Hemodynamic effects of orally administered carvedilol in healthy conscious dogs

Jonathan A. Abbott, DVM; Richard V. Broadstone, DVM, PhD; Daniel L. Ward, PhD; R. Lee Pyle, VMD, MS

Objective—To evaluate the hemodynamic effects of orally administered carvedilol in healthy dogs with doses that might be used to initiate treatment in dogs with congestive heart failure.

Animals—24 healthy dogs.

Procedure—Dogs were randomly allocated to receive carvedilol PO at a dose of 1.56, 3.125, or 12.5 mg, twice daily for 7 to 10 days; 6 dogs served as controls. Investigators were blinded to group assignment. Hemodynamic variables were recorded prior to administration of the drug on day 1 and then 2, 4, and 6 hours after the morning dose on day 1 and days 7 to 10. Change in heart rate after IV administration of 1 µg of isoproterenol/kg and change in systemic arterial blood pressure after IV administration of 8 µg of phenylephrine/kg were recorded 2 and 6 hours after administration of carvedilol.

Results—Administration of carvedilol did not significantly affect resting hemodynamic variables or response to phenylephrine. The interaction of day and carvedilol dose had a significant effect on resting heart rate, but a significant main effect of carvedilol dose on resting heart rate was not detected. Increasing carvedilol dose resulted in a significant linear decrease in heart rate response to isoproterenol.

Conclusions and Clinical Relevance—In healthy conscious dogs, orally administered carvedilol at mean doses from 0.08 to 0.54 mg/kg given twice daily did not affect resting hemodynamics. Over the dose range evaluated, there was a dose-dependent attenuation of the response to isoproterenol, which provided evidence of β-adrenergic receptor antagonism. (*Am J Vet Res* 2005;66:637–641)

Recently, attention has been directed toward the use of β-adrenergic receptor antagonists in the management of **congestive heart failure (CHF)** in humans.[1-4] When given chronically, these drugs improve clinical signs, improve hemodynamic variables, and reduce mortality rate in patients receiving standard medical treatment.[2,3,5-7] Carvedilol is a third-generation β-adrenoceptor antagonist that possesses α-receptor blocking activity.[8-10] This drug has proven efficacy in the management of CHF in humans and may have a role in the treatment of affected dogs.[11] The acute hemodynamic effects of carvedilol administered IV have been evaluated,[9,10,12] as have the effects of a single orally administered dose of carvedilol in healthy dogs and dogs with induced mitral valve regurgitation.[13] The effects of chronic administration of relatively high doses of orally administered carvedilol have also been investigated.[9,10] However, when carvedilol is administered to human patients with heart failure, a low dose is used initially and the dose is titrated to effect over the course of 6 to 8 weeks.[1-3]

The purpose of the study reported here was to evaluate the hemodynamic, β-receptor blocking, and α-receptor blocking effects of orally administered carvedilol in healthy dogs with doses that might practically be administered as initial doses to dogs with heart disease.

Materials and Methods

Eighteen healthy dogs that weighed from 16.4 to 28.4 kg were randomly allocated to receive carvedilol[a] PO at a dose of 1.56, 3.125, or 12.5 mg given twice daily for 7 to 10 days; 6 dogs served as controls. The control group received a small quantity of commercial dog food similar to that in which the drug was administered, but they did not receive a placebo. The investigators were blinded to group assignment. In the 2 weeks prior to the study, each dog had 10 training sessions during which they were manually restrained while laterally recumbent for 10 minutes. On day 1, a 20-gauge, 1.88-inch cannula[b] was placed in a dorsal pedal artery and a 5-F, multilumen, flow-directed catheter[c] equipped with a thermistor device was advanced to the pulmonary artery after percutaneous introduction[d] into the left or right external jugular vein. The subcutis overlying the vein and artery was infiltrated with 2% lidocaine before vessel puncture was attempted. The dogs were instrumented again in the same fashion 7 to 10 days later. In some instances, placement of the intra-arterial cannula proved difficult and recording was postponed for 24 to 48 hours. The number of attempts necessary to obtain arterial access was not recorded but was determined by practical considerations and attention to the dog's comfort.

