

The Effect of Pimobendan on Left Atrial Pressure in Dogs with Mitral Valve Regurgitation

S. Suzuki, R. Fukushima, T. Ishikawa, L. Hamabe, D. Aytemiz, H. Huai-Che, S. Nakao, N. Machida, and R. Tanaka

Background: The effects of pimobendan on left atrial pressure (LAP) in dogs with mitral valve disease (MR) have not been documented in a quantitative manner.

Objective: The objective was to document and study the short-term effects of pimobendan on LAP and echocardiographic parameters in MR dogs.

Animals: Eight healthy Beagle dogs weighing 10.0–14.7 kg (3 males and 5 females; aged 2 years) were used.

Methods: Experimental, cross-over, and interventional study. Dogs with surgically induced MR received pimobendan at either 0.25 mg/kg or 0.50 mg/kg PO q12h for 7 days and then, after a 7-day wash-out period, the other dosage. LAP was measured for 30 minutes at baseline and again on days 1, 2, 4, and 7 of pimobendan administration.

Results: Mean LAP was significantly decreased after the administration of 0.25 mg/kg (15.81 ± 5.44 mmHg to 12.67 ± 5.71 mmHg, $P < .001$) and 0.50 mg/kg (15.76 ± 5.45 mmHg to 10.77 ± 5.23 mmHg, $P < .001$). Also, the 0.50 mg/kg group led to a significantly lower LAP ($P < .01$) compared with the 0.25 mg/kg group. Significant reduction was seen for the first time 4 days after the administration of 0.25 mg/kg and a day after the administration of 0.50 mg/kg.

Conclusions and Clinical Importance: Pimobendan decreased LAP in a dose-dependent manner in dogs with acute MR caused by experimental chordal rupture. This study did not evaluate adverse effects of high-dose pimobendan, and additional studies in clinical patients are warranted.

Key words: High-dose; Inodilator; Radiotelemetry.

Mitral valve disease (MVD) is the most common cardiac disease in dogs. Moreover, as many as 75% of all dogs with signs of congestive heart failure suffer from mitral regurgitation (MR) caused by myxomatous degeneration of the valve leaflets or chordae tendineae.^{1,2} MR increases left atrial pressure (LAP), potentially resulting in dilatation of the left atrium. Increased LAP causes pulmonary edema, which can lead to cough, dyspnea, and even death.³ Reduction of LAP is a desirable goal for drugs used to treat congestive heart failure in MVD.

The inodilator pimobendan is a phosphodiesterase (PDE) III inhibitor with positive inotropic activity (via increased sensitivity of the contractile apparatus to calcium), vasodilatory (via phosphodiesterase inhibition), and some additional PDE V inhibitory effects.^{4–6} As a result, possible effects of pimobendan include increasing cardiac output (CO) and myocardial contractility, and decreasing preload and afterload. Pimobendan extends survival time and improves the quality of life in chronic heart failure (CHF) patients with MVD and dilated cardiomyopathy.^{7–11} Previous studies have also suggested that pimobendan has adverse cardiac functional and morphologic effects in dogs with asymptomatic MVD.^{12,13}

Abbreviations:

LAP	left atrial pressure
MR	mitral regurgitation

However, pimobendan's effect on LAP has not been fully evaluated in a quantitative manner because of difficulties in directly measuring LAP.

We have previously used a radiotelemetry system to report the effects of angiotensin-converting enzyme (ACE) inhibitors and furosemide in dogs with experimentally induced MR,^{14–16} and we believe that this system would be useful for evaluation of hemodynamic changes after administration of pimobendan.

In the present study, we used a radiotelemetry system to monitor LAP in dogs with experimentally induced MR and evaluated the effects of pimobendan. Also, we evaluated echocardiography, blood pressure (BP), and the effects of pimobendan on MR for analysis of pathophysiological changes.

Materials and Methods

Animals

Before the start of the study, the health of eight 2-year-old Beagle dogs (3 males and 5 females) weighing 12.4 ± 1.9 kg (range, 10.0–14.7 kg) was evaluated by general clinical examination, blood and serum biochemical evaluations, electrocardiography, thoracic radiography, and echocardiography. All dogs were acclimatized to the experimental environment and human handling. During all phases of the study, the dogs were managed and cared for in accordance with the standards established by the Tokyo University of Agriculture and Technology (TUAT) and described in its "Guide for the Care and Use of Laboratory Animals." This study was approved by the Experimental Animal Committee of TUAT (acceptance no. 21-19).

