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The Effect of Angiotensin-Converting Enzyme Inhibitors of Left Atrial Pressure in Dogs with Mitral Valve Regurgitation

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Background: Despite many epidemiological reports concerning the efficacy of angiotensin-converting enzyme (ACE) inhibitors in dogs with mitral regurgitation (MR), the hemodynamic effects of ACE inhibitor administration have not been fully evaluated.

Objectives: To document left atrial pressure (LAP) in dogs with MR administered ACE inhibitors, in order to obtain interesting information about daily LAP changes with administration of ACE inhibitors.

Animals: Five healthy Beagle dogs weighing 9.8 to 14.2 kg (2 males and 3 females; aged 2 years).

Methods: Experimental, crossover, and interventional study. Chordae tendineae rupture was induced, and a radiotelemetry transmitter catheter was inserted into the left atrium. LAP was recorded for 72 consecutive hours during which each of 3 ACE inhibitors—enalapril (0.5 mg/kg/d), temocapril (0.1 mg/kg/d), and alacepril (3.0 mg/kg/d)—were administered in a crossover study.

Results: Averaged diurnal LAP was significantly, but slightly reduced by alacepril ($P = .03$, 19.03 ± 3.01–18.24 ± 3.07 mmHg). The nightly drops in LAP caused by alacepril and enalapril were significantly higher than the daily drops ($P = .03$, −0.98 ± 0.19 to −0.07 ± 0.25 mmHg, and $P = .03$, −0.54 ± 0.21–0.02 ± 0.17 mmHg, respectively), despite the fact that the oral administrations were given in the morning. Systolic blood pressure (122.7 ± 14.4–117.4 ± 13.1 mmHg, $P = .04$) and systemic vascular resistance (5800 ± 2685–5144 ± 2077 dyne×s/cm^5, $P = .03$) were decreased by ACE inhibitors.

Conclusions and Clinical Importance: ACE inhibitors decrease LAP minimally, despite reductions in left ventricular afterload. ACE inhibitors should not be used to decrease LAP.

Key words: Chronobiology; Daily rhythm; Diurnal monitoring; Radio telemetry; Rennin-angiotensin aldosterone system.

Mitral valve regurgitation (MR) secondary to degeneration of the mitral valve apparatus is the most common cardiac disease in dogs, and the incidence of MR is approximately 30% in dogs aged 13 years and older.[1,2] MR is a progressive disease that in severe instances can result in death, despite medical treatment. The progressive character of MR is intimately related to the rennin-angiotensin aldosterone system (RAAS) that regulates blood pressure (BP), tissue perfusion, and fluid balance.[3] Like the other cardiac disorders, the dysregulation of RAAS is a key to the process of chronic heart failure (CHF) in dogs with MR.[3,4] Pharmacological inhibition of the RAAS with angiotensin-converting enzyme (ACE) inhibitors plays an important role in the management of MR, as indicated by many reports describing how the long-term efficacy of inhibiting ACE resulted in an improvement of congestive heart failure in dogs with MR.[5–9]

ACE inhibitors, known as vasodilators, include the possible effects of decreasing systemic vascular resistance and decreasing left atrial pressure; several drug varieties are available in Japan. However, the effects of these ACE inhibitors have not been fully evaluated in a quantitative manner: unknowns include the exact effects of hemodynamic change after administration of ACE inhibitors as well as differences among these chemicals. We have previously reported the 24-hour left atrial pressure (LAP) profiles of experimentally induced MR by a radio telemetry system, and this system seems very useful for the evaluation of hemodynamic change after the administration of ACE inhibitors.

In the present study, we monitored the LAP of dogs with experimentally induced MR by a radio telemetry system and evaluated the effects of a number of ACE inhibitors (enalapril, temocapril, and alacepril). ECG evaluation and BP measurements were also conducted, and the effects of ACE inhibitors for MR were evaluated for the analysis of pathophysiological change.

Materials and Methods

Animals

Five 2-year-old Beagles (2 males and 3 females) weighing 11.8 ±1.6 kg (range: 9.8–14.2 kg) were used. Dogs were housed in individual metal cages (size: *W* 90 cm × *D* 100 cm × *H* 110 cm) in an air-conditioned room (temperature: 22 ± 2°C; humidity: 50 ± 10%). Fresh drinking water was freely accessible, and the dogs were fed commercial dry food[a] twice a day from 0800 to 0830 and 2000 to 2030 hours under a 12 : 12-hour light/dark cycle (lights on at 0800 hours; lights off at 2000 hours). Except for the 2 daily feeding periods, access to the room was restricted to avoid unnecessary stress. All dogs had acclimatized to the experimental environment and human handling. During all phases of the present study, these dogs were managed and cared for in accordance with the standards established by Tokyo University of Agriculture and Technology (TUAT) and described in its "Guide for the Care and Use of Laboratory Animals," and the present study was approved by TUAT's Animal Experimental Committee (acceptance no. 20-70).

