D, two-dimensional; SMOD, Simpson's method of discs.

clinically relevant effects of sotalol on ventricular performance have not been well characterized in dogs to date. This study indicates that sotalol has mild but significant negative inotropic and chronotropic effects in large breed, healthy dogs. Conventional echocardiographic techniques provided almost uniform evidence of a reduction in systolic function, including a mean reduction in M-mode FS of 7.6% and mean reduction in 2D EF of 5.8%.

These findings are consistent with some of the experimental studies that have shown a reduction in systolic function in dogs from β-blockade because of sotalol [23—25] but in contrast to one study that did not identify a myocardial depressant effect of sotalol, including no change in the force—velocity curve from sotalol-induced β-blockade in the canine arm of the experiment [26]. Although β-blockade would be expected to influence RV systolic function as well, no significant change was noted in the measured indices of RV systolic function in our study population. The study may have been underpowered to detect small changes in these measurements, and non-volumetric indices are likely relatively insensitive measures of RV systolic function [27].

The present study also showed a negative chronotropic effect of sotalol, although this was reflected in only the maximum heart rate on Holter monitor and the heart rate on physical examination, with no significant difference in the mean or minimum heart rates or the number of pauses noted. This may reflect a more important influence in conditions, where sympathetic tone is high, such as in the hospital or during periods of excitement or activity at home. However, this is in contrast to a study in Boxers with ventricular arrhythmias where 16 dogs treated with sotalol showed a reduction in minimum, mean, and maximum heart rates on Holter monitor [28]. However, that study used a higher dose range of sotalol (1.5—3.5 mg/kg) and therefore the effect on heart rate may be dose dependent. It is also possible a larger number of dogs would have yielded detection of a smaller difference between groups.

The apparent negative inotropic effect of sotalol is often attributed to direct influence of β-adrenergic blockade, but some part of the reduction in systolic function may be related to a reduction in contractility at slower heart rates because of the force—frequency relationship [29].

Table 2 Three-dimensional echocardiographic volumetric indices of left ventricular systolic function at baseline and after treatment with sotalol in seven normal dogs; data are presented as median (interquartile range).

Echocardiographic parameter	Baseline	Post-treatment	Median of differences	95% CI of median of differences	*p*-value
ESV (mm^3)	26.5 (16.5—36.5)	28.3 (23.5—34.9)	1.87	−7.04—8.33	0.219
SV (mm^3)	29.2 (27.1—38.6)	31.0 (22.2—37.9)	0.53	−5.70—5.20	0.938
EF (%)	52.5 (51.5—59.2)	51.1 (49.3—53.8)	2.20	−14.20—6.03	0.375

CI, confidence interval; ESV, end-systolic volume; SV, stroke volume; EF, ejection fraction.

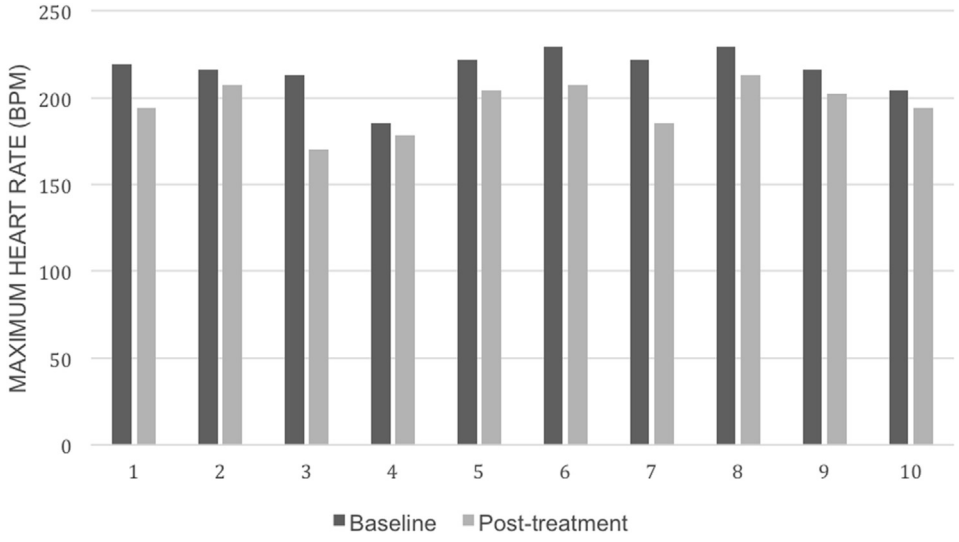

Figure 5 Maximum heart rate on 24-h Holter monitor at baseline and after treatment. BPM, beats per minute.

The relative contributions of direct antagonism of β-receptors and a slower heart rate to a reduction in systolic function in this study is unknown. Because the force-frequency response becomes flat or negative at higher heart rates in heart failure [30], this relationship may be altered in dogs with heart disease.

