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Carvedilol in Dogs with Dilated Cardiomyopathy

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Background: Dilated cardiomyopathy (DCM) is characterized by reduced systolic function, heightened sympathetic tone, and high morbidity and mortality. Little is known regarding the safety and efficacy of β-blocker treatment in dogs with DCM.

Hypothesis: Carvedilol improves echocardiographic and neurohormonal variables in dogs with DCM over a 4-month treatment period.

Methods: Prospective, placebo-controlled, double-blinded randomized study. Dogs with DCM underwent echocardiography, ECG, thoracic radiographs, and neurohormonal profiling, followed by titration onto carvedilol (0.3 mg/kg q12h) or placebo over a 4-week period and subsequently received 3 months of therapy. Primary study endpoints included left ventricular volume and function.

Results: Sixteen dogs received carvedilol and 7 received placebo. At study end, 13 carvedilol dogs and 5 placebo dogs were alive. There was no difference in the mean percentage change in left ventricular volume at end-diastole (LVVd), left ventricular end-systolic volume (LVVs), and ejection fraction (EF) between treatment groups, suggesting that both groups experienced similar amounts of disease progression. Carvedilol treatment did not result in significant changes in neurohormonal activation, radiographic heart size, heart rate, or owner perceived quality-of-life. Baseline B-type natriuretic peptide (BNP) predicted dogs in the carvedilol-treated group that maintained or improved their EF over the study duration.

Conclusions and Clinical Importance: Carvedilol administration did not improve echocardiographic or neurohormonal indicators of heart function. The lack of effect may be related to severity of disease, carvedilol dose, or brevity of follow-up time. Statistical power of the present study was adversely affected by a high fatality rate in study dogs and small sample size.

Key words: Beta-blocker treatment; Heart disease; Neurohormones; Quality of life; Ventricular remodeling

Chronically high sympathetic tone is an important pathologic feature of heart disease because it results in persistent tachycardia, activation of the renin-angiotensin aldosterone system, myocyte necrosis and apoptosis, down-regulation of β-receptor–mediated signaling, reduced myocardial energetic efficiency, myocardial hypertrophy, and decreased intrinsic myocyte contractility.[1–3] Accordingly, treatment with β-adrenergic blocking agents, such as carvedilol, improves cardiac function and survival in humans with heart disease.[4–6] Dilated cardiomyopathy (DCM) is a common cardiac disease of large-breed dogs such as Doberman Pinschers and Great Danes and is accompanied by high circulating concentrations of epinephrine and norepinephrine.[7] Morbidity and case fatality from DCM remains very high despite conventional treatment with angiotensin converting enzyme (ACE)-inhibitors, diuretics, and positive inotropes and, in part, might be caused by a failure to suppress β-adrenergic activity. Use of β-blocking agents in dogs with DCM has been previously reported,[8–10] but these reports have been limited by their retrospective nature, lack of controls, and limited duration and extent of follow-up. Carvedilol is a 3rd-generation nonselective β-blocker with ancillary vasodilatory and antioxidant properties, and when administered to dogs with experimental heart failure, improves contractility, reduces heart size, and suppresses arrhythmia formation.[11–14] Based on these properties, we sought to prospectively determine the effects of 4-month oral carvedilol administration on echocardiographic, radiographic, neurohormonal, and quality of life parameters in dogs with moderate to severe DCM.

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Materials and Methods

This was a prospective, placebo-controlled, masked, randomized clinical trial of the efficacy of carvedilol in dogs with DCM. Dogs presenting to the veterinary teaching hospitals of the University of Illinois and The Ohio State University and the Animal Emergency & Critical Care Center for evaluation of suspected heart disease were recruited. Dogs were considered eligible for the study if echocardiographic examination revealed a left ventricular end-systolic volume (LVVs) index >35 mL/m^2 in the absence of an identifiable underlying cause and did not have active congestive heart failure. If dogs had been previously diagnosed as hypothyroid, they had to have been receiving a consistent and appropriate dose of thyroid supplementation for at least 12 weeks before entry into the study. Dogs that were ineligible due to active congestive heart failure were treated with diuretics and ACE-inhibitors and asked to return in several weeks for reevaluation and inclusion into the study. Dogs were allowed to receive background cardiac medications, including digoxin, as long as the dose had been consistent for at least 2 weeks.

Table 1. Baseline echocardiographic, hemodynamic, radiographic, neurohormonal, and biochemical characteristics of 16 dogs treated with carvedilol and 7 dogs treated with placebo. Values reported as mean (SD) except where indicated. Unadjusted *P* values are displayed.