Preparing MR and Transmitter Implantation

Surgical and postoperative care procedures were followed as described previously.[10] Follow-up care included the auscultation of lung/cardiac sound and blood tests (CBC count, blood urea nitrogen, creatinine, alkaline phosphatase, and electrolytes). Thoracic radiography and ECG were performed to evaluate pulmonary

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venous congestion and cardiac dilation (supporting information Fig S1).

LAP Measurement Method

All radio telemetry system[b] and recording procedures were the same as described in our previous report.[10] The maximum, mean, and minimum LAP were obtained as the averages of 10-second recorded segments from continuous waveform recordings (supporting information Fig S2).

Daily LAP Monitoring Protocol

After the radio telemetry transmitter[c] implantation, the dogs were not used for the study for at least 4 weeks, until no major changes were identified in ECG evaluations and LAP. During this examination period, all dogs were housed in individual metal cages sized as described above. Before the administration of ACE inhibitors, we recorded LAP for 72 consecutive hours as the no-medication period. Subsequently, one of the ACE inhibitors—enalapril[d] (0.5 mg/kg/d), temocapril[e] (0.1 mg/kg/d), or alacepril[f] (3.0 mg/kg/d)—was administered PO to each dog at 0800 hours with morning food for 7 days. The selection of ACE inhibitor was followed in a crossover study. The recorded LAP for the last 72 consecutive hours of the 7 days was used for the study. The interval between administrations was at least 1 week. Daytime and nighttime LAP were each calculated following by defining daytime (1300–1700 hours) and nighttime (0100–0500 hours), respectively, in order to minimize the influence of individual activities.

ECG

Before and after administration of ACE inhibitors, ECG measurement was performed along with BP and LAP measurement. Transthoracic conventional ECG as well as 2-dimensional spectral Doppler and tissue Doppler ECG were performed by a single investigator. Each dog was positioned in left and right recumbency, and ECG examinations were performed by means of a digital ultrasonographic system[g] with a 5.0 MHz sector transducer. Sweep speed during the Doppler and M-mode recordings was 150 to 200 mm/s. Optimized right parasternal projections were used to measure heart dimensions. LA/Ao was assessed in a short-axis M-mode at heart base level for assessing the scale of LA enlargement. Based on the scale of LV enlargement by the use of a short-axis M-mode projection, left ventricular end-diastolic diameter (LVEDD) was assessed at mitral valve chordal level. Mitral valve regurgitation was also assessed from the ratio of maximal mitral regurgitant jet area to left atrial area (ARJ/LAA) determined via color Doppler ECG mapping. For the assessment of systolic function, fractional shortening (%FS) was calculated after the established equation.[11] Optimized left apical parasternal projections of the left ventricular inflow and outflow tracts were used for assessing mitral inflow and MR flow by a 2-chamber view, entailing the use of 6 mm of the sample volume. Forward stroke volume and cardiac output (CO) were calculated by the use of a left ventricular outflow projection. The same mitral inflow tract view at the 2-chamber view was used to evaluate lateral mitral annulus velocities[12] with pulsed TDI, entailing the use of 2 mm of the sample volume. Using the Doppler signals of the mitral inflow, peak transmitral early diastolic wave (E wave) velocity was measured, and E/Ea was calculated. MR flow was recorded with a high-intensity continuous wave spectral Doppler signal, and we calculated the MR pressure gradient (MRPG) based on a modified Bernoulli's equation. These ECG profiles were obtained for 3 consecutive beats, and the averages were used. All the ECG recordings were stored on the internal hard drive of the ECG and transmitted to the DICOM server online.[h]

BP Measurements

All indirect arterial BP readings were obtained by the oscillometric method.[i] Cuff size appropriate for tail circumference was selected for each dog and the BP measured. BP measurements were performed simultaneously with MR velocity measurements by ECG, and 3 consecutive measurements were averaged for each dog and used in our calculations. Estimated LAP was calculated as systolic BP (SBP)−MRPG. Systemic vascular resistance (SVR) was calculated as SVR = 80×(SBP–RAP)/CO, and RAP was tentatively defined as 5 mmHg owing to a lack of right-sided heart failure signs.