The goal of this study was to evaluate the effect of sotalol as it is most often used clinically, as chronic oral therapy. The findings of this study cannot be extrapolated to dogs with heart disease, especially given the different neurohormonal conditions and variation in sotalol's effects in those with cardiac dysfunction [31,32]. However, even a small reduction in systolic function may have clinical importance in some disease states, and this should be considered before initiating sotalol in dogs with poor systolic function and/or CHF. On the other hand, the demonstrated negative inotropic and chronotropic effects of sotalol support a reduction in myocardial oxygen demand, which may be desirable in dogs at risk for ischemia or in heart failure.

None of the 3DE measurements in the present study changed significantly with sotalol therapy, but the interpretation of these data is limited by the small number of dogs and lack of experience with 3DE in veterinary medicine. There are three studies in dogs on volumetric assessment of the LV using real-time 3DE compared with cardiac magnetic resonance or computed tomography as the reference standard [10—12]. These studies suggest that with the exception of ESV, indices of function such as EF and stroke volume may not be accurately reflected by real-time 3DE. These findings are in contrast to those in human medicine, where EF based on 3DE shows good agreement with magnetic resonance, despite underestimation of LV volumes [33—35]. It is important to note that the LV volumes measured using 3DE in this study were obtained from the RPS four-chamber view rather than the left apical view and as such cannot be directly compared to measurements reported in the literature.

The authors found that imaging from the left apical view in this cohort of healthy, unsedated, large breed dogs led to suboptimal quality for 3DE volume quantification compared with the RPS views. This may reflect improved image quality and less technically demanding image acquisition from the right side, especially in large, deep-chested dogs [36,37]. One study of 3DE obtained from the left apical view in unsedated dogs with degenerative valve disease showed good intra-observer acquisition and measurement variability for global LV volumes; however, these dogs were all <15 kg [38]. Another study using 3DE in dogs representing a larger variety of breeds and body weights showed higher but still acceptable coefficients of variation [39]. Neither of these studies had a reference standard for comparison to determine accuracy. Notably, the large majority of the dogs used in the veterinary validation studies were Beagles, which have a smaller body size and slightly broader chest conformation than most of the dogs in this study, possibly also contributing to better image quality from the left apical view.

The RPS four-chamber view has shown good agreement with the left apical view for volumetric measurements using 2D echocardiography [37,40,41]. Apical foreshortening is less of an issue with 3DE provided that the entire LV chamber is included in the data set, as 3DE obviates the need for geometric assumptions based on a single plane, whereas image quality and border detection is paramount. Based on the experience in this study and because good-quality echocardiographic images can be more universally obtained from the RPS view in a wider range of dogs, this may be a preferable view for routine 3DE evaluation of the LV in clinical practice. Future studies to validate 3DE of the LV from the RPS view should be considered.

The limitations of the present study are primarily related to the small number of dogs, and therefore the study may have been underpowered to detect changes in indices of RV function or to identify changes in the 3DE measurements. Additionally, echocardiography is not the most accurate way to measure systolic function. However, the goal of this study was to assess systolic function in awake and unsedated dogs as a more clinically relevant measure of sotalol's effects, precluding advanced imaging or cardiac catheterization. In addition, the relative impact of heart rate on contractility was not evaluated for each dog, and this may be a confounding factor masking the direct effects of the drug. One dog had evidence of clinically significant arrhythmias of unknown cause noted only after Holter analysis. This dog was included in the study because the heart was structurally unremarkable echocardiographically at the time of inclusion, with a FS of 28.5% on M-mode and a 2D EF of 56.9%. This dog could conceivably have had myocardial dysfunction that was unapparent and thus may not represent a normal control, although the reported changes in indices of LV systolic function remained statistically significant when this dog was excluded from the data set. Similarly, a dog with mild degenerative valve disease was included based on the lack of chamber enlargement and only trace to

mild valvular regurgitation but very mild dysfunction or remodeling secondary to volume overload cannot be entirely excluded in this dog.

Conclusions

Sotalol has a mild negative inotropic effect in healthy, large breed dogs based on conventional 2D echocardiography, and a negative chronotropic effect is present at high heart rates. Three-dimensional LV volumetric analysis from the RPS four-chamber view in awake, large-breed dogs may provide superior image quality to that obtained from the left apical view.

Conflicts of Interest Statement

The authors declare no conflicts of interest.

Funding

This study was supported by an ACVIM cardiology resident research grant.

Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jvc.2019.07.001.

