Retrospective review of carvedilol administration in 38 dogs with preclinical chronic valvular heart disease

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KEYWORDS
Beta-blocker; Canine; Cavalier King Charles Spaniel; Mitral regurgitation

Abstract  Objectives: Report the effect of carvedilol administration on clinical and echocardiographic parameters and outcome in dogs with preclinical (ACVIM Stage B) chronic valvular heart disease (CVD).

Animals, materials and methods: Retrospective case series of 38 client-owned dogs. Demographic, physical examination and diagnostic imaging findings, blood pressure (BP), administration details and outcome were obtained from medical records of dogs receiving carvedilol for preclinical CVD. When possible, additional follow-up information was obtained through telephone interviews with referring veterinarians and owners.

Results: Baseline data and follow-up were evaluated. Median and interquartile range (IQR) for age and weight were 8.6 (7.2–10.8) years and 8.5 (7.6–9.6) kg. 14/38 were male; 33/38 were Cavalier King Charles Spaniels; 33/38 had Stage B2 CVD. The initial dose of carvedilol was 0.31 (0.26–0.35) mg/kg PO twice daily. The carvedilol dose achieved following up titration was 1.11 (0.81–1.32) mg/kg twice daily. No adverse effects were recorded during up titration. Median survival for all dogs was 48.5 months with a 95% CI of 38.3–58.6.

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Conclusions: This study suggests that carvedilol at the dose reported herein is well tolerated in small breed dogs with preclinical CVD. Prospective studies to evaluate efficacy are warranted.
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Introduction

Chronic valvular heart disease (CVD) is the most common etiology of both heart disease and congestive heart failure (CHF) in the dog. The incidence increases with age in all dogs but small breed dogs, in particular the Cavalier King Charles Spaniel (CKCS), have increased risk. CVD is characterized by a long preclinical period. Based on the classification scheme presented in the American College of Veterinary Internal Medicine (ACVIM) Consensus Statement guidelines on the diagnosis and treatment of CVD, dogs with preclinical CVD are categorized as Stage B. Prior to the onset of cardiac remodeling, dogs with preclinical CVD are classified as Stage B1. Dogs are classified as Stage B2 once remodeling has progressed to an extent that can be readily detected by radiography and/or echocardiography. Progressive remodeling and the attendant neuroendocrine activation are associated with the development of CHF (Stage C) in some but not all dogs with Stage B CVD. A timely effective therapeutic intervention in dogs with Stage B CVD has the potential to delay the onset of CHF and prolong survival.

Currently there is no definitive proof that any medication initiated in either Stage B1 or B2 CVD can delay disease progression or improve survival. This lack of convincing evidence was reflected in the ACVIM Consensus Statement guidelines on the diagnosis and treatment of CVD; although this document did comment on the potential utility of both angiotensin converting enzyme inhibitors (ACEI) and beta-blockers (BB) in a subset of Stage B dogs. The reported benefits of chronic beta-blockade in models of chronic mitral regurgitation (MR) are likely multi-factorial and may involve limiting the consequences of chronic adrenergic stimulation on cardiomyocytes, changes in loading conditions and reductions in cardiomyocyte work related in part to reductions in heart rate (HR), indirect systemic systolic blood pressure (BP), left ventricular (LV) contractility and potentially regurgitant volume.

Carvedilol is a 3rd generation non-selective BB and alpha1-blocker with ancillary antioxidant effects and thus combines the potential benefit of non-selective beta-blockade with the afterload reduction properties of an alpha1-blocker. Additionally, the ancillary antioxidant properties may decrease oxidant stress associated with progressive heart failure.

The Texas A&M University (TAMU) cardiology service routinely offers clients the option to initiate carvedilol administration once their dog is diagnosed with early or mild preclinical CVD. Dogs with substantial remodeling that are considered to be at imminent risk of CHF are typically excluded from this option. This retrospective review reports the outcome in a case series that had carvedilol initiated for preclinical CVD.