Statistical Analysis

All data are represented as mean plus or minus the standard deviation. Statistical significance was defined as $P < .05$. A 2-way analysis of variance in conjunction with a Bonferroni's multiple comparison test was used for comparing 24-hour LAP variations before and after each ACE inhibitor administration. The 2 parameters were time of day and ACE inhibitor. A Friedman's test with Dunn's multiple comparisons was used to compare mean 24-hour heart rate (HR). Wilcoxon's signed-rank test was used for comparing daytime and nighttime drops of LAP. A Student's paired *t*-test was used to examine the efficacy of ACE inhibitors with no distinction for the particular inhibitor used, while a Mann-Whitney *U*-test was used to compare the hemodynamic parameters for each ACE inhibitor. GraphPad Prism version 5.0a[j] and EXCEL 2003[k] were used to perform these statistical analyses.

Results

The operation to rupture the mitral valvular chordae tendineae and implant the transmitter was successful in all dogs. The severity of the regurgitation jet varied among dogs, and these dogs were numbered and arranged in the order of MR severity on the basis of their ECG profiles. At this point, ECG findings of 5 dogs are shown below; LVEDD were 3.7 to 4.6 cm (normal range is 2.99–3.26 cm), LA/Ao by use of short-axis projection were 1.28 to 1.8 (< 1.3), mitral *E* wave velocity were 1.08 to 1.65 m/s (0.86 ± 0.10 m/s), E/Ea were 7.68 to 14.11 (7.9 ± 1.8), the ratio of maximal mitral ARJ to LA area were 25.4% to 56.9%.[12–14] Three dogs (numbers 1–3) did not have clinical signs associated with MR; 2 other dogs (numbers 4 and 5) had less activity and appetite, although these traits were judged not objectively but subjectively. In dog 5, LAP increased suddenly after successful data collection after the administration of 2 kinds of ACE inhibitors (alacepril and temocapril). Therefore, diurnal LAP and HR were remeasured without any ACE inhibitor administration before enalapril administration, and the no-medication recordings used for the evaluation of enalapril in dog 5.

24-Hour LAP Monitoring

Individual 24-hour LAP profiles with and without ACE inhibitors were calculated (Table 1). Maximum LAP was significantly decreased by alacepril (19.03 ± 3.01–18.24 ± 3.07 mmHg, $P = .03$), and LAP was not significantly decreased by temocapril and enalapril (19.03 ± 3.01–20.14 ± 3.23 mmHg, $P = .29$, and 20.63 ± 3.61–19.37 ± 3.46 mmHg, $P = .16$, respectively). Results were similar for mean LAP and minimum LAP.

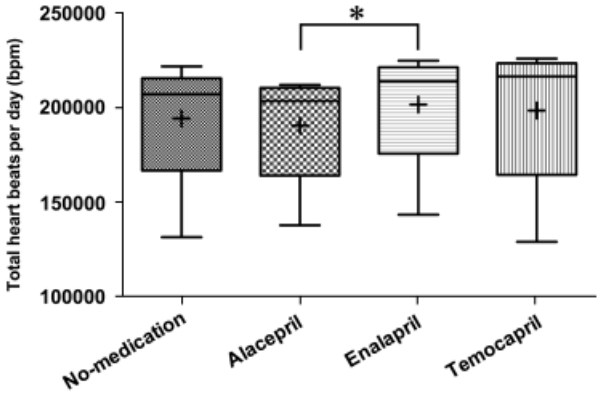

Fig 1. Total heartbeats per day with and without angiotensin-converting enzyme inhibitors (n = 5 for each bar). *Total heartbeats per day differed significantly with $P < .05$. 119 × 72 mm (600 × 600 DPI).

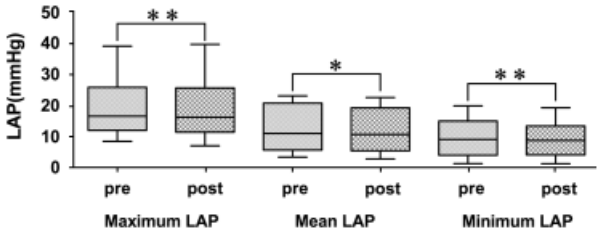

Fig 2. Each left atrial pressure (LAP) showed a significant decrease with oral administration of angiotensin-converting enzyme inhibitors (n = 15 for each pair). *LAP significantly decreased with $P < .05$, **$P < .01$. 104 × 40 mm (600 × 600 DPI).