References

[1] Betapace [package insert]. Wayne, NJ: Bayer HealthCare Pharmaceuticals; 2011.
[2] Taylor SH. Beta-blocking drugs and myocardial function. J Cardiovasc Pharmacol 1986;8:S75—82.
[3] Yamakawa H, Takeuchi M, Takaoka H, Hata K, Mori M, Yokoyama M. Negative chronotropic effect of beta-blockade therapy reduces myocardial oxygen expenditure for nonmechanical work. Circulation 1996;94:340—5.
[4] Levy JV. Comparative action of propranolol and sotalol (MJ-1999) on myocardial oxygen consumption in dogs: hemodynamic correlates. Proc Soc Exp Biol Med 1970;133:114—9.
[5] Dorian P. Antiarrhythmic action of beta-blockers: potential mechanisms. J Cardiovasc Pharmacol Ther 2005;10:S15—22.
[6] Eason BD, Fine DM, Leeder D, Stauthammer C, Lamb K, Tobias AH. Influence of beta blockers on survival in dogs with severe subaortic stenosis. J Vet Intern Med 2014;28:857—62.
[7] Meurs KM, Lehmkuhl LB, Bonagura JD. Survival times in dogs with severe subvalvular aortic stenosis treated with balloon valvuloplasty or atenolol. J Am Vet Med Assoc 2005;227:420—4.
[8] Johnson MS, Martin M, Edwards D, French A, Henley W. Pulmonic stenosis in dogs: balloon dilation improves clinical outcome. J Vet Intern Med 2004;18:656—62.
[9] Locatelli C, Spalla I, Domenech O, Sala E, Brambilla PG, Bussadori C. Pulmonic stenosis in dogs: survival and risk factors in a retrospective cohort of patients. J Small Anim Pract 2013;54:445—52.
[10] Meyer J, Wefstaedt P, Dziallas P, Beyerbach M, Nolte I, Hungerbuhler SO. Assessment of left ventricular volumes by use of one-, two-, and three-dimensional echocardiography versus magnetic resonance imaging in healthy dogs. Am J Vet Res 2013;74:1223—30.
[11] Eskofier J, Wefstaedt P, Beyerbach M, Nolte I, Hungerbuhler SO. Quantification of left ventricular volumes and function in anesthetized beagles using real-time three-dimensional echocardiography: 4D-TomTec analysis versus 4D-AutLVQ analysis in comparison with cardiac magnetic resonance imaging. BMC Vet Res 2015;11:260.
[12] Scollan KF, Stieger-Vanegas SM, Sisson DD. Assessment of left ventricular volume and function in healthy dogs by use of one-, two-, and three-dimensional echocardiography versus multidetector computed tomography. Am J Vet Res 2016;77:1211—9.
[13] Visser LC, Kaplan JL, Nishimura S, Gunther-Harrington CT, Belanger C, Oldach MS, Stern JA, Mueller MS. Acute echocardiographic effects of sotalol on ventricular systolic function in dogs with ventricular arrhythmias. J Vet Intern Med 2018;32:1299—307.
[14] Schnelle K, Garrett ER. Pharmacokinetics of the -adrenergic blocker sotalol in dogs. J Pharm Sci 1973;62:362—75.
[15] Tilley LP. Principles of electrocardiographic recording. Essentials of canine and feline electrocardiography: interpretation and treatment. 3rd ed. Philadelphia, PA: Lea & Febiger; 1992. p. 21—30.
[16] Visser LC, Scansen BA, Schober KE, Bonagura JD. Echocardiographic assessment of right ventricular systolic function in conscious healthy dogs: repeatability and reference intervals. J Vet Cardiol 2015;17:83—96.
[17] Pariaut R, Saelinger C, Strickland KN, Beaufrere H, Reynolds CA, Vila J. Tricuspid annular plane systolic excursion (TAPSE) in dogs: reference values and impact of pulmonary hypertension. J Vet Intern Med 2012;26:1148—54.
[18] Thomas WP, Gaber CE, Jacobs GJ, Kaplan PM, Lombard CW, Moise NS, Moses BL. Recommendations for standards in transthoracic two-dimensional echocardiography in the dog and cat. Echocardiography committee of the specialty of cardiology, American College of veterinary internal medicine. J Vet Intern Med 1993;7:247—52.
[19] Rishniw M, Erb HN. Evaluation of four 2-dimensional echocardiographic methods of assessing left atrial size in dogs. J Vet Intern Med 2000;14:429—35.
[20] Wess G, Domenech O, Dukes-McEwan J, Haggstrom J, Gordon S. European society of veterinary cardiology screening guidelines for dilated cardiomyopathy in doberman pinschers. J Vet Cardiol 2017;19:405—15.
[21] Choi J, Kim H, Yoon J. Pulsed tissue Doppler imaging of the left ventricular septal mitral annulus in healthy dogs. J Vet Sci 2013;14:85—90.
[22] Chetboul V. Tissue Doppler Imaging: a promising technique for quantifying regional myocardial function. J Vet Cardiol 2002;4:7—12.
[23] Gomoll AW, Braunwald E. Comparative effects of sotalol and propranolol on myocardial contractility. Arch Int Pharmacodyn Ther 1973;205:338—54.
[24] Antonaccio MJ, Gomoll A. Pharmacologic basis of the antiarrhythmic and hemodynamic effects of sotalol. Am J Cardiol 1993;72:27A—37A.