	Carvedilol	Placebo	*P*
Echocardiographic			
LVId (cm)	5.71 (0.75)	5.51 (1.1)	.62
LVIs (cm)	4.90 (0.70)	4.78 (1.2)	.75
LVId-Ao index	2.34 (0.51)	2.33 (0.47)	.95
LVIs-Ao index	2.02 (0.49)	2.01 (0.53)	.99
FS (%)	14.1 (5.1)	14.5 (7.7)	.90
2D LA : Ao	1.68 (0.37)	1.60 (0.37)	.62
LVVd (mL)	124.8 (30.0)	119.7 (52.2)	.77
LVVs (mL)	78.1 (19.5)	83.8 (49.8)	.69
LVVd-BSA index	100.0 (18.4)	104.4 (15.1)	.56
LVVs-BSA index	62.8 (15.7)	70.7 (17.6)	.30
EF (%)	37.3 (7.0)	32.7 (9.8)	.22
PEP/LVET	0.375 (0.123)	0.453 (0.107)	.16
EPSS (cm)	13.4 (5.7)	15.4 (6.1)	.47
Vcf (circ/s)	0.900 (0.410)	0.846 (0.461)	.79
Blood pressure (mmHg)			
Systolic	119 (17)	124 (18)	.57
Diastolic	73 (10)	80 (11)	.11
Mean	90 (10)	98 (11)	.11
Heart rate (bpm)	122 (33)	121 (25)	.97
Radiographic			
VHS	10.9 (0.77)	10.9 (0.55)	.85
Pulmonary score[a]	0 (0–2)	1 (0–1)	.83
Neurohormonal[b]			
ANP (nmol/mL)	0.678 (0.421) [13]	0.630 (0.308) [6]	.81
BNP (pg/mL)	18.5 (17.6) [16]	8.81 (8.26) [7]	.18
PRA (mg/mL/h)	4.56 (5.63) [11]	14.7 (15.9) [5]	.07
ALD (pg/mL)	156 (237) [12]	135 (113) [5]	.85
NE (pg/mL)	293 (206) [11]	329 (199) [4]	.77
EPI (pg/mL)	151 (88) [11]	127 (68.5) [4]	.63
Bloodwork			
T4 (nM)	22.9 (8.5)	22.7 (5.7)	.96
Taurine (nmol/mL)	111.2 (29.5)	89.7 (13.2)	.10
BUN (mg/dL)	21.0 (6.0)	18.2 (2.5)	.26
Creatinine (mg/dL)	1.14 (0.33)	0.99 (0.30	.31
Na (nM)	149 (4.3)	148 (6.2)	.51
K (nM)	4.44 (0.40)	4.30 (0.26)	.39
Digoxin[b] (ng/mL)	0.92 (0.32) [14]	1.34 (0.63) [4]	.08
Quality of Life[a]			
Activity	1 (1–1)	1 (1–1)	1.00
Mobility	1 (1–2)	1 (1–2)	.76
Attitude	2 (1–2)	2 (1–2)	.95
Appetite	2 (1–2)	2 (1–3)	.81

SD, standard deviation; LVId, left ventricular end-diastolic internal diameter; LVIs, left ventricular end-systolic internal diameter; Ao, aorta; FS, fractional shortening; 2D, 2 dimensional; LA, left atrial diameter; LVVd, left ventricular end-diastolic volume; LVVs, left ventricular end-systolic volume; BSA, body surface area; EF, ejection fraction; PEP, pre-ejection period; LVET, left ventricular ejection time; EPSS, E-point to septal separation; Vcf, velocity of circumferential fiber shortening; VHS, vertebral heart size; ANP, atrial natriuretic peptide; BNP, B-type natriuretic peptide; PRA, plasma renin activity; ALD, aldosterone; NE, norepinephrine; EPI, epinephrine; T4, thyroid hormone; BUN, blood urea nitrogen.

Table 2. Interobserver coefficients of variation of baseline echocardiographic parameters from 10 randomly selected dogs that were entered into the study.

Variable	CV% (SD)
LVId	4.3 (7.2)
LVIs	5.5 (8.8)
LA/Ao	0.1 (12.6)
EPSS	5.3 (27.6)
PEP/LVET	15.3 (38.0)
LVVd	12.9 (11.4)
LVVs	13.9 (8.4)
EF	0.9 (26.0)

CV, coefficient of variation; SD, standard deviation; LVId, left ventricular end-diastolic internal diameter; LVIs, left ventricular end-systolic internal diameter; FS, fractional shortening; LA, left atrial diameter; Ao, aorta; EPSS, E-point to septal separation; PEP, pre-ejection period; LVET, left ventricular ejection time; LVVd, left ventricular end-diastolic volume; LVVs, left ventricular end-systolic volume; EF, ejection fraction.

Exclusion criteria included plasma taurine concentration <50 nM, previous history of doxorubicin treatment, systolic blood pressure <90 mmHg, or previous or current treatment with pimobendan, sotalol, or any other β-blocking agent. Chest radiographs, 2-dimensional (2D), M-mode and Doppler echocardiogram, oscillometric blood pressure measurement, serum digoxin assay (if applicable), serum chemistry, and neurohormone profiling were performed at baseline and 4 months. The neurohormone profile included plasma epinephrine (EPI), norepinephrine (NE), NT-pro-atrial natriuretic peptide (ANP), B-type natriuretic peptide (BNP), renin activity (PRA), and serum aldosterone (ALD) measurement by previously described techniques.[7,15] Echocardiographic examinations were performed without sedation and followed the conventional standards and recommendations.[16,17] Internal dimensions of the left ventricle, left atrium and aortic root were calculated from 2-dimensional (2D) loops obtained from the right parasternal short axis views. Left ventricular volumes were calculated by the modified Simpson's rule after tracing the endocardial-blood pool border from the left apical 4 chamber view. All echocardiographic measurements were done in triplicate, except for those dogs with atrial fibrillation, in which case measurements were done on 5–7 consecutive beats. Vertebral heart size was measured from the lateral chest radiograph,[18] and the pulmonary parenchymal pattern evaluated by means of a 5-point grading system wherein a score ranging from 0–4 indicated a normal, mild interstitial, moderate interstitial, alveolar, and severe consolidated pattern, respectively.