There was a significant decrease in HR for alacepril compared with enalapril, but not compared with no medication (Fig 1). Interestingly, the nightly drops in LAP caused by alacepril and enalapril were significantly higher than the daily drops ($P = .03$, -0.98 ± 0.19 to -0.07 ± 0.25 mmHg, and $P = .03$, -0.54 ± 0.21 to 0.02 ± 0.17 mmHg, respectively), despite the fact that the oral administrations were given in the morning. These results were mirrored in mean and minimum LAP observations. To validate the observation duration, day-to-day variability over 3 days was calculated, and the results are shown in Table 1. In all dogs, day-to-day variability is smaller than the largest changes of LAP in each dog, which could indicate that the LAP changes were derived more from the efficacy of ACE inhibitor administrations than from day-to-day variability (data not shown).

All LAP values recorded during ECG were significantly decreased by ACE inhibitor medication (maximum LAP; 19.87 ± 9.57–19.19 ± 9.80 mmHg, $P = .009$, mean LAP; 12.57 ± 7.26–12.03 ± 6.97 mmHg, $P = .01$, minimum LAP; 9.14 ± 5.65–8.64 ± 5.38 mmHg, $P = .007$) (Fig 2). However, significant decreases in LAP were not observed for any ACE inhibitor (Fig 3). CO was not affected by ACE inhibitor administration (2.02 ± 0.93 versus 2.11 ± 0.95 L/min, $P = .50$), but SVR (5800 ± 2685 versus 5144 ± 2077 dyne×s/cm^5, $P = .03$) and SBP (122.7 ± 14.4 versus 117.4 ± 13.1 mmHg, $P = .04$) declined significantly after ACE inhibitor administration as shown in Figure 4. With the exception of LVEDD, other variables did not show significant changes (Table 2). There was not a significant change in SBP-MRPG after ACE inhibitor administration.

Discussion

The hemodynamic action mechanisms of ACE inhibitors for dogs with MR have not been subject to detailed analysis, especially preload. LAP and its alternatives, PCWP and LVEDP, cannot be measured by cardiac catheterization without general anesthesia in dogs with MR. In the present study, LAP under ACE inhibitor administration was monitored in conscious dogs by a radio telemetry system, and averaged diurnal LAP was significantly lowered by alacepril, although the difference was not sufficiently large. SBP and SVR decreased significantly after ACE inhibitor administration, indicating the sufficient vasodilating activity of ACE inhibitors. Taken together, our study indicates that ACE inhibitors have more potential for the vasodilating activity and BP-lowering effect in LAP. Other drugs, including diuretics

Table 1. Summary of daily LAP profiles by ACE inhibitor; averaged 24-hour maximum LAP profiles, day-to-day variability in maximum LAP, and comparison of maximum LAP between daytime (1300–1700 hours) and nighttime (0100–0500 hours).

	No Medication	Enalapril	Temocapril	Alacepril
Averaged 24-hour maximum LAP (mmHg)	$19.0 \pm 3.01/20.6 \pm 3.21$[a]	20.1 ± 3.73[a]	19.4 ± 3.46	18.2 ± 3.07[b]
Day-to-day variability (mmHg)	$0.24 \pm 0.18/0.24 \pm 0.18$[a]	0.22 ± 0.07[a]	0.28 ± 0.12	0.19 ± 0.08
Decreases in LAP by ACEi (mmHg)				
Daytime		0.02 ± 0.17[a]	1.07 ± 1.06	-0.07 ± 0.25
Nighttime		-0.54 ± 0.21[a,c]	-0.41 ± 0.43	-0.98 ± 0.19[c]

[a]In dog number 5, we remeasured LAP after an abrupt LAP elevation due to the progression of CHF and compared between before and after enalapril.

[b]LAP decreased significantly with each ACE inhibitor administration with $P < .05$.

[c]Nighttime drops of LAP are significantly lower than daytime drops.

ACE, angiotensin-converting enzyme; LAP, left atrial pressure.