Intravascular and intracardiac pressures were obtained by use of a fluid-filled transducer system[e] when the dogs were manually restrained while laterally recumbent. Pressures and an ECG monitoring lead were recorded for later review by use of a physiologic monitor[f] equipped with a printer.

Systemic arterial blood pressure (SBP) was obtained when the **heart rate (HR)** was apparently stable and had decreased from values observed during the time that catheter-transducer attachments were made. This was typically after approximately 5 minutes and was at a time when respiratory sinus arrhythmia was distinct. **Pulmonary artery blood pressure (PBP)**, pulmonary capillary wedge pressure, and **right atrial pressure (RAP)** were recorded sequentially.

Received March 22, 2004.
Accepted August 2, 2004.
From the Department of Small Animal Clinical Sciences, Virginia-Maryland Regional College of Veterinary Medicine, Virginia Tech, Blacksburg, VA 24061-0442.
Supported by a Virginia-Maryland Regional College of Veterinary Medicine New Initiative grant.
Presented in part as an abstract at the 21st Annual American College of Veterinary Internal Medicine Forum, Charlotte, NC, June 2003.
The authors thank Christine Cohen, John Strauss, and Cindy Harris for technical assistance.
Address correspondence to Dr. Abbott.

All pressure measurements consisted of the mean of 3 consecutive recordings of mean pressure provided by the physiologic monitor. All recordings were visually inspected to ensure that the determination had not been distorted by motion artifact. Resting HR was obtained from the ECG recording as the mean HR from a 15-second period during the time that SBP was obtained. Cardiac output was determined by thermodilution with a cardiac output computer[g] after injection of 5 mL of iced 5% dextrose in water. Three determinations were used to determine the mean value, and the result was indexed to body surface area.

The following hemodynamic variables were obtained prior to administration of carvedilol on day 1 and then 2, 4, and 6 hours after the morning dose on days 1 and 7 to 10: resting HR, SBP, PBP, RAP, pulmonary capillary wedge pressure, and **cardiac index (CI)**. Indices of pulmonary and systemic vascular resistance were calculated by use of measured CI and the difference in mean pressure across the appropriate vascular bed.

The **change in HR (ΔHR)** after IV administration of a single bolus of 1 µg of isoproterenol/kg and then the **change in SBP (ΔP)** after IV administration of 8 µg of phenylephrine/kg were recorded 2 and 6 hours after administration of carvedilol. Mean HRs during consecutive 6-second intervals after the injection of isoproterenol were calculated; the highest of these mean HRs was considered to be the maximal HR. The ΔHR was the difference between maximal and baseline HRs. The ΔP was determined in a similar fashion, but maximal and baseline pressures were the mean of 3 consecutive recordings provided by the physiologic recorder. Phenylephrine was injected only after hemodynamic variables had returned to baseline. Phenylephrine is a selective α-1–adrenergic receptor agonist, and isoproterenol is a nonselective β-adrenergic agonist.[14] All of the same variables, including responses to isoproterenol and phenylephrine, were obtained from control dogs at the same time intervals. For control dogs, hour zero was the time that they were fed the bolus of commercial dog food. This investigation was approved by the Animal Care Committee of Virginia Tech.

Statistical analyses—Repeated-measures ANOVA was used to evaluate the effects of day, hour after administration, carvedilol dose, and their interactions on hemodynamic variables. The control group was considered to have received a carvedilol dose of zero and was included in all analyses. In the results and discussion, hour refers to hour after administration of carvedilol or, for the control dogs, hour after the dog received a small quantity of commercial dog food as described. Baseline data obtained from all dogs prior to drug administration were included in the statistical model as covariates. Significant ($P < 0.05$) effects were further investigated by testing for linear and quadratic trends or by comparing means by use of the Tukey highly significant differences test. Repeated-measures ANOVA was used to evaluate the responses to isproterenol and phenylephrine. For all comparisons, $P < 0.05$ was considered significant. Unless otherwise noted, data are expressed as mean (95% **confidence interval [CI]**) values.

Results

Mean (range) administered carvedilol dose for the 3 groups that received 1.56, 3.125, and 12.5 mg of

Table 1—Hemodynamic variables recorded after administration of carvedilol to healthy dogs.