Owners were asked to assess their animal's activity and well-being by means of a quality of life questionnaire adapted from a previously reported study.[19] In brief, owners were asked to judge their dog's activity, mobility, attitude, and appetite by means of an ordinal scale wherein perceived high quality was ranked as 1 and lower quality ranked from 2 to 6 depending on the parameter in question (activity, 1–5; mobility, 1–6; attitude, 1–3; appetite, 1–4).

After baseline examination, dogs were randomized by the University of Illinois veterinary pharmacy in a 2 : 1 fashion to either carvedilol or placebo. Study investigators and owners were blinded

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[a] Values reported as median (range).

[b] Values in brackets [ ] indicate the number of samples included in the analysis.

Table 3. Echocardiographic, hemodynamic, radiographic, neurohormonal, and biochemical characteristics of 13 dogs treated with 4 months of carvedilol and 5 dogs treated with 4 months of placebo. Values reported as mean (SD) except where indicated. Unadjusted *P* values are displayed. Those that meet the Bonferroni-adjusted threshold within each diagnostic group are underlined.

	Carvedilol			Placebo			*P*
							Carvedilol versus Placebo
Echocardiographic	Baseline	4 Months	% Change	Baseline	4 Months	% Change	(% Change)
LVId (cm)	5.81 (0.80)	5.95 (0.92)	2.32 (6.00)	5.73 (0.77)	5.85 (0.55)	2.20 (7.64)	.972
LVIs (cm)	4.98 (0.70)	4.96 (0.83)	−0.40 (7.46)	5.09 (0.95)	5.04 (0.63)	−0.90 (7.89)	.902
FS (%)	14.2 (5.6)	16.4 (7.8)	15.1 (54.4)	11.7 (6.1)	14.0 (6.1)	19.4 (29.1)	.870
2D LA : Ao	1.68 (0.40)	2.43 (0.52)	5.42 (18.2)	1.57 (0.40)	2.58 (0.46)	19.7 (20.7)	.170
LVVd (mL)	125.5 (32.9)	136.3 (37.4)	8.62 (10.9)	127.7 (59.3)	141.8 (47.3)	11.0 (13.4)	.703
LVVs (mL)	78.2 (20.4)	90.0 (26.9)	15.1 (18.3)	93.1 (57.3)	98.9 (43.1)	6.21 (19.1)	.374
EF (%)	37.5 (71)	34.5 (9.2)	−8.53 (15.8)	30.5 (10.8)	32.0 (11.4)	4.87 (26.8)	.202
PEP/LVET	0.396 (0.113)	0.410 (0.148)	3.66 (33.2)	0.478 (0.112)	0.453 (0.105)	−5.33 (21.7)	.586
EPSS (mm)	13.3 (6.0)	15.0 (5.8)	12.9 (39.0)	13.4 (4.2)	14.7 (4.3)	9.72 (34.9)	.878
Vcf (circ/s)	0.955 (0.432)	0.954 (0.500)	−0.09 (98.9)	0.773 (0.484)	0.866 (0.503)	12.1 (60.0)	.801
Blood pressure							
Systolic (mmHg)	120 (18)	125 (18)	4.11 (21.7)	120 (18)	107 (17)	−10.4 (7.50)	.171
Diastolic (mmHg)	74 (10)	81 (16)	9.98 (21.7)	78.8 (11)	65 (13)	−17.3 (11.3)	.020
Mean (mmHg)	91 (10)	97 (16)	6.81 (19.2)	95 (10)	80 (15)	−16.1 (10.1)	.027
Heart rate (bpm)	127 (34)	117 (38)	−8.16 (37.1)	116 (26)	124 (30)	7.06 (15.4)	.394
Radiographic							
VHS	10.9 (0.8)	10.9 (1.2)	0.47 (28.5)	10.9 (0.7)	10.8 (0.5)	−0.92 (3.48)	.916
Pulmonary score[a]	1 (0–1)	1 (0–1)	—	0 (0–2)	0 (0–2)	—	—
Neurohormonal[b]							
ANP (nmol/mL)	0.693 (0.533) [8]	0.770 (0.668) [8]	11.0 (37.9)	0.603 (0.330) [4]	0.609 (0.460) [4]	1.08 (48.5)	.703
BNP (pg/mL)	18.0 (19.2) [13]	18.9 (17.2) [13]	4.48 (1160)	8.24 (8.95) [5]	20.5 (29.3) [5]	148 (387)	.792
PRA (ng/mL/h)	5.70 (6.91) [7]	2.69 (2.84) [7]	−52.8 (37.5)	8.03 (6.36) [4]	10.0 (10.0) [4]	24.7 (56.0)	NS (.022)
ALD (pg/mL)	185 (290) [8]	158 (200) [8]	−14.5 (184)	151 (123) [4]	128 (84) [4]	−15.7 (101)	.991
NE (pg/mL)	326 (256) [6]	376 (295) [6]	15.2 (71.3)	355 (235) [3]	258 (104) [3]	−27.3 (27.1)	.365
EPI (pg/mL)	167 (98) [6]	206 (101) [6]	23.1 (123)	127 (68) [4]	103 (72) [4]	−19.0 (35.4)	.531
Biochemical							
T4 (nM)	22.1 (7.5)	—	—	19.8 (3.4)	—	—	—
Taurine (nmol/mL)	111.9 (30.2)	—	—	90.0 (14.7)	—	—	—
BUN (mg/dL)	22.0 (6.1)	23.4 (11.3)	6.21 (33.6)	18.1 (3.0)	20.8 (9.6)	15.1 (59.8)	.692
Creatinine (mg/dL)	1.19 (0.34)	1.28 (0.42)	7.10 (11.5)	0.94 (0.21)	1.04 (0.25)	10.6 (31.7)	.724
Na (mM)	148 (4)	148 (4)	−0.050 (2.78)	147 (3)	149 (6)	1.22 (5.17)	.504
K (mM)	4.44 (0.36)	4.60 (0.27)	3.64 (8.19)	4.40 (0.16)	4.12 (0.08)	−6.36 (3.58)	NS (.019)
Digoxin[b] (ng/mL)	0.95 (0.36) [11]	—	—	1.52 (0.63) [3]	—	—	—