[25] Goldstein RE, Hall CA, Epstein SE. Comparison of relative inotropic and chronotropic effects of propranolol, practolol, and sotalol. Chest 1973;64:619—27.
[26] Brooks H, Banas Jr J, Meister S, Szucs Jr M, Dalen J, Dexter L. Sotalol-induced beta blockade in cardiac patients. Circulation 1970;42:99—110.
[27] Leong DP, Grover S, Molaee P, Chakrabarty A, Shirazi M, Cheng YH, Penhall A, Perry R, Greville H, Joseph MX, Selvanayagam JB. Nonvolumetric echocardiographic indices of right ventricular systolic function: validation with cardiovascular magnetic resonance and relationship with functional capacity. Echocardiography 2012;29:455—63.
[28] Meurs KM, Spier AW, Wright NA, Atkins CE, DeFrancesco TC, Gordon SG, Hamlin RL, Keene BW, Miller MW, Moise NS. Comparison of the effects of four antiarrhythmic treatments for familial ventricular arrhythmias in Boxers. J Am Vet Med Assoc 2002;221:522—7.
[29] Opie LH, Perlroth MG. Ventricular function. Heart physiology: from cell to circulation. 4th ed. Philadelphia: Lippincott Williams & Wilkins; 2004. p. 365—7.
[30] Mulieri LA, Hasenfuss G, Leavitt B, Allen PD, Alpert NR. Altered myocardial force-frequency relation in human heart failure. Circulation 1992;85:1743—50.
[31] Chugh SS, Johnson SB, Packer DL. Amplified effects of d,l-sotalol in canine dilated cardiomyopathy. Pacing Clin Electrophysiol 2001;24:1783—8.
[32] Holubarsch C, Schneider R, Pieske B, Ruf T, Hasenfuss G, Fraedrich G, Posival H, Just H. Positive and negative inotropic effects of DL-sotalol and D-sotalol in failing and nonfailing human myocardium under physiological experimental conditions. Circulation 1995;92:2904—10.
[33] Wood PW, Choy JB, Nanda NC, Becher H. Left ventricular ejection fraction and volumes: it depends on the imaging method. Echocardiography 2014;31:87—100.
[34] Dorosz JL, Lezotte DC, Weitzenkamp DA, Allen LA, Salcedo EE. Performance of 3-dimensional echocardiography in measuring left ventricular volumes and ejection fraction: a systematic review and meta-analysis. J Am Coll Cardiol 2012;59:1799—808.
[35] Mor-Avi V, Jenkins C, Kuhl HP, Nesser HJ, Marwick T, Franke A, Ebner C, Freed BH, Steringer-Mascherbauer R, Pollard H, Weinert L, Niel J, Sugeng L, Lang RM. Real-time 3-dimensional echocardiographic quantification of left ventricular volumes: multicenter study for validation with magnetic resonance imaging and investigation of sources of error. JACC Cardiovasc Imaging 2008;1:413—23.
[36] Dukes-McEwan J. Comparison between right and left cardiac windows to determine left ventricular volumes and ejection fraction in six dog breeds with differing somatotypes. Eur J Ultrasound 2002;15:S4—5.
[37] Wess G, Maurer J, Simak J, Hartmann K. Use of Simpson's method of disc to detect early echocardiographic changes in Doberman Pinschers with dilated cardiomyopathy. J Vet Intern Med 2010;24:1069—76.
[38] Ljungvall I, Hoglund K, Carnabuci C, Tidholm A, Haggstrom J. Assessment of global and regional left ventricular volume and shape by real-time 3-dimensional echocardiography in dogs with myxomatous mitral valve disease. J Vet Intern Med 2011;25:1036—43.
[39] Tidholm A, Westling AB, Hoglund K, Ljungvall I, Haggstrom J. Comparisons of 3-, 2-dimensional, and M-mode echocardiographical methods for estimation of left chamber volumes in dogs with and without acquired heart disease. J Vet Intern Med 2010;24:1414—20.
[40] Smets P, Daminet S, Wess G. Simpson's method of discs for measurement of echocardiographic end-diastolic and end-systolic left ventricular volumes: breed-specific reference ranges in Boxer dogs. J Vet Intern Med 2014;28:116—22.
[41] Seckerdieck M, Holler P, Smets P, Wess G. Simpson's method of discs in Salukis and Whippets: echocardiographic reference intervals for end-diastolic and end-systolic left ventricular volumes. J Vet Cardiol 2015;17:271—81.