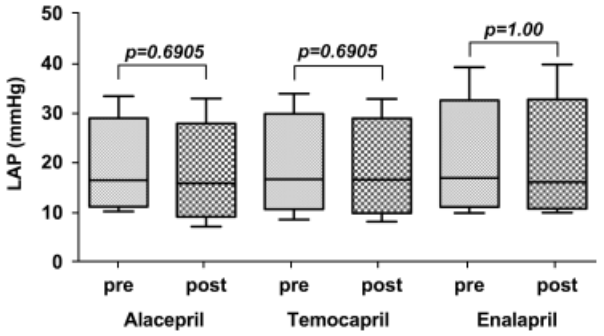

Fig 3. Oral administration of 3 kinds of angiotensin-converting enzyme inhibitor did not significantly reduce maximumleft atrial pressure (n = 5 for each pair). 82 × 48 mm (600 × 600 DPI).

should be considered to decrease LAP for acute lung edema in MR dogs.

In the present study, the LAP-lowering effect on ACE inhibitors was predominant in the nighttime compared with the daytime. The inhibitory activity of ACE by enalapril continued to decrease significantly for 24 hours after oral administration, with peak inhibitory activity at 3 hours after morning oral administration, indicating that captopril has less potentials on the basis of the fact that it decreased ACE levels to a much lesser degree and for a shorter time in Beagle dogs.[15] Considering that all dogs received ACE inhibitors PO once a day at 0800 hours in this report, LAP was not influenced by the inhibitory activity of ACE in plasma, and other factors seem to be more significant for the regulation of LAP. Unfortunately, we cannot definitively state that the regulation of LAP is fully independent of the inhibitory activity of ACE, because data for alacepril and temocapril was not provided in the report.[15]

Five kinds of ACE inhibitors are commercially available in Japan, and there was no evidence to determine which ACE inhibitor is superior to the others. The difference in LAP among 3 ACE inhibitors in the present study was smaller than we have expected. We cannot determine the superiority of some ACE inhibitors from the standpoint of their LAP-lowering effect, and the selection of ACE inhibitors should be based on factors other than their LAP-lowering effect. The decrease in total daily HR might be a reasonable criterion for the selection of ACE inhibitors, because it is well known that CHF is characterized not only by profound abnormalities in the hemodynamic profile but also by changes in sympathetic cardiovascular function.[16] Over-beating would increase mortality in human patients with a history of acute MI or heart failure, and HR reduction by β-blockers and other heart-rate lowering drugs might have the effect of lowering mortality.[17,18] A few reports have indicated that captopril which is the 1st ACE inhibitor as an antihypertensive agent and is the precursor of alacepril improves vagal activity in dogs with CHF[19] and enhances vagal nerve stimulation-evoked bradycardia in rats.[20] Unfortunately, to our knowledge, there is no report comparing vagal nerve activity among ACE inihibitors. That the highest drop in total daily HR was triggered by alacepril reflects its superiority in enhancing vagal activity.

Table 2. Comparison of ECG variables before and after ACE inhibitor administration.

Variable	Before ACEI	After ACEI	*P* Value
MR velocity (mmHg)	112.7 ± 15.5	113.9 ± 14.6	.49
SBP−MRPG (mmHg)	13.1 ± 14.0	5.6 ± 9.5	.16
E wave (m/s)	1.37 ± 0.22	1.35 ± 0.25	.57
E/Ea	10.5 ± 1.8	10.4 ± 2.2	.56
LA/Ao	1.46 ± 0.20	1.43 ± 0.21	.30
LVEDD (cm)	4.17 ± 0.36	4.27 ± 0.42	.02
%FS	43.0 ± 4.1	43.0 ± 3.5	.93

A Student's paired *t*-test was used to compare these parameters, and only LVEDD evidenced a significant difference.

LVEDD, left ventricular end-diastolic diameter; MR, mitral regurgitation; MRPG, MR pressure gradient; %FS, fractional shortening; SBP, systolic BP; SBP−MRPG, the value of MRPG subtracted from SBP. See Table 1 for the remainder of ECG parameters.

It is difficult to explain why LAP increased when temocapril was administered. Dog activity might be the reason for the LAP increase, as LAP measured by telemetry recordings can be influenced by body motion. LAP variations could be caused by the intensity of stimuli such as feeding and excitement, although there was no difference in body motion counts among the ACE inhibitors in the present study. In addition, we should consider the characteristics of temocapril. To date, there are no reports that temocapril is inferior to other ACE inhibitors in preload reduction, vasodilating activity or myocardial preservation, and we do not know why temocapril had less pronounced LAP-lowering effects in this study, although it did fail to decrease averaged 24-hour maximum LAP in all 5 dogs.