Table 3. Continued.

Echocardiographic	Carvedilol			Placebo			*P* Carvedilol versus Placebo
	Baseline	4 Months	% Change	Baseline	4 Months	% Change	(% Change)
Quality of Life[a]							
Activity	1 (1–1)	1 (1–1)	—	1 (1–1)	1 (1–2)	—	—
Mobility	1 (1–2)	1 (1–2)	—	1 (1–2)	1 (1–2)	—	—
Attitude	2 (1–2)	2 (1–2)	—	2 (1–2)	2 (1–2)	—	—
Appetite	2 (1–3)	2 (1–2)	—	2 (1–2)	2 (1–2)	—	—

SD, standard deviation; LVId, left ventricular end-diastolic internal diameter; LVIs, left ventricular end-systolic internal diameter; FS, fractional shortening; 2D, 2 dimensional; LA, left atrial diameter; Ao, aorta; LVVd, left ventricular end-diastolic volume; LVVs, left ventricular end-systolic volume; EF, ejection fraction; PEP, pre-ejection period; LVET, left ventricular ejection time; EPSS, E-point to septal separation; Vcf, velocity of circumferential fiber shortening; VHS, vertebral heart size; ANP, atrial natriuretic peptide; BNP, B-type natriuretic peptide; PRA, plasma renin activity; ALD, aldosterone; NE, norepinephrine; EPI, epinephrine; T4, thyroid hormone; BUN, blood urea nitrogen.

[a] Values reported as median (range).

[b] Values in brackets [] indicate number of samples used in the analysis.

as to randomization. Carvedilol or placebo, compounded into similar appearing capsules, was then prescribed over a 4-week titration period. During this time dogs initially received 0.05 mg/kg PO q12h for 7 days, then underwent weekly dose increases to 0.1, 0.2, and finally to 0.3 mg/kg PO q12h. Owners were instructed to monitor their dogs for respiratory distress, poor appetite, and weakness during the titration phase and not to administer the next highest dose if any of these signs were noted. Following the 4-week titration phase, dogs received 3 months of uninterrupted drug treatment at a dose of 0.3 mg/kg PO q12h. During this time, changes to the dog's digoxin or thyroid supplementation were not permitted. Upon completion of the 4-month protocol, dogs underwent a re-examination similar to their baseline visit.

The study's primary endpoints were prospectively defined as left ventricular volume at end-diastole (LVVd), LVVs, and ejection fraction (EF = [LVVd − LVVs]/LVVd). The study was prospectively designed to detect a 5% change in ventricular volumes. Secondary endpoints included left ventricular and atrial dimensions, systolic time intervals, and neurohormonal parameters. At the end of the study, dogs that had received placebo during the blinded phase were eligible to enroll in a crossover protocol wherein open-label carvedilol (0.3 mg/kg PO q12h) was added to their treatment regimen. These dogs underwent a 4-week titration and 3-month chronic treatment phase similar to the original study protocol. Echocardiographic interobserver coefficients of variation (CV) (MAO, BJB) were determined from 10 randomly selected dogs that underwent 2 separate echocardiographic exams at baseline (CV = 100 mean difference/average value). In an attempt to identify parameters that predicted response to carvedilol treatment, analysis of 2 subgroups within the carvedilol cohort was retrospectively performed. The baseline characteristics of those dogs with little disease progression (ie, no change or positive change in 12-week EF) were compared with the baseline characteristics of those patients with progressive loss of contractile function (ie, negative change in 12-week EF or death). The study protocol was approved by the University of Illinois Institutional Animal Care and Use Committee, and owners were required to provide written informed consent.

Statistical Analysis

Analysis was performed by a PC-based software program.[a] Data were assessed for normality before statistical analysis. Unpaired 2-tailed Student's *t*-tests and Mann-Whitney *U*-tests were used to compare patient groups at baseline. Between each patient group, Bonferroni-adjusted *P* values were used for the paired Student's *t*-test comparison of the percentage change in baseline versus 4-month values within the echocardiographic, neurohormonal, biochemical, and quality of life families of comparisons. Prospective and post hoc calculation of study power and detectable differences was calculated by a PC-based software program.[b] Statistical significance was defined as $P < .05$. Data are reported as mean ± standard deviation (SD).