Abbreviations

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Definition</th>
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<tbody>
<tr>
<td>ACEI</td>
<td>angiotensin converting enzyme inhibitor</td>
</tr>
<tr>
<td>ACVIM</td>
<td>American College of Veterinary Internal Medicine</td>
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<tr>
<td>BB</td>
<td>beta-blocker</td>
</tr>
<tr>
<td>BP</td>
<td>indirect systemic systolic blood pressure</td>
</tr>
<tr>
<td>CI</td>
<td>confidence interval</td>
</tr>
<tr>
<td>CKCS</td>
<td>Cavalier King Charles Spaniel</td>
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<tr>
<td>CHF</td>
<td>congestive heart failure</td>
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<tr>
<td>CVD</td>
<td>chronic valvular heart disease</td>
</tr>
<tr>
<td>FS%</td>
<td>left ventricular fractional shortening measured from short-axis M-mode</td>
</tr>
<tr>
<td>HR</td>
<td>heart rate</td>
</tr>
<tr>
<td>IQR</td>
<td>interquartile range</td>
</tr>
<tr>
<td>LA:Ao (M-mode)</td>
<td>Ratio of left atrium to aorta as measured from short-axis M-mode</td>
</tr>
<tr>
<td>LA:Ao (2D)</td>
<td>Ratio of left atrium to aorta as measured from short-axis 2 dimensional image</td>
</tr>
<tr>
<td>LV</td>
<td>left ventricle</td>
</tr>
<tr>
<td>LVIDd</td>
<td>left ventricular internal dimension in diastole as measured from short axis</td>
</tr>
<tr>
<td>LVIDd-N</td>
<td>left ventricular internal dimension in diastole normalized</td>
</tr>
<tr>
<td>LVIDs</td>
<td>left ventricular internal dimension in systole as measured from short axis</td>
</tr>
<tr>
<td>LVIDs-N</td>
<td>left ventricular internal dimension in systole normalized</td>
</tr>
<tr>
<td>MR</td>
<td>mitral regurgitation</td>
</tr>
<tr>
<td>VHS</td>
<td>vertebral heart scale</td>
</tr>
<tr>
<td>NL</td>
<td>normal</td>
</tr>
<tr>
<td>PH</td>
<td>pulmonary hypertension</td>
</tr>
</tbody>
</table>
Animals, material and methods

The electronic medical records data base of TAMU Veterinary Medical Teaching Hospital was searched for all canine cases of Stage B CVD that received carvedilol between Jan 2002 and Jan 2011. Fifty dogs with Stage B CVD were identified as having received carvedilol. For the purpose of this study a diagnosis of Stage B1 CVD was defined as the presence of a characteristic murmur in a preclinical dog with a vertebral heart scale (VHS) \( \leq 10.5 \). Stage B2 CVD was determined by the presence of a characteristic murmur in a preclinical dog and a VHS \( > 10.5 \). Table 1

To be eligible for inclusion in the baseline and follow-up analysis, dogs must have had carvedilol initiated between Jan 2002 and Jan 2011, had a baseline clinical evaluation performed immediately prior to initiation of carvedilol and weigh \( < 20 \) kg. Additionally, chronic carvedilol administration had to be confirmed based on review of the electronic and paper medical records or phone contact with the referring veterinarian or owners. Dogs that had only one appointment where carvedilol was recommended or prescribed but no available follow-up information were not included. No dog was excluded due to death or development of CHF during up titration. Thirty-eight of 50 dogs fulfilled the inclusion criteria for baseline and follow-up analysis. For inclusion in the paired follow-up analysis dogs were required to have received carvedilol from the time of initiation until the time of follow-up clinical evaluation which had to occur 3–8 months following the initiation of carvedilol. Twenty of 38 dogs fulfilled these criteria. Clinical outcome was assessed in all dogs and included time to death, time until lost to follow-up, and time to onset of CHF. Data were collected from the medical record and when possible, additional follow-up data were collected by telephone interviews with referring veterinarians and owners.

For each dog, baseline demographic data, results of physical examination, BP and imaging (thoracic radiography, echocardiography) were reviewed. Additional information obtained from the medical records included initial and maximum carvedilol dose as well as up titration details when available. Particular attention was paid to identification of any adverse events that may have occurred during carvedilol up titration. Lastly, any carvedilol dosage reductions were recorded. Other baseline cardiac medications and any cardiac medications that were initiated later and the reason for initiation were recorded. Date of CHF and death were recorded. Cause of death was recorded if known but when available information was inadequate to determine the cause of death it was recorded as unknown. If a clinical evaluation occurred between 3 and 8 months following initiation of carvedilol, results of physical examination, BP and imaging (thoracic radiography, echocardiography) were recorded.