From the Department of Veterinary Surgery, Faculty of Veterinary Medicine, Tokyo University of Agriculture and Technology, Tokyo, Japan

Corresponding author: Ryou Tanaka, DVM, PhD, 3-5-8 Saiwaicho, Fuchu-shi, Tokyo 183-8509, Japan; e-mail: ryo@vet.ne.jp

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Mitral Regurgitation and Transmitter Implantation

Dogs were premedicated with meloxicam^a (0.2 mg/kg SC), atropine sulfate^b (0.04 mg/kg SC), butorphanol tartrate^c (0.2 mg/kg IV), and midazolam hydrochloride^d (0.2 mg/kg IV). Induction was achieved with propofol^e (4 mg/kg IV), after which the dog was intubated. General anesthesia was maintained with inhalation of isoflurane^f mixed with oxygen. A left lateral thoracotomy was performed at the 5th intercostal space, and the pericardium was opened by standard procedures. The left atrium was purse-string sutured with 3-0 nylon, and a small incision was made at the center of the purse-string suture. The suture then was loosened, and 5-inch curved Halsted mosquito forceps were inserted through the small incision to grasp and rupture the mitral valvular chordae tendineae. The position of the chordae tendineae and the degree of induced MR were monitored by transeophageal echocardiography, and these procedures were repeated until visible MR was identified without any manual manipulation. The telemetry transmitter catheter^g was then inserted 1 cm into the small incision, and the catheter was fixed to the left atrium with a suture. The telemetry transmitter body was implanted under the triceps brachii muscle, and the catheter was fixed to abdominal trunk muscles with 3-0 nylon suture. The chest was then closed in layers and air was evacuated by standard procedures. Postoperatively, cefamedin^h was administered (50 mg/kg/day IV or PO) for 7 days and postoperative pain was treated with meloxicam (0.2 mg/kg SC) for 3 days. Thoracic radiography and echocardiography were performed to evaluate pulmonary venous congestion and cardiac dilatation (supporting information, Fig S1). Thoracic radiographic and echocardiographic examinations were performed to check for the presence of pulmonary edema and cardiac dilatation. After the radiotelemetry transmitter implantation, the dogs were rested for at least 5 weeks, until no major variations were identified in echocardiographic evaluation and LAP. Also, dogs that had been classified into ISACHC III were treated with furosemideⁱ (1 mg/kg PO q12h) after surgery. Furosemide was discontinued 3 days before pimobendan administration was started.

Pimobendan Administration and Left Atrial Pressure Measurement

Pimobendan^j was administered at a dosage of 0.25 or 0.50 mg/kg PO q12h to 8 dogs for 7 days. After a 7-day washout period, the other dosage of pimobendan was administered for 7 days, using a crossover study design.

All radiotelemetry systems^k and recording procedures were the same as those described in a previous report.¹⁴ The maximum, mean, and minimum LAP were obtained as the averages of 10-second segments from continuous waveform recordings (supporting information, Fig S2).^{17,18} LAP was measured for 30 minutes from 2100 to 2130 hours at baseline and again on days 1, 2, 4, and 7 of pimobendan administration. The sampling frequency was every 10 seconds.

Echocardiography

Before and after administration of pimobendan, echocardiographic measurements were performed along with blood pressure and LAP measurements. A single investigator performed transthoracic conventional echocardiography as well as two-dimensional spectral Doppler and tissue Doppler echocardiography. Each dog was positioned in left and right recumbency, with echocardiographic examinations performed by means of a digital ultrasonographic system^l with a 5.0 MHz sector transducer. Sweep speed during the Doppler and M-mode recordings was

150–200 mm/s. Right parasternal views were used to measure heart dimensions. LA/Ao was assessed in a right parasternal short-axis view of the heart base for assessing LA enlargement.¹⁹ We measured the internal diameter of the aorta along the commissure between the noncoronary and right coronary aortic valve cusp and internal diameter of the left atrium in a line extending from and parallel to the commissure between the noncoronary and left coronary aortic valve cusp to the distant margin of the left atrium on the first frame after aortic valve closure. A short-axis M-mode view at the chordal level was used to measure left ventricular end-diastolic diameter (LVEDD). Left apical views of the left ventricular inflow and outflow tracts were used to measure mitral inflow and aortic flow using a pulsed wave sample volume of 4 mm. Forward stroke volume (SV) and cardiac output (CO) were calculated using a left ventricular outflow view. SV was calculated as SV = velocity time integral × cross-sectional area. CO was calculated as CO = SV × heart rate (HR). The systolic (Sa) and early diastolic (Ea) myocardial velocities by pulsed tissue Doppler imaging were measured at lateral mitral annulus in the left apical views. Peak transmitral early diastolic wave (E wave) velocity was measured from Doppler signals of the mitral inflow, and E/Ea was calculated. MR flow was recorded using the two-chamber view with a high-intensity continuous wave spectral Doppler signal, and MR pressure gradient was calculated based on a modified Bernoulli's equation, $\Delta P = 4$ (MR velocity)². The measurements of the maximal area of the regurgitant jet signals (ARJ) was performed in the apical four-chamber view; the left atrium area (LAA) was also measured in the same frame in which the maximal ARJ was seen, and ARJ/LAA was calculated. Color gain was decreased until background noise just disappeared.²⁰ All echocardiographic variables were averaged from 10 consecutive beats. All of the echocardiographic recordings were stored on the internal hard drive of the echocardiograph and transmitted to the DICOM server online.^m