Results

Twenty-three dogs were recruited into the study (University of Illinois, 20; Animal Emergency and Critical Care, 2; The Ohio State University, 1). Sixteen dogs were randomized to carvedilol and 7 to placebo. The 2 groups were well matched with respect to radiographic, echocardiographic, and neurohormonal characteristics (Table 1). Technical complications involving the neurohormonal profile resulted in the loss of some samples, thus evaluation of neurohormonal indices was incomplete (Table 1). Dog breeds included the

Doberman Pinscher (carvedilol, 9; placebo, 6), Great Dane (carvedilol, 4; placebo, 1), Rottweiler (carvedilol, 2), and Bouvier des Flandres (carvedilol, 1). Four dogs had atrial fibrillation (carvedilol, 3; placebo, 1). In each group, 1 dog died suddenly during the titration period. During the chronic treatment phase, 2 dogs in the carvedilol group died suddenly and 1 dog in the placebo group was euthanized due to heart failure, resulting in 13 dogs in the carvedilol group and 5 dogs in the placebo group completing the study. Titration of study drug was well tolerated in both groups. One dog in the carvedilol group experienced a modest increase in respiratory rate and effort approximately 2 weeks into the titration phase. Titration was slowed and subsequently achieved over a 6-week period. Interobserver CVs for the various echocardiographic variables ranged from 0.1 to 15.3% (Table 2).

Three months of chronic treatment with carvedilol did not significantly improve LVVd, LVVs, or EF as compared with dogs receiving placebo (Table 3). Treatment with carvedilol did not significantly improve left ventricular and atrial dimensions, systolic time intervals, or neurohormonal parameters (Table 3). Dogs receiving placebo experienced a small but significant decrease in diastolic and mean blood pressure (Table 3). Neither treatment altered owner-perceived indices of quality of life (Table 3).

Subgroup analysis of the 16 dogs originally receiving carvedilol indicated a wide variation in individual response with regards to EF and outcome. Based on the difference between baseline and 12-week EF, 6 dogs maintained systolic function, while 10 dogs experienced deterioration of systolic function over the study period (EF-maintained, 1.6 ± 1.3%; EF-deteriorated, −7.3 ± 3.7%). Of various baseline echocardiographic, hemodynamic, and neurohormonal characteristics, only BNP predicted which dogs experienced deterioration of systolic function (Table 4).

Four dogs originally randomized to the placebo group were re-enrolled in a crossover protocol that added open-label carvedilol to their treatment regimen. One dog experienced congestive heart failure 2 weeks into the titration period and the owner opted to discontinue carvedilol and start pimobendan treatment. The dog died suddenly 6 weeks later. The remaining 3 dogs completed the 4-month crossover, but no significant differences were detected in left ventricular dimensions, volumes, or ejection indices over their 4-month treatment with open-label carvedilol (data not shown).

Post hoc analysis based on the sample size and SD in the response of the matched pairs within the carvedilol group indicated that, as performed, the study possessed requisite power (ie, >80% at $\alpha = 0.05$) to detect differences in LV dimensions ≥8.1%, in LV volumes ≥17.6%, and in EF ≥23.9% between the treatment groups.

Table 4. Baseline characteristics of 6 dogs that maintained systolic function versus 10 dogs that experienced progressive loss of systolic function during 4 months of carvedilol treatment.

	Maintained	Progressed	*P*
LVVd-BSA index	96.1 (27.3)	101.9 (11.6)	NS
LVVs-BSA index	60.2 (23.8)	64.4 (9.35)	NS
EF (%)	38.4 (7.5)	36.7 (7.0)	NS
2D LA : Ao	1.61 (0.49)	1.72 (0.29)	NS
Mean blood pressure (mmHg)	89.8 (12.2)	89.4 (9.8)	NS
Heart rate (bpm)	130 (33)	117 (34)	NS
ANP (nmol/mL)	0.632 (0.255)	0.707 (0.515)	NS
BNP (pg/mL)	6.35 (8.09)	25.75 (18.03)	.027
EPI (pg/mL)	134 (28)	161 (110)	NS
NE (pg/mL)	296 (180)	291 (234)	NS

LVVd, left ventricular end-diastolic volume; BSA, body surface area; NS, nonsignificant; LVVs, left ventricular end-systolic volume; EF, ejection fraction; 2D, 2 dimensional; LA, left atrial diameter; Ao, aorta; ANP, atrial natriuretic peptide; BNP, B-type natriuretic peptide; EPI, epinephrine; NE, norepinephrine.

Discussion

Chronic therapy with carvedilol did not improve ventricular volume or systolic function in dogs with moderate to severe DCM as compared with placebo. In addition, carvedilol treatment did not significantly change circulating neurohormone concentrations or improve owner-perceived quality of life. The findings of the present study differ from previous reports involving canine models of heart failure or humans with idiopathic DCM. There is improved LV dP/dt, stroke volume, and cardiac output and suppressed plasma NE concentrations after oral carvedilol administration to dogs undergoing rapid ventricular pacing.[14] Carvedilol treatment in humans with idiopathic DCM results in improved systolic function, regression of LV hypertrophy, suppression of neurohormonal activation, and longer survival, making β-blockade a cornerstone of chronic heart failure therapy.[20–24] The reported benefits of β-blocker therapy are owing to a complex combination of events, including restoration of β-receptor signaling, myocardiocyte protection against oxidative stress and apoptosis, mitigation of cyclic adenosine monophosphate (cAMP)-induced hyperphosphorylation, improved Ca^{2+} cycling, and improved efficiency of myocardial energetics.[11,12,25–27] The results of the present study may be due to differences in the severity, progression, and differing etiology of canine and human DCM, inadequate drug dosages, and the brevity of follow-up.