The focus in the chronopharmacology of cardiovascular diseases in human medicine has been on the prevalence of cardiovascular events and death.[21,22] Some studies (morning versus evening dosing) with oral administration of ACE inhibitors in essential hypertension have reported that evening dosing of benazepril, enalapril, and perindopril resulted in a greater nightly drop of BP and that the 24-hour profiles were distorted by evening enalapril. Nozawa et al[23] reported that the mortality of stroke-prone spontaneously hypertensive rats with evening dosing of temocapril was lower than with morning dosing. Although there are a few reports about diurnal changes in circulatory parameters in veterinary medicine,[24] we should be more focused on further research in chronopharmacology of not only cardiovascular diseases but also renal and intestinal diseases, which are dependent on autonomic nervous activity (Fig 4).

Limitations

In the present study, ECG and BP measurements were performed during the daytime. To evaluate the nightly drop in LAP via the afterload reduction by ACE inhibitors, nighttime ECG and BP measurements were desirable; however, nighttime examinations could disturb physical and neural activity, which affect diurnal

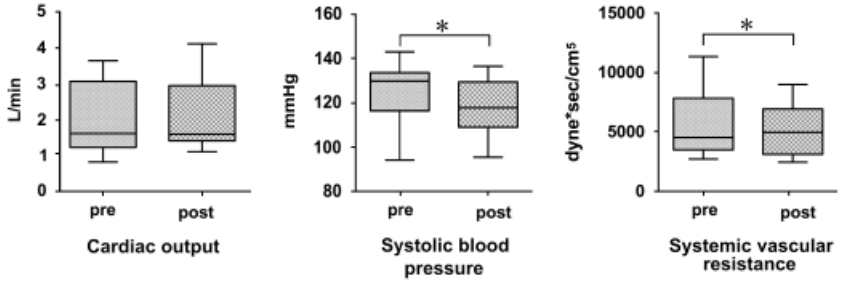

Fig 4. Circulatory parameters changed before and after administration of angiotensin-converting enzyme inhibitors (n = 15 for each pair). *Circulatory parameters changed significantly with $P < .05$. 109 × 34 mm (600 × 600 DPI).

circulatory function including LAP. Alternately, simultaneous and continuous BP measurement by means of another transmitter implantation into the aorta or a more peripheral artery was desirable. However, the problem of crosstalk among transmitters prevented the implantation of >1 radiotelemetry transmitter in each dog.

We defined a 5-week period as the subchronic period. We are not entirely sure whether this period was long enough. We observed changes in heart function and morphology by means of weekly telemetry recordings and ECG, and the acute changes shortly after MR creation were the main pathogenic factor in this model. Therefore, our model might be closer to an acute model and different from clinical dogs from the standpoint of myocardial tissue damage. ACE inhibitors affect both circulating and tissue RAAS; however, circulating RAAS mainly relates to hemodynamic status, while the tissue RAAS mainly relates to myocardial involvement or late consequence. Late consequence should be evaluated by clinical trials, and our focus in this study was on highlights circulating RAAS.

Conclusions

In conclusion, oral administration of alacepril in dogs with surgically induced MR resulted in slight but significant decreases in LAP. In addition, the LAP-lowering effect was predominant in the nighttime compared with the daytime, which might indicate that the inhibitory activity of ACE inhibitors might be an inappropriate criterion for their selection.

Footnotes

[a] Healthy Label, Nisshin Pet Food Inc, Tokyo, Japan
[b] DSI Dataquest A.R.T. 4.1, Data Sciences International, St Paul, MN
[c] TA11PA-D70, Data Sciences International
[d] Enacard, Merial Japan Ltd, Tokyo, Japan
[e] AceWorker, Novartis Animal Health K.K., Tokyo, Japan
[f] Apinac, Dainippon Sumitomo Pharma Co Ltd, Osaka, Japan
[g] SSD-5000, Aloka Co Ltd, Tokyo, Japan
[h] DICOM server, ImageONE Co Ltd, Tokyo, Japan
[i] BP-100D, Fukuda ME, Tokyo, Japan
[j] GraphPad Prism version 5.0a, GraphPad, San Diego, CA
[k] EXCEL 2003 for Macintosh, Microsoft, Redmond, WA

Acknowledgments

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Supporting Information

Additional Supporting Information may be found in the online version of this article:

Figure S1. Dorsoventral and right radiographic images of a dog used in this experiment. The tip of the radiotelemetry transmitter catheter was inserted at the left atrial appendage, although the tip is not visible on film. The transmitter body was implanted under the triceps brachii muscle of the left foreleg.[10]

Figure S2. The scheme of left atrial pressure measurement by a radio telemetry system in this experiment.[10]

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