Day	Hour	Dose (mg)	HR (beats/min)	SM (mm Hg)	PM (mm Hg)	PCWP (mm Hg)	RA (mm Hg)	CI L/min/m^2	SVRI mm Hg ·min·m^2/L	PVRI mm Hg ·min·m^2/L
1	2	3.125	87.3 ± 6.43	95.11 ± 3.34	14.16 ± 1.00	5.25 ± 0.68	1.83 ± 0.54	4.61 ± 0.28	34.39 ± 2.55	3.1 ± 0.37
1	4	3.125	83.3 ± 6.26	96.11 ± 3.45	15.16 ± 1.10	6.92 ± 0.73	3.67 ± 0.58	4.04 ± 0.29	38.91 ± 3.4	3.2 ± 0.46
1	6	3.125	82.63 ± 5.44	97.45 ± 3.26	15.32 ± 0.99	5.75 ± 0.66	2.83 ± 0.56	3.87 ± 0.31	42.16 ± 3.58	4.03 ± 0.44
7–10	2	3.125	95.96 ± 6.43	97.95 ± 3.34	13.82 ± 1.00	5.08 ± 0.68	3 ± 0.54	3.79 ± 0.28	43.91 ± 2.55	3.86 ± 0.37
7–10	4	3.125	83.3 ± 6.26	100.45 ± 3.45	14.32 ± 1.1	6.08 ± 0.73	3.83 ± 0.58	3.61 ± 0.29	45.27 ± 3.4	3.71 ± 0.46
7–10	6	3.125	85.32 ± 5.73	99.28 ± 3.26	14.66 ± 0.99	5.75 ± 0.66	3 ± 0.56	3.7 ± 0.31	44.61 ± 3.58	3.86 ± 0.44
1	2	6.25	87.51 ± 6.42	94.53 ± 3.38	16.1 ± 0.99	6.9 ± 0.69	2.79 ± 0.54	4.2 ± 0.28	36.64 ± 2.52	3.38 ± 0.37
1	4	6.25	83.51 ± 6.25	97.86 ± 3.49	16.6 ± 1.10	6.07 ± 0.74	3.63 ± 0.59	4.02 ± 0.29	41.91 ± 3.38	4.11 ± 0.46
1	6	6.25	81.51 ± 5.43	99.86 ± 3.3	17.43 ± 0.99	7.4 ± 0.67	4.13 ± 0.56	3.66 ± 0.31	44.63 ± 3.57	4.41 ± 0.43
7–10	2	6.25	87.51 ± 6.42	90.69 ± 3.38	14.93 ± 0.99	4.57 ± 0.69	2.46 ± 0.54	3.59 ± 0.28	39.56 ± 2.52	4.46 ± 0.37
7–10	4	6.25	82.18 ± 6.25	89.53 ± 3.49	14.93 ± 1.10	5.57 ± 0.74	2.96 ± 0.59	3.26 ± 0.29	44.96 ± 3.38	4.53 ± 0.46
7–10	6	6.25	84.18 ± 5.43	92.86 ± 3.3	15.1 ± 0.99	6.07 ± 0.67	2.79 ± 0.56	3.49 ± 0.31	42.22 ± 3.57	3.94 ± 0.43
1	2	25	98.03 ± 6.41	95.11 ± 3.35	15.35 ± 1.00	5.75 ± 0.68	1.66 ± 0.53	4.53 ± 0.28	35.5 ± 2.67	3.48 ± 0.37
1	4	25	98.03 ± 6.24	99.44 ± 3.47	15.52 ± 1.11	6.25 ± 0.73	2.33 ± 0.58	3.75 ± 0.29	41.25 ± 3.49	3.86 ± 0.46
1	6	25	92.7 ± 5.42	100.44 ± 3.28	15.18 ± 1.00	5.75 ± 0.66	3 ± 0.55	4.24 ± 0.31	37.88 ± 3.67	3.46 ± 0.43
7–10	2	25	79.36 ± 6.41	94.94 ± 3.35	14.02 ± 1.00	6.92 ± 0.68	3.33 ± 0.53	3.37 ± 0.28	41.24 ± 2.67	3.43 ± 0.37
7–10	4	25	72.7 ± 6.24	94.11 ± 3.47	13.52 ± 1.11	5.58 ± 0.73	3.33 ± 0.58	3.31 ± 0.29	41.39 ± 3.49	3.66 ± 0.46
7–10	6	25	82.7 ± 5.42	100.94 ± 3.28	14.68 ± 1.00	6.42 ± 0.66	3.16 ± 0.55	3.7 ± 0.31	40.85 ± 3.67	3.61 ± 0.43
1	2	C	82.92 ± 6.42	95.92 ± 3.51	15.9 ± 0.99	5.58 ± 0.68	3.2 ± 0.53	4.41 ± 0.28	34.92 ± 2.55	3.85 ± 0.37
1	4	C	86.25 ± 6.25	95.09 ± 3.62	16.23 ± 1.10	6.58 ± 0.73	3.87 ± 0.58	3.85 ± 0.29	40.29 ± 3.4	4.09 ± 0.45
1	6	C	88.92 ± 5.43	97.92 ± 3.44	16.56 ± 0.99	6.75 ± 0.66	4.03 ± 0.56	4.15 ± 0.31	37.46 ± 3.59	3.63 ± 0.43
7–10	2	C	88.92 ± 6.42	87.42 ± 3.51	15.73 ± 0.99	4.75 ± 0.68	3.2 ± 0.53	4.54 ± 0.28	30.35 ± 2.55	3.84 ± 0.37
7–10	4	C	90.92 ± 6.25	88.92 ± 3.62	15.06 ± 1.10	5.57 ± 0.77	3.17 ± 0.61	3.75 ± 0.29	38.91 ± 3.4	4.24 ± 0.45
7–10	6	C	90.92 ± 5.43	91.42 ± 3.44	14.73 ± 0.99	5.25 ± 0.66	2.7 ± 0.56	4.03 ± 0.31	37.25 ± 3.59	3.83 ± 0.43