Statistical analysis

Continuous variables are reported as median values, 25th–75th interquartile range (IQR), minimum and maximum value [range]. For each continuous variable, follow-up data are summarized in the same manner as the baseline. Paired baseline to follow-up comparisons were performed using the Wilcoxon matched-pairs signed-ranks test for medians and an exact McNemar’s test for proportions. Parametric survival models including Weibull, exponential and gamma, were evaluated by the use of Akaike’s information criterion. Multivariate model selection was performed with a backward stepwise approach. All two variable interactions were considered and only those significant at the 5% level were retained in the parsimonious model. All statistical tests were performed with commercially available software. Values of \( P < 0.05 \) were considered significant.

Results

Baseline

The baseline study population consisted of 38 dogs. Dogs weighed 8.5 kg (7.6–9.6) [3.0–13.8] and 14/38 (36.8%) were males. The median age of all 38 dogs was 8.6 years (7.2–10.8) [3.0–12.8]. The majority of dogs were CKCS 33/38(86.8%). There was one each of Maltese, Cocker Spaniel, Pomeranian, Miniature Poodle and small mixed-breeds. All dogs had a murmur characteristic of MR and had no current or prior signs or symptoms of CHF. Five of 38 dogs (13.2%) had a VHS \( \leq 10.5 \) and were categorized as Stage B1. The remaining 33/38 (86.8%) had a VHS \( > 10.5 \) and were categorized as Stage B2. Table 1

\cite{c} Stata LLP, College Station, Tex.
Carvedilol

The initial dose of carvedilol in this cohort was 0.31 mg/kg (0.26–0.35) [0.15–0.53] given by mouth twice daily. The carvedilol dose achieved following up titration was 1.11 mg/kg (0.81–1.32) [0.27–2.02] twice daily. In dogs that started carvedilol in the first 3rd of the study (Jan 2002–Jan 2005, N = 16) 4/16 (25%) received maximum doses <0.6 mg/kg twice daily, while 8/16 (50%) received maximum doses >1.0 mg/kg twice daily, 1/16 (6%) recorded in 15/38 dogs. Ten of these 15 (67%) had increases used to reach the maximum dose was reported in 15/38 dogs. Ten of these 15 (67%) had increases used to reach the maximum dose. No dogs with a normal VHS demonstrated LV dilation or left atrial enlargement based on echocardiography.

Table 1 Examination parameters.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Baseline (when available)</th>
<th>Follow-up (when available)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
<td>Median (IQR)</td>
</tr>
<tr>
<td>Murmur grade (1–6)</td>
<td>38</td>
<td>4 (4–4)</td>
</tr>
<tr>
<td>BP (mmHg)</td>
<td>35</td>
<td>120 (110–143)</td>
</tr>
<tr>
<td>Heart rate (bpm)</td>
<td>37</td>
<td>120 (108–132)</td>
</tr>
<tr>
<td>Respiration Rate (per min)</td>
<td>22</td>
<td>29 (24–32)</td>
</tr>
<tr>
<td>VHS</td>
<td>37</td>
<td>11.2 (11–11.70)</td>
</tr>
<tr>
<td>LVIDd (cm)</td>
<td>36</td>
<td>3.21 (2.95–3.47)</td>
</tr>
<tr>
<td>LVIDd-N</td>
<td>36</td>
<td>1.70 (1.57–1.87)</td>
</tr>
<tr>
<td>LVIDs (cm)</td>
<td>36</td>
<td>1.97 (1.65–2.11)</td>
</tr>
<tr>
<td>LVIDs-N</td>
<td>36</td>
<td>0.97 (0.86–1.05)</td>
</tr>
<tr>
<td>LA: Ao (M-mode)</td>
<td>33</td>
<td>1.18 (1.06–1.43)</td>
</tr>
<tr>
<td>LA: Ao (2D)</td>
<td>22</td>
<td>1.40 (1.23–1.59)</td>
</tr>
<tr>
<td>TR velocity (m/s)</td>
<td>16</td>
<td>2.71 (2.49–2.99)</td>
</tr>
<tr>
<td>FS (%)</td>
<td>36</td>
<td>40.6 (36.6–45.0)</td>
</tr>
<tr>
<td>PH (% yes)</td>
<td>34</td>
<td>23.53%</td>
</tr>
</tbody>
</table>