The dogs in this study suffered from relatively severe disease as indicated by markedly high LV volumes and reduced EF. As disease worsens, the amount of irreversible injury to the myocardium presumably increases, making response to therapeutic intervention less likely. Investigation in humans suggests that carvedilol administration is effective in advanced disease (ie, EF <25%[4,5]) as well as in very elderly patients[28]; however, one report indicated that response was suboptimal in patients with larger heart sizes, worse systolic function, and more advanced clinical heart failure class.[29] Advanced canine DCM is accom-

panied by progressive myocyte loss due to necrosis, apoptosis, atrophy, and fibrous or fatty infiltration.[30,31] The remaining myocytes demonstrate significant abnormalities of transcription of basic cellular components as well as deficiencies in mitochondrial protein expression.[32–34] In the later stages of disease, these changes may preclude effective response to β-blockade as the myocardial substrate becomes irrevocably injured.

Positive response to β-blockade in the form of ventricular remodeling generally requires that patients receive medication for at least 3 months. This effect is influenced by both dose and time, in that patients receiving higher doses of drug for longer periods of time experience the most dramatic results.[35] Thus, consensus opinion involving human patients recommends initiating β-blocker therapy in patients with relatively mild disease (NYHA II) and titrating to the highest tolerable doses.[36,37] High-dose therapy in veterinary medicine is made difficult by the advanced nature of disease in dogs that present with congestive heart failure. Moreover, the deterioration of clinical status in dogs with DCM is relatively rapid as compared with humans, as evidenced by a 1-year survival rate in dogs of 17.5% versus a value between 50 and 95% in human patients depending on the exact cohort studied.[38] Thus, long-term treatment and resultant benefit may not be achievable in dogs with relatively advanced disease. Earlier and more aggressive treatment in dogs necessitates effective strategies to detect asymptomatic (ie, occult) disease in a widely available and accurate manner.

The ideal dose of carvedilol for dogs with heart disease is unknown. In healthy dogs, doses ranging from 0.08–1.5 mg/kg q12h have been reported.[39–41] In dogs with experimental heart disease, doses ranging from 0.2–0.4 mg/kg q24h have been shown to significantly reduce heart rate.[42] Recently, Nikolaidis et al reported using considerably higher doses (1.5–1.7 mg/kg q12h) in dogs undergoing rapid ventricular pacing; however, the dogs were only treated for 3 days before being euthanized.[14] In this study, it is interesting to note that treatment with carvedilol did not suppress circulating NE and EPI, nor did treatment decrease heart rate. Thus, the results of the present study may have been influenced by an overly conservative dose of carvedilol; however, we note that heart rate response may not be a reliable means to assess carvedilol dose insofar as a considerably higher dose of carvedilol (1.5 mg/kg PO q12h) did not consistently reduce heart rate in healthy dogs.[40] In the authors' experience, more aggressive titration can be associated with acute clinical deterioration that is difficult to treat and can lead to substantial morbidity and mortality. It is very difficult to prospectively determine which animals could tolerate higher doses and which ones could not. While none of the dogs in this study experienced catastrophic exacerbation of heart failure signs, 1 dog did require slowing of the titration protocol due to presumed worsening of heart failure. This experience suggested that a maximally tolerated dose had been reached in that individual patient.

There was a wide degree of individual response within the group of dogs receiving carvedilol. Six of the 16 dogs originally randomized to carvedilol demonstrated preserved or slightly improved cardiac function as evidenced by their EF values. At time of study enrollment, this subgroup of dogs possessed BNP concentrations significantly lower than dogs considered as not responding to the study protocol. BNP is a marker of cardiac stress and possesses prognostic value in a wide variety of human patients with heart disease.[43–46] In general, humans with lower BNP concentrations possess risk for cardiac morbidity and mortality 2–3 times lower then the cohort with higher concentrations. In at least 1 study,[47] baseline BNP predicted which human patients received the greatest survival benefit after receiving carvedilol, and in another study,[48] NT-proBNP predicted mortality in both carvedilol-treated and non-treated patients. Further studies investigating the predictive value of neurohormonal activation in dogs are warranted. This study was limited because it was not specifically designed to prospectively identify predictors of response, nor could we be entirely sure that the changes seen in the responder group were necessarily the result of carvedilol therapy or would ultimately result in reduced mortality.

This study was limited by the small number of patients and inherent variability associated with the echocardiographic technique, which affected the ability to detect changes in cardiac diameters, volumes, and ejection indices. Thus, even moderate changes in ventricular function might not have been detected by the current study. A primary goal of any therapeutic intervention is to improve patient survival. This study was specifically designed to investigate the effect of carvedilol on ventricular remodeling and function, and additional studies are needed to determine if carvedilol improves survival. In summary, carvedilol therapy can be safely administered to dogs with moderate to severe DCM; however, doses >0.3 mg/kg q12h are likely to be required to effect changes in ventricular remodeling and function. The potential benefit of earlier and more aggressive treatment with β-blocking agents requires further study.