Day = Day of study. Hour = Hour after administration of carvedilol or (for control dogs) after being fed a small quantity of dog food. Dose = Daily dose of carvedilol. HR = Heart rate. SM = Mean systemic arterial pressure. PM = Mean pulmonary arterial pressure. PCWP = Mean pulmonary capillary wedge pressure. RA = Mean right atrial pressure. CI = Cardiac index. SVRI = Systemic vascular resistance index. PVRI = Pulmonary vascular resistance index. C = Control dogs. Data are expressed as mean ± SE.

Each of the 3 dose groups and the control group consisted of 6 healthy dogs.

Table 2—Results (*P* values) of a repeated-measures ANOVA model for tests of all effects on hemodynamic variables in healthy dogs administered carvedilol.

Effect	HR	SM	PM	PCWP	RA	CI	SVRI	PVRI
Day	0.358	0.053	**0.009**	0.123	0.994	**0.015**	0.303	0.256
Dose	0.935	0.490	0.622	0.894	0.685	0.410	0.255	0.569
Day·dose	**0.016**	0.087	0.802	0.366	0.187	0.510	0.521	0.808
Hour	0.345	**0.002**	0.102	0.073	**0.001**	**0.001**	**0.001**	0.223
Hour·day	0.398	0.711	0.429	0.885	**0.005**	0.186	0.384	0.118
Hour·dose	0.591	0.743	0.650	0.084	0.298	0.302	0.479	0.247
Hour·dose·day	0.632	0.551	0.366	0.263	0.989	0.491	0.271	0.131

Dose = Dose of carvedilol (dogs in the control group were considered to have received a dose of 0 mg).
P values < 0.05 are indicated in bold.
See Table 1 for remainder of key.