N = number of dogs. Summary of baseline and follow-up exam parameter observations. Median (IQR) and absolute range are reported. BP; blood pressure, VHS; vertebral heart scale, LVIDd; left ventricular internal dimension during diastole, LVIDd-N; normalized left ventricular internal dimension during diastole, LVIDs; left ventricular internal dimension during systole, LVIDs-N; normalized left ventricular internal dimension during systole, LA: Ao (M-mode); ratio of LA to Ao measured from M-mode short axis, LA: Ao (2D); ratio of LA to Ao measured from short axis, TR; tricuspid regurgitation, FS%; fractional shortening percent, PH; pulmonary hypertension.
was recorded in 19/38 dogs. When the percent increase was different between up titration intervals the maximum percent increase was recorded. The median percent dosage increase was 56% (IQR 50.0–83.5, range 25–200%). No adverse effects including onset of CHF were reported during up titration in this study population, thus the maximum carvedilol dose was not related to the development of an adverse event in any dog in this study.

The dose of carvedilol was reduced during chronic administration (i.e. following the onset of CHF) in 7/38 dogs (18%) due to the development of signs suggestive of progressive or end stage heart failure, in particular those suggestive of poor forward cardiac output. Onset of these signs was considered to be a consequence of disease progression and not an adverse event secondary to carvedilol. In 6 of the 7 dogs, dose reduction protocols were well described and the dose was reduced by approximately 50%. In 2 dogs carvedilol was then discontinued 1–2 weeks later. In 3 dogs it was continued chronically at the new lower dose. In 1 dog the lower dose was reduced by another 50% (i.e. 25% of the maximum dose) 4 weeks later and continued chronically. Two of the 7 dogs who underwent dose reductions and were maintained on the new lower dose are still alive.

In addition to carvedilol, other cardiac medications were initiated at some time during Stage B CVD (i.e. prior to CHF) in 14/38 (36.8%) dogs. ACEI were used in 13/14 (92.9%) dogs, and in 11/14 (78.6%) it was the only additional cardiac medication used. In the 1 dog that did not receive an ACEI spironolactone was used. One dog each received a combination of an ACEI and pimobendan or an ACEI and furosemide for cough due to left mainstem bronchial compression.

Follow-up and outcome

The median time to follow-up for all parameters evaluated in the paired analysis was 4.9 months (3.9–5.4) with a range of 3.4–7.8 months. Table 2 displays the results of the paired tests to compare baseline to follow-up showing that the majority of parameters evaluated during follow-up examinations were not significantly different from those at baseline. There was a significant reduction in HR and FS% and significant increase in LVIDs and LVIDs-N. The apparent small absolute decrease in median LVIDs at follow-up (0.02 cm) was a consequence of 2/15 dogs that demonstrated a decrease in LVIDs.

Twenty-nine of 38 (76.3%) dogs were dead at the time of writing. In 9/29 (31%) the cause of death was categorized as being related to their cardiac disease, 6/29(21%) were clearly due to another non-cardiac cause. In 14/29 (48.3%) there was insufficient information available to categorize the

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Table 2  Paired tests of difference in baseline to follow-up parameters.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Median (IQR) Min–Max</th>
<th>N</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>BP (mmHg)</td>
<td>124 (110–148) 100–155</td>
<td>17</td>
<td>0.461</td>
</tr>
<tr>
<td>Heart rate (bpm)</td>
<td>124 (120–144) 88–148</td>
<td>19</td>
<td>0.030</td>
</tr>
<tr>
<td>Respiration rate (per min)</td>
<td>27 (24–40) 20–40</td>
<td>6</td>
<td>0.753</td>
</tr>
<tr>
<td>VHS</td>
<td>11.2 (11.0–11.6) 10.7–12.7</td>
<td>20</td>
<td>0.419</td>
</tr>
</tbody>
</table>