Footnotes

[a] Prism 4 for Windows Version 4.0, GraphPad Software Inc, San Diego, CA

[b] PS Power and Sample Size Program Version 2.1.3, Dupont WD and Plummer WD. Visual Components 2003. Available at: http://biostat.mc.vanderbilt.edu/twiki/bin/view/Main/PowerSampleSize

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References

1. Adams KF Jr. Pathophysiologic role of the renin-angiotensin-aldosterone and sympathetic nervous systems in heart failure. Am J Health Syst Pharm 2004;61(Suppl):S4–S13.

2. Colucci WS. The effects of norepinephrine on myocardial biology: Implications for the therapy of heart failure. Clin Cardiol 1998;21:I20–I24.

3. Laks MM, Morady F, Swan HJ. Myocardial hypertrophy produced by chronic infusion of subhypertensive doses of norepinephrine in the dog. Chest 1973;64:75–78.

4. Packer M, Coats AJ, Fowler MB, et al. Effect of carvedilol on survival in severe chronic heart failure. N Engl J Med 2001;344:1651–1658.

5. Krum H, Sackner-Bernstein JD, Goldsmith RL, et al. Double-blind, placebo-controlled study of the long-term efficacy of carvedilol in patients with severe chronic heart failure. Circulation 1995;92:1499–1506.

6. Lowes BD, Gill EA, Abraham WT, et al. Effects of carvedilol on left ventricular mass, chamber geometry, and mitral regurgitation in chronic heart failure. Am J Cardiol 1999;83:1201–1205.

7. Sisson DD. Neuroendocrine evaluation of cardiac disease. Vet Clin North Am Small Anim Pract 2004;34:1105–1126.

8. Rush JE, Freeman LM, Hiler C, et al. Use of metoprolol in dogs with acquired cardiac disease. J Vet Cardiol 2002;4:23–28.

9. Tidholm A. Beta-blocker use in canine DCM. Proceedings of the 24th Annual Form of the American College of Veterinary Internal Medicine. Louisville, KY, June. 2006.

10. Amberger CN. Effect of carvedilol on ventricular function, symptoms, and survival time in 25 dogs with heart failure ISACHC class III Proceedings of the European College of Veterinary Internal Medicine: Neuchatel, Switzerland, September 2000.

11. Xue SR, Xue Y, Xue R. Carvedilol restore cardiac calcium release channel structure and function in heart failure. Int J Cardiol 2007;116:231–235.

12. Zhang S, Sun Z, Liu L, et al. Carvedilol attenuates CPB-induced apoptosis in dog heart: Regulation of Fas/FasL and caspase-3 pathway. Chin Med J (Engl) 2003;116:761–766.

13. Hamburger SA, Barone FC, Feuerstein GZ, et al. Carvedilol (Kredex) reduces infarct size in a canine model of acute myocardial infarction. Pharmacology 1991;43:113–120.

14. Nikolaidis LA, Poornima I, Parikh P, et al. The effects of combined versus selective adrenergic blockade on left ventricular and systemic hemodynamics, myocardial substrate preference, and regional perfusion in conscious dogs with dilated cardiomyopathy. J Am Coll Cardiol 2006;47:1871–1881.

15. Oyama MA, Sisson DD, Solter PF. Prospective screening for occult cardiomyopathy in dogs by measurement of plasma atrial natriuretic peptide, B-type natriuretic peptide, and cardiac troponin-I concentrations. Am J Vet Res 2007;68:42–47.

16. Sahn DJ, DeMaria A, Kisslo J, et al. Recommendations regarding quantitation in M-mode echocardiography: Results of a survey of echocardiographic measurements. Circulation 1978;58:1072–1083.

17. Thomas WP, Gaber CE, Jacobs GJ, et al. 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;7:247–252.

18. Buchanan JW, Bucheler J. Vertebral scale system to measure canine heart size in radiographs. J Am Vet Med Assoc 1995;206:194–199.

19. The IMPROVE Study Group. Acute and short-term hemodynamic, echocardiographic, and clinical effects of enalapril maleate in dogs with naturally acquired heart failure: Results of the Invasive Multicenter PROspective Veterinary Evaluation of Enalapril study. J Vet Intern Med 1995;9:234–242.

20. Di Lenarda A, Sabbadini G, Salvatore L, et al. Long-term effects of carvedilol in idiopathic dilated cardiomyopathy with persistent left ventricular dysfunction despite chronic metoprolol. The Heart-Muscle Disease Study Group. J Am Coll Cardiol 1999;33:1926–1934.

21. Gerson MC, Craft LL, McGuire N, et al. Carvedilol improves left ventricular function in heart failure patients with idiopathic dilated cardiomyopathy and a wide range of sympathetic nervous system function as measured by iodine 123 metaiodobenzylguanidine. J Nucl Cardiol 2002;9:608–615.

22. Hirooka K, Yasumura Y, Ishida Y, et al. Comparative left ventricular functional and neurohumoral effects of chronic treatment with carvedilol versus metoprolol in patients with dilated cardiomyopathy. Jpn Circ J 2001;65:931–936.

23. Packer M, Bristow MR, Cohn JN, et al. The effect of carvedilol on morbidity and mortality in patients with chronic heart failure. N Engl J Med 1996;334:1349–1355.

24. Packer M, Colucci WS, Sackner-Bernstein JD, et al. Double-blind, placebo-controlled study of the effects of carvedilol in patients with moderate to severe heart failure. The PRECISE Trial. Prospective Randomized Evaluation of Carvedilol on Symptoms and Exercise. Circulation 1996;94:2793–2799.