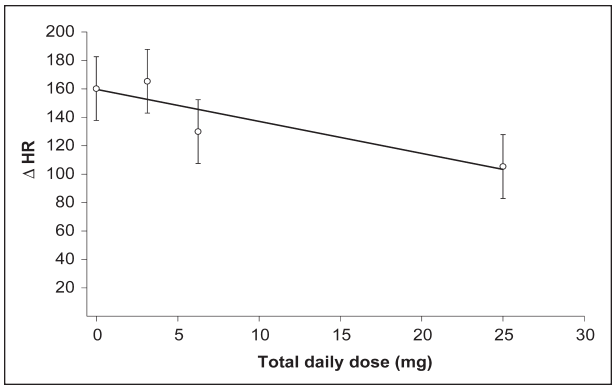

Figure 1—Heart rate response (beats/min [ΔHR]) to 1 µg/kg of isoproterenol/kg administered IV, relative to daily carvedilol dose in dogs. Each open circle represents the mean (95% confidence interval) of 24 observations (6 dogs evaluated 2 and 6 hours after administration of carvedilol, or for control dogs [dose, 0 mg], a small quantity of commercial dog food, on days 1 and 7 to 10). Solid line represents the significant ($P < 0.001$) linear relationship between dose and ΔHR in response to isoproterenol administration.

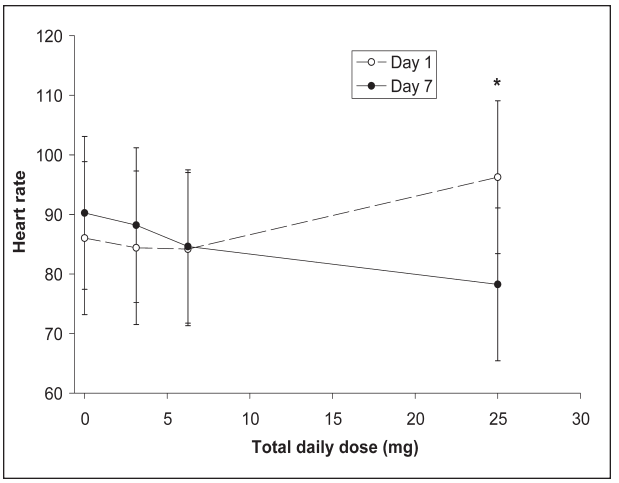

Figure 2—Mean (95% confidence interval) resting heart rate (beats/min) of carvedilol-treated dogs by days after initiation and total daily dose. Each point is the mean of 18 observations (6 dogs each evaluated at 2, 4, and 6 hours after administration of carvedilol, or for control dogs, after a small quantity of commercial dog food). *Significantly ($P \leq 0.05$) different means at that dose between days.

carvedilol twice daily was 0.08 (0.07 to 0.09) mg/kg, PO, every twelve hours; 0.15 (0.13 to 0.17) mg/kg, PO, every twelve hours; and 0.54 (0.44 to 0.76) mg/kg, PO, every twelve hours, respectively. Carvedilol had no effect on resting hemodynamic variables or on resting HR (**Tables 1 and 2**). In response to increasing carvedilol dose, there was a significant ($P < 0.001$) linear decrease in ΔHR caused by isoproterenol administration (**Figure 1**).

The interaction of carvedilol dose and day had a significant ($P = 0.016$) effect on resting HR. That is, the relationship between carvedilol dose and resting HR was different on days 1 and 7. However, a main effect of carvedilol dose on resting HR was not detected. When days 1 and 7 were considered separately, tests of linear and quadratic trends across doses did not reveal a significant effect. However, when the effect of day was evaluated for each dose separately, resting HR at the highest dose was lower on days 7 to 10 than on day 1 ($P = 0.002$; **Figure 2**).

Carvedilol had no effect on ΔP ($P = 0.19$), although the mean response to phenylephrine was smaller with higher doses of carvedilol (mean, 51.1 [95% CI, 41 to 61.2], 45.4 [35.4 to 55.3], 43.8 [33.9 to 53.8], and 35.8 [25.8 to 45.7] mm Hg for the control and 0.08-, 0.15-, and 0.54-mg/kg groups, respectively). After administration of phenylephrine, 2 control dogs struggled in association with the development of marked systemic hypertension; for one of these, data collection was interrupted and the effect of that injection was excluded from analysis.

Discussion

Carvedilol administered orally to healthy conscious dogs at mean doses from 0.08 to 0.54 mg/kg given twice daily did not affect resting hemodynamic variables. However, the effect of bolus IV administration of isoproterenol on HR was attenuated by carvedilol such that there was a linear decrease in HR response to isoproterenol administration with increasing carvedilol dose. The latter finding provides evidence of β-adrenergic receptor blockade, despite the lack of effect on resting hemodynamic variables. By use of IV bolus administration of phenylephrine, we did not detect an α-adrenergic receptor antagonist effect of carvedilol. Although the effect was not significant, the pressor response to phenylephrine administration was smaller with higher doses of carvedilol, suggesting that a larger number of subjects might have allowed detection of an α-receptor blocking effect.