Echo Parameters

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Median (IQR) Min–Max</th>
<th>N</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>LVIDd (cm)</td>
<td>3.09 (2.8–3.5) 2.25–4.01</td>
<td>15</td>
<td>0.061</td>
</tr>
<tr>
<td>LVIDd-N</td>
<td>1.70 (1.6–1.9) 1.35–2.12</td>
<td>15</td>
<td>0.061</td>
</tr>
<tr>
<td>LVIDs (cm)</td>
<td>1.98 (1.6–2.2) 1.24–2.37</td>
<td>15</td>
<td>0.012</td>
</tr>
<tr>
<td>LVIDs-N</td>
<td>0.96 (0.9–1.1) 0.72–1.27</td>
<td>15</td>
<td>0.012</td>
</tr>
<tr>
<td>LA:Ao (M-mode)</td>
<td>1.22 (1.1–1.5) 0.92–1.96</td>
<td>15</td>
<td>0.181</td>
</tr>
<tr>
<td>LA:Ao (2D)</td>
<td>1.42 (1.2–1.6) 0.97–1.95</td>
<td>11</td>
<td>0.755</td>
</tr>
<tr>
<td>TR velocity (m/s)</td>
<td>2.84 (2.7–3.0) 2.66–3.02</td>
<td>2</td>
<td>0.180</td>
</tr>
<tr>
<td>FS (%)</td>
<td>42.6 (37.6–45.1) 28.9–54.0</td>
<td>15</td>
<td>0.047</td>
</tr>
<tr>
<td>PH (% yes)</td>
<td>22.2% 11.1%</td>
<td>9</td>
<td>0.317</td>
</tr>
</tbody>
</table>

N = number of dogs. Summary of baseline and follow-up exam parameter observations for those dogs evaluated at both baseline and follow-up (between 3 and 8 months following baseline evaluation). Median, 25th and 75th percentile, and minimum and maximum are reported. P-value for Wilcoxon sign-rank test for paired data is shown. Test for PH is McNemar’s test of proportion for paired data. BP; blood pressure, VHS; vertebral heart scale, LVIDd; left ventricular internal dimension during diastole, LVIDd-N; normalized left ventricular internal dimension during diastole, LVIDs; left ventricular internal dimension during systole, LVIDs-N; normalized left ventricular internal dimension during systole, LA:Ao (M-mode); ratio of LA to Ao measured from M-mode short axis, LA:Ao (2D); ratio of LA to Ao measured from short axis, TR; tricuspid regurgitation, FS%; fractional shortening percent, PH; pulmonary hypertension.
death as cardiac or non-cardiac and thus cause of
death was recorded as unknown. Three of the 14
(21.4%) dogs who died of an unknown cause had
a history of CHF following the study period. There
was no significant difference in the time to death
between the groups.

Fourteen of the 38 (36.8%) dogs developed CHF
(Stage C or D) and 13 of these 14 (92.8%) were
death at the time of writing. In 9/13 (69.2%) the cause
of death was categorized as cardiac, 1/13 (7.7%) was
euthanized for non-cardiac reasons and in 3/13
(23.1%) the cause of death could not be deter-
mined. Concurrent treatment for CHF was recor-
ded in 13/14 dogs and consisted of an ACEI in 9/13
(69.2%), pimobendan in 12/13 (92.3%), furosemide
in 11/13 (84.6%), spironolactone in 3/13 (23%),
sildenafil in 2/13 (15.4%) and sotalol in 1/13
(7.7%). Combination therapy was used in all 13
dogs with CHF.

The observed survival range for all dogs (N = 38)
was 5.5–92.6 months and neither of the 2 dogs
that contributed to the observed maximum and
minimum range were censored. The observed
median survival was 44.3 months with an IQR of
22.6–59.5 months.

A parametric proportional hazards model with
a Weibull distribution (multivariable analysis) was
performed to estimate median survival time and
the effect of all evaluated baseline parameters.
For survival analysis, all-cause mortality was the
primary endpoint. The median survival for all dogs
(N = 38) was 48.5 months with a 95% CI of
38.3–58.6. Median survival for Stage B2 dogs
(N = 33) was 48.5 months with a 95% CI of
38.3–61.4. Median survival for Stage B1 dogs
(N = 5) was 40.9 months with a 95% CI of
25.3–59.5. There was no significant difference in
survival times between the Stage B1 and B2 dogs.

Fig. 1 summarizes selected parameters from the
univariate analysis. The significant variables
retained in the parsimonious model were
maximum carvedilol dose administered, age, HR
and onset of CHF. Maximum carvedilol dose
administered (hazard ratio = 0.82; 95% CI
0.67–0.99; P = 0.049), age (hazard ratio = 19.0;
95% CI 2.8–126; P = 0.00), higher baseline HR (i.e.
for every 5 bpm increase in HR at baseline, hazard
ratio = 2.4; 95% CI 1.27–4.65; P = 0.01) and onset
of CHF during follow-up (hazard ratio 5.1; 95% CI
2.0–12.6; P = 0.00) were all significant. The only
significant interaction was between age and HR.
The interaction between HR and age is negative
indicating that a higher HR is worse in younger dogs
and is associated with a reduced median survival.