25. Asanuma H, Minamino T, Sanada S, et al. Beta-adrenoceptor blocker carvedilol provides cardioprotection via an adenosine-dependent mechanism in ischemic canine hearts. Circulation 2004;109:2773–2779.

26. Feuerstein GZ, Yue TL, Cheng HY, et al. Myocardial protection by the novel vasodilating beta-blocker, carvedilol: Potential relevance of anti-oxidant activity. J Hypertens Suppl 1993;11:S41–S48.

27. Kaye DM, Johnston L, Vaddadi G, et al. Mechanisms of carvedilol action in human congestive heart failure. Hypertension 2001;37:1216–1221.

28. Franciosa JA, Nelson JJ, Lukas MA, et al. Heart failure in community practice: Relationship to age and sex in a beta-blocker registry. Congest Heart Fail 2006;12:317–323.

29. Ho WJ, Tsay PK, Chu PH, et al. Predictors of stable outcome in treating chronic heart failure patients with carvedilol. Jpn Heart J 2004;45:823–832.

30. Calvert CA, Hall G, Jacobs G, et al. Clinical and pathologic findings in Doberman Pinschers with occult cardiomyopathy that died suddenly or developed congestive heart failure: 54 cases (1984–1991). J Am Vet Med Assoc 1997;210:505–511.

31. Sandusky GEJ, Capen CC, Kerr KM. Histological and ultrastructural evaluation of cardiac lesions in idiopathic cardiomyopathy in dogs. Can J Comp Med 1984;48:81–86.

32. Oyama MA, Chittur S. Genomic expression patterns of cardiac tissues from dogs with dilated cardiomyopathy. Am J Vet Res 2005;66:1140–1155.

33. Lopes R, Solter PF, Sisson DD, et al. Characterization of canine mitochondrial protein expression in natural and induced forms of idiopathic dilated cardiomyopathy. Am J Vet Res 2006;67:963–970.

34. Lopes R, Solter PF, Sisson DD, et al. Correlation of mitochondrial protein expression in complexes I to V with natural and induced forms of canine idiopathic dilated cardiomyopathy. Am J Vet Res 2006;67:971–977.

35. Hall SA, Cigarroa CG, Marcoux L, et al. Time course of improvement in left ventricular function, mass and geometry in patients with congestive heart failure treated with beta-adrenergic blockade. J Am Coll Cardiol 1995;25:1154–1161.

36. Hunt SA, Baker DW, Chin MH, et al. ACC/AHA guidelines for the evaluation and management of chronic heart failure in the adult: Executive summary. A report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee to revise the 1995 Guidelines for the Evaluation and Management of Heart Failure). J Am Coll Cardiol 2001;38:2101–2113.

37. McMurray J, Cohen-Solal A, Dietz R, et al. Practical recommendations for the use of ACE inhibitors, beta-blockers, aldosterone antagonists and angiotensin receptor blockers in heart failure: Putting guidelines into practice. Eur J Heart Fail 2005;7:710–721.

38. Konstam MA. Progress in heart failure management? Lessons from the real world. Circulation 2000;102:1076–1078.

39. Abbott JA, Broadstone RV, Ward DL, et al. Hemodynamic effects of orally administered carvedilol in healthy conscious dogs. Am J Vet Res 2005;66:637–641.

40. Gordon SG, Arsenault WG, Longnecker M, et al. Pharmacodynamics of carvedilol in conscious, healthy dogs. J Vet Intern Med 2006;20:297–304.

41. Arsenault WG, Boothe DM, Gordon SG, et al. Pharmacokinetics of carvedilol after intravenous and oral administration in conscious healthy dogs. Am J Vet Res 2005;66:2172–2176.

42. Uechi M, Sasaki T, Ueno K, et al. Cardiovascular and renal effects of carvedilol in dogs with heart failure. J Vet Med Sci 2002;64:469–475.

43. Tsutamoto T, Wada A, Maeda K, et al. Attenuation of compensation of endogenous cardiac natriuretic peptide system in chronic heart failure: Prognostic role of plasma brain natriuretic peptide concentration in patients with chronic symptomatic left ventricular dysfunction. Circulation 1997;96:509–516.

44. Bettencourt P, Frioes F, Azevedo A, et al. Prognostic information provided by serial measurements of brain natriuretic peptide in heart failure. Int J Cardiol 2004;93:45–48.

45. Latini R, Masson S, Anand I, et al. The comparative prognostic value of plasma neurohormones at baseline in patients with heart failure enrolled in Val-HeFT. Eur Heart J 2004;25:292–299.

46. Berger R, Huelsmann M, Strecker K, et al. Neurohormonal risk stratification for sudden death and death owing to progressive heart failure in chronic heart failure. Eur J Clin Invest 2005;35:24–31.

47. Richards AM, Doughty R, Nicholls MG, et al. Neurohumoral prediction of benefit from carvedilol in ischemic left ventricular dysfunction. Australia-New Zealand Heart Failure Group. Circulation 1999;99:786–792.

48. Hartmann F, Packer M, Coats AJ, et al. Prognostic impact of plasma N-terminal pro-brain natriuretic peptide in severe chronic congestive heart failure: A substudy of the Carvedilol Prospective Randomized Cumulative Survival (COPERNICUS) trial. Circulation 2004;110:1780–1786.