The interaction of dose and day had a significant effect on resting HR. Tests for linear or quadratic trends did not reveal a significant effect of carvedilol dose on

resting HR when days 1 and 7 to 10 were considered separately. However, at the highest carvedilol dose, resting HR on days 7 to 10 was lower than resting HR on day 1. Possibly, a larger sample size might have disclosed an effect of carvedilol dose on HR. We did not detect a significant effect of carvedilol dose on resting HR when day 1 was considered separately, but the mean HR of dogs that received the highest dose was higher than the mean HR of the other groups. An increase in HR associated with carvedilol administration could be explained by activation of the baroreceptor reflex, as has been suggested by others[12]; however, we did not observe a dose-related decrease in blood pressure that might explain this. A decrease in resting HR with chronic carvedilol administration might reflect drug accumulation and more complete β-receptor blockade with long-term use, but it should be recognized that on the basis of our results, this is speculation.

A few hemodynamic variables were significantly affected by hour or day but not by administration of carvedilol. The investigators were blinded to group assignment and a control group was included, so there was little opportunity for bias and measurement errors were presumably random.

Others have evaluated the effect of carvedilol on anesthetized and conscious healthy dogs,[9,10,12,13] but to our knowledge, this is the first investigation of the effects of daily oral administration of carvedilol by use of doses that might practically be used as initial doses in dogs with cardiac disease. Sawangkoon et al[12] evaluated the cumulative effect of incremental IV administration of carvedilol in healthy dogs anesthetized with morphine and α-chloralose. Cumulative doses in excess of 30 µg/kg increased HR and CI. The latter was explained by the increase in HR because stroke volume was unaffected. The increase in HR might have resulted from activation of the baroreceptor reflex, although there was no effect on SBP.[12] Other hemodynamic variables were not affected, although high doses of carvedilol prevented the increase in systolic PBP that was observed in the control group and attributed to the administration of saline solution vehicle.[12]

Sponer et al[9] evaluated the β-receptor blocking effect of IV and oral administration of carvedilol in healthy conscious dogs. They developed a dose-response curve on the basis of carvedilol's inhibition of the tachycardia that resulted from administration of a single bolus of isoproterenol. Inhibition of isoproterenol-induced tachycardia was evident 16 hours after the administration of 3 mg of carvedilol/kg, PO.[9] These investigators also detected a reduction in SBP after IV administration of carvedilol. Mean SBP decreased by 8 mm Hg after IV administration of 0.1 mg/kg.[9] The same group reported a decrease in systemic vascular resistance after IV administration of carvedilol to healthy conscious dogs.[10] In the same publication, Strein et al[10] reported the neuroendocrine and hypotensive effects of 4 times daily administration of 6 mg of carvedilol/kg, PO. Kawada et al[8] constructed dose response curves on the basis of the inhibitory effect of IV administration of carvedilol on the increase in SBP that resulted from the administration of 1- or 3-µg of phenylephrine/kg boluses and in so doing demonstrated α-adrenergic receptor blockade by carvedilol.

More recently and of greatest relevance to our work, Uechi et al[13] evaluated the hemodynamic effects of a single oral administration of carvedilol at doses of 0.2 and 0.4 mg/kg. Dogs with iatrogenic mitral regurgitation and healthy dogs were included in that study. In the group of healthy dogs, both doses decreased HR 3 hours after administration but HR 24, 36, and 48 hours after administration was not different from controls.[13] The higher dose decreased mean arterial blood pressure, but other reported hemodynamic variables were unaffected.[13] The HR response to bolus administration of isoproterenol was suppressed by both doses of carvedilol, but the effect of IV administration of phenylephrine on mean arterial blood pressure was unaffected.[13]