Fig. 2 shows the predicted survival of dogs with
a HR of either 110 or 140 bpm as a function of the
maximum carvedilol dose. Fig. 3 shows the
predicted survival of dogs with an age of either 4 or
9 years as a function of maximum carvedilol dose.

Fig. 4 shows the predicted survival of dogs that did
or did not develop CHF during follow-up as a func-
tion of maximum carvedilol dose. Based on this
model, overall predicted survival time is reduced
in the lower carvedilol dose regardless of HR, age,
and CHF status but predicted survival is worse in
dogs with a higher HR, increasing age and in those
that developed CHF.
Discussion

There is emerging interest in evaluation of chronic beta-blockade for the treatment of moderate to severe chronic primary MR in human patients. In one retrospective study the use of beta-blockade was reported to have an independent survival benefit in human patients with chronic severe MR characterized by a normal LV ejection fraction however this has not been substantiated in prospective studies.\textsuperscript{15} One small pilot study\textsuperscript{8} reported that short-term treatment (14 days) with a beta-blocker (BB) (sustained release metoprolol) did not change beat-by-beat mitral regurgitant volume but decreased mitral regurgitant volume per min as well as LV work. This study concluded by emphasizing the need for a large randomized clinical trial to determine if the favorable short-term effects on LV work will translate to a reduction in the risk of progressive LV systolic dysfunction and symptomatic deterioration.

The pharmacodynamics of chronic oral carvedilol administration (0.05–1.5 mg/kg) in normal conscious dogs has been reported.\textsuperscript{16–19} While pharmacokinetic data demonstrated a low and variable oral bioavailability suggesting the requirement for a 6-h dosing interval, the pharmacodynamic data suggested a 12–24-h dosing interval is adequate to ensure beta-blockade.\textsuperscript{16,17,19,20} Uechi et al. reported the cardiovascular and renal effects of oral carvedilol (0.2–0.8 mg/kg q 24 h) in dogs with experimental MR and control dogs suggesting that a dose of 0.4 mg/kg PO q 24 h may be a reasonable target dose in dogs with heart disease.\textsuperscript{20}

Carvedilol is currently used by some veterinarians in preclinical CVD and other cardiac diseases, however dosing is variable.\textsuperscript{21,22} Evaluation of the baseline data in the current study confirms that although 87% of the dogs were Stage B2, they were for the most part quite early in this stage. Median LA:Ao(M-mode) was just above the normal reference range and the LA:Ao(2D) was within the normal range. The median LVId-N and LVIds-N were within the reference range.\textsuperscript{13} In fact only one dog had a LVId-N above the reference range suggesting that, based on this echocardiographic parameter, LV chamber systolic function was preserved in the majority of these dogs. Dogs with this stage of CVD may represent the ideal...
population to initiate beta-blockade because they are the least likely to experience adverse events and the pathophysiology of chronic MR suggests that the adverse effects of excessive adrenergic stimulation may be an important factor relatively early in disease progression.9,15,23,24

Short-term effects of BB administration would be expected to cause negative inotropy and chronotropy, findings reported in human degenerative valvular disease.8 The reported beneficial effects of BB on remodeling and systolic function are typically thought to represent a long-term change following gradual beta-blockade. Most studies that reported beneficial effects have follow-up times of at least 3 months25 which is why dogs in this study were only included in the paired follow-up analysis if they had been evaluated between 3 and 8 months after initiation of carvedilol. This time frame was selected to ensure dogs were on a target dose of carvedilol for a minimum of 6 weeks prior to re-evaluation and that the duration of lapsed time was not more than 8 months to limit the effect of disease progression. Evaluation of the paired follow-up analysis revealed that LVIDd and LVIDd-N were both significantly increased and FS% decreased suggesting that LV systolic function was reduced when compared to baseline. Although this may be a consequence of CVD progression, the fact that other parameters related to overall remodeling (VHS, LVIDd, LVIDd-N, LA:Ao) were not significantly different from baseline and the median time to re-evaluation was relatively short (median 4.59 months) with respect to CVD progression necessitates consideration of alternative explanations. At baseline, based on a LVIDd-N that fell within the normal reference range (95% CI 0.71—1.26) all but 1 dog had normal LV systolic function.13 However, this is a crude estimate of LV contractility recognized to be difficult to interpret in the setting of MR.26 It is possible that dogs with evidence of volume overload due to CVD could have impaired LV contractility on a cellular level but still have normal ejection phase indices such as LVIDd-N. Gradual chronic beta-blockade may unmask pre-existing reductions in contractility by attenuating adrenergic support, but ultimately have the beneficial effect of limiting myocardial work. It is possible that chronic beta-blockade may delay or halt the progression of systolic dysfunction in CVD but not reverse it and that the majority of dogs with Stage B2 CVD may already suffer from important reductions in innate LV contractility. It is tempting to equate a reduction in LV systolic function (increased LVIDd and LVIDd-N) with a negative effect, but historically, relatively short-term hemodynamic changes have not proven to be good predictors of important long-term outcomes like survival.27 In fact, both the univariate and multivariable analysis showed that baseline LVIDd and LVIDd-N were not significantly associated with all-cause mortality in this group of dogs. Finally, the potential benefit of chronic reductions in HR should be considered. As expected, the paired analysis revealed that HR was significantly reduced. Chronic reductions in HR could reduce the mitral regurgitant volume per min which may lead to reductions in left atrial pressure.8