In general, our results are consistent with those reported previously. β-Receptor blockade was evident in the effect of carvedilol on isoproterenol-induced tachycardia. However, we failed to detect an effect on resting hemodynamic variables or evidence of α-adrenergic receptor blockade. The discrepancies are likely explained by differences in carvedilol dose, route of administration, and perhaps the temporal relationship of measurements and dosing. As stated, carvedilol decreases SBP in healthy conscious dogs.[9,10] This effect may result from α-receptor blockade–induced vasodilation,[8] although it has been suggested that the hypotensive effect of carvedilol results from a decrease in venous return.[15] In general, decreases in SBP result from relatively high doses of carvedilol; indeed, Strein et al[10] reported that the hypotensive dose of orally administered carvedilol that was equipotent to oral administration of 1 mg of hydralazine/kg was 6 mg/kg. Obviously, this is much higher than the doses used in our study. Uechi et al[13] failed to detect an α-receptor blocking effect of oral administration of 0.2 to 0.8 mg of carvedilol/kg in healthy conscious dogs by use of bolus injection of 5 µg of of phenylephrine/kg. Furthermore, in a study[16] of humans receiving long-term carvedilol for management of CHF, there was no functionally important α-adrenoceptor antagonism. That carvedilol results in α-adrenergic receptor blockade has been established.[8] However, the published evidence and our results suggest that the effect may not be clinically relevant at low doses.

Carvedilol may have a role in the management of canine patients with CHF caused by systolic myocardial dysfunction.[11] When administered to human patients with CHF, a low dose is used initially to limit the prevalence of clinical decompensation that may result from the negatively inotropic effect of β-adrenoceptor blockade. The dose is then incrementally increased to a target dose unless adverse signs develop.[17] Results of our study indicated that orally administered carvedilol at doses from 0.08 to 0.54 mg/kg results in β-adrenoceptor blockade, despite a lack of effect on resting HR or hemodynamic variables. These doses were chosen because we believed them to be clinically relevant in that they might be practically administered as initial doses, were this drug used in the management of dogs with cardiac disease. The lowest

dose represented half of the smallest manufactured carvedilol tablet. This is the smallest dose that can be practically given without reformulating the drug. The higher doses were a single 3.125-mg tablet given twice daily and the equivalent of a 12.5-mg tablet given twice daily. The appropriate dose for clinical use can only be determined through study of dogs with cardiac disease, which may respond differently than the healthy dogs we evaluated.

Sawangkoon et al[12] reported an elimination half-life of IV-administered carvedilol of only 53.87 minutes, and this might suggest that carvedilol should be administered more frequently than every 12 hours. However, others have shown that the β-receptor blocking effect of carvedilol in dogs persists longer than 16 hours.[9,13] It would have been better to measure hemodynamic variables throughout the 12 hours between doses, but the timing of measurements was dictated by practicality.

Possibly, the dose of phenylephrine was excessively high so that the agonist displaced carvedilol from α-adrenergic receptors and overwhelmed the effect of carvdilol. Two dogs in the control group became obviously but transiently uncomfortable in association with development of marked systemic hypertension after injection of phenylephrine. In part, the dose was chosen on an empirical basis after administration of phenylephrine to a healthy dog during preparation for this study. Large intersubject variability in hemodynamic variables and response to α-receptor agonism was expected in a study of conscious dogs, and it was anticipated that a relatively high dose would be required to detect an effect of phenylephrine administration. The dose was within the range suggested in a veterinary formulary[18] and was much lower than the 32 µg/kg used by other investigators evaluating the effects of α-1 receptor antagonists on urethral tone.[19]

The dogs were randomly allocated to receive commercially available tablets or portions thereof. Our method was chosen on the basis of practicality. We used the doses and dogs that were available. We had hoped to procure dogs that were relatively uniform with regard to body size, but limited availability forced us to use dogs of disparate sizes. We did not want to reformulate the pills because that is not how we use the drug in clinical cases. However, it would have been better if we had randomized on the basis of dose calculated by use of body weight because this would have narrowed the ranges of doses received.

Oral administration of carvedilol in our study did not affect resting hemodynamics or result in appreciable α-adrenergic blockade. Over the dose range evaluated, there was a dose-dependent attenuation of the response to isoproterenol, which provided evidence of β-adrenergic antagonism. These data may be useful in the management of dogs with heart disease.

a. SmithKline Beecham Pharmaceuticals, Philadelphia, Pa.
b. Angiocath, Becton- Dickinson, Sandy, Utah.
c. Maxxim Medical, Argon Division, Athens, Tex.
d. Utah Medical Products, Midvale, Utah.
e. Fast Cath, St Jude Medical, Daig Division, Mennetona, Minn.
f. PROPAQ model 106, Welch/Allyn Protocol Inc, Beaverton, Ore.
g. Edwards Com-2, Baxter Healthcare Corp, Round Lake, Ill.

References

1. Effect of metoprolol CR/XL in chronic heart failure: Metoprolol CR/XL Randomised Intervention Trial in Congestive Heart Failure (MERIT—CHF). *Lancet* 1999;353:2001–2007.

2. Packer M, Bristow MR, Cohn JN, et al. The effect of carvedilol on morbidity and mortality in patients with chronic heart failure. U.S. Carvedilol Heart Failure Study Group. *N Engl J Med* 1996;334:1349–1355.

3. 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.

4. The Cardiac Insufficiency Bisoprolol Study II (CIBIS-II): a randomised trial. *Lancet* 1999;353:9–13.

5. 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.

6. Hjalmarson A, Goldstein S, Fagerberg B, et al. Effects of controlled-release metoprolol on total mortality, hospitalizations, and well-being in patients with heart failure: the Metoprolol CR/XL Randomized Intervention Trial in congestive heart failure (MERIT-HF). MERIT-HF Study Group. *JAMA* 2000;283:1295–1302.

7. Gilbert EM, Abraham WT, Olsen S, et al. Comparative hemodynamic, left ventricular functional, and antiadrenergic effects of chronic treatment with metoprolol versus carvedilol in the failing heart. *Circulation* 1996;94:2817–2825.

8. Kawada T, Ishibashi T, Nakazawa M, et al. Adrenoceptor-blocking activity and cardiohemodynamic effects of carvedilol in animals. *J Cardiovasc Pharmacol* 1990;16:147–153.

9. Sponer G, Bartsch W, Strein K, et al. Pharmacological profile of carvedilol as a beta-blocking agent with vasodilating and hypotensive properties. *J Cardiovasc Pharmacol* 1987;9:317–327.

10. Strein K, Sponer G, Muller-Beckmann B, et al. Pharmacological profile of carvedilol, a compound with beta-blocking and vasodilating properties. *J Cardiovasc Pharmacol* 1987;10(suppl 11):S33–S41.

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

12. Sawangkoon S, Miyamoto M, Nakayama T, et al. Acute cardiovascular effects and pharmacokinetics of carvedilol in healthy dogs. *Am J Vet Res* 2000;61:57–60.

13. 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.

14. Hoffman BB, Lefkowitz RJ. Catecholamines, sympathomimetic drugs, and adrenergic receptor antagonists. In: Hardman JG, Limbird LE, ed. *Goodman & Gilman's the pharmacological basis of therapeutics*. 9th ed. New York: McGraw-Hill Book Co, 1996;199–248.

15. Ishibashi T, Okuhira M, Hamaguchi M, et al. Effect of carvedilol on venous return: a mechanism of reduction in blood pressure. *Jpn J Pharmacol* 1991;55:186–189.

16. Kubo T, Azevedo ER, Newton GE, et al. Lack of evidence for peripheral alpha(1)-adrenoceptor blockade during long-term treatment of heart failure with carvedilol. *J Am Coll Cardiol* 2001;38:1463–1469.

17. Cleland JG. Beta-blockers for heart failure: why, which, when, and where. *Med Clin North Am* 2003;87:339–371.

18. Papich MG. *Saunders handbook of veterinary drugs*. Philadelphia: WB Saunders Co, 2002;412–413.

19. Hancock AA, Brune ME, Witte DG, et al. Actions of A-131701, a novel, selective antagonist for alpha-1A compared with alpha-1B adrenoceptors on intraurethral and blood pressure responses in conscious dogs and a pharmacodynamic assessment of in vivo prostatic selectivity. *J Pharmacol Exp Ther* 1998;285:628–642.