Many prognostic markers for both onset of CHF and all-cause mortality in dogs with Stage B CVD have been reported.28—30 In the study reported herein, the univariate analysis showed that development of CHF, age, LVIDd, and LVIDd-N were significantly related to all-cause mortality. All of these parameters have been previously reported.28—30 In this study the multivariable analysis confirmed not only the independence of age and development of CHF but also revealed that HR and carvedilol dose were significant. As with CHF and age, HR has been previously reported as significant with respect to prognosis in CVD. The finding that the carvedilol dose was significantly associated with all-cause mortality is interesting and suggests that a higher dose garners longer survival or alternatively that dogs with less severe disease tolerated up titration better and/or received a higher carvedilol dose, subsequently living longer. No dog in this study had adverse events reported during up titration indicating that maximum carvedilol dose was not related to when a dog developed adverse events, but that in general dogs with more severe remodeling received lower doses of carvedilol. Ten of 38 dogs (26.3%) did not reach the target dose range of 1.0—1.5 mg/kg twice daily. Seven of these 10 had an LVIDd-N >1.7 which has been reported to be a poor prognostic indicator in dogs with CVD.30 If we assume a dose dependent effect, the finding that a higher dose of carvedilol was associated with a lower hazard ratio even when other covariates including, onset of CHF were taken into account, provides indirect evidence that carvedilol was well tolerated in this cohort of dogs. The median survival in the Stage B2 dogs in this study was 48.5 months with a 95% CI range of 38.3—61.4. Any conclusions regarding survival would require a well-designed prospective, randomized, blinded, placebo controlled study.

There are obvious limitations in a retrospective case series which include the absence of a control population for direct comparison, the fact that 37% of dogs were receiving cardiac medications other than carvedilol before the onset of CHF, and that
87% were Cavalier King Charles Spaniels. Twelve of 50 dogs were excluded from the study analysis due to lack of baseline and/or follow-up data and this could have inadvertently masked the development of adverse events. Echocardiographic examinations were not consistent in method and multiple echocardiographers’ contributed data. In addition, follow-up evaluations were not performed in all dogs within the specified time of 3–8 months and the specified time period was broader than what could be achieved in a prospective study. Overall, this limited the number of dogs that were included in the paired baseline to follow-up analysis. Plasma carvedilol concentrations were not measured which is a significant limitation, given the reported high variability in carvedilol oral bioavailability in the dog. Finally, due to the small sample size and limited ability to accurately classify cause of death in many of the dogs, the survival analysis was based on an endpoint of all-cause mortality as opposed to cardiac mortality.

Conclusions

This study suggests that carvedilol at an initial dose of 0.31 mg/kg PO twice daily (0.26–0.35; range 0.15–0.53) and a target dose of 1.11 mg/kg twice daily (0.81–1.32; range 0.27–2.02) is safe and well tolerated in dogs with Stage B1 and early Stage B2 (normal LVIDs and LVIDs-N) if an up titration protocol is used that involves a 50–100% increase in dose every 7–14 days until the target dose is reached. Median survival for all dogs was 48.5 months with a 95% CI of 38.3–58.6. This study suggests that carvedilol at the doses reported is well tolerated in small breed dogs with Stage B CVD. Additional prospective studies to assess efficacy are warranted.

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Conflict of interest statement

The authors have no conflict of interest.

References


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