Blood Pressure Measurements

All indirect arterial BP recordings were obtained by the oscillometric method.ⁿ Cuff size width was set to approximately 40% of tail circumference for each dog.²¹ BP measurements were performed simultaneously with echocardiography for MR velocity measurements, and five consecutive measurements were averaged for each dog for use in the calculations. Systemic vascular resistance (SVR) was calculated as $SVR = 79.9 \times (\text{Mean BP} - \text{central venous pressure})/\text{CO}$,²² and central venous pressure was defined as 5 mmHg due to a lack of right-sided heart failure signs, jugular distension, or positive hepatjugular reflex.

Statistical Analysis

All data are represented as mean plus or minus standard deviation (SD). All data were normally distributed. A one-way analysis of variance (ANOVA) in conjunction with a Bonferroni's multiple comparison test was used for comparing LAP and echocardiographic variables before and 7 days after administration of each dose. A two-way repeated measures ANOVA in conjunction with a Bonferroni's multiple comparison test was used to compare LAP of each day after the administration of pimobendan. Statistical significance was defined as $P < .05$. GraphPad Prism version 5.0a^o and EXCEL 2008^p were used to perform these statistical analyses.

Results

The operation to rupture the mitral valvular chordae tendineae and implant the transmitter was successful

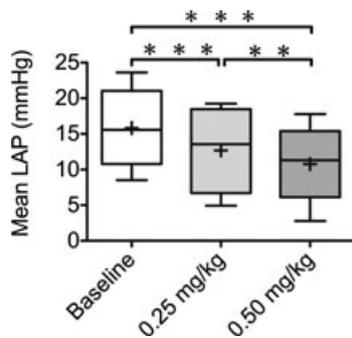


Fig 1. Left atrial pressure (LAP) 7 days after administration of pimobendan (0.25 and 0.50 mg/kg) q12h PO in 8 dogs with MR. No medication values were those obtained before drug administration. The box and whiskers plot demonstrates the mean (+), the median (line), 5 and 95% confidence limits (box), and range (bars). * $P < .05$, ** $P < .01$, *** $P < .001$.

in all dogs. Mean LAP was 15.81 ± 5.44 mmHg, LVEDD was 4.05 ± 0.61 cm, LA/Ao by use of short-axis projection was 1.68 ± 0.33 , and E wave velocity was 0.98 ± 0.23 m/s. Three dogs were stage C, and 5 other dogs were stage B2 in guidelines for the diagnosis and treatment of canine chronic valvular heart disease of the American College of Veterinary Internal Medicine (ACVIM).²³ No obvious adverse effects were observed during periods of pimobendan administration.

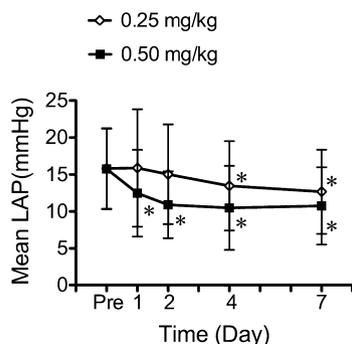


Fig 2. Temporal variation of LAP after administration of pimobendan in 8 dogs with MR. *Significant differences ($P < .05$) compared with each baseline.

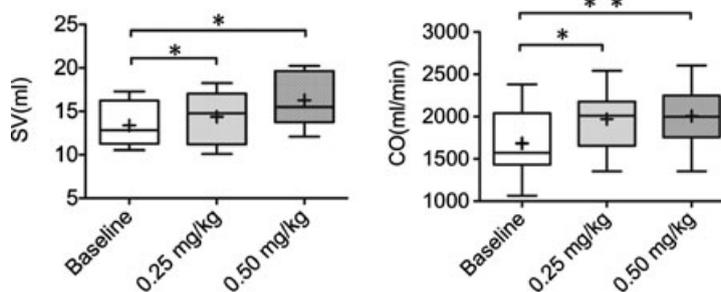


Fig 3. Stroke volume (SV) and cardiac output (CO) 7 days after administration of pimobendan (0.25 and 0.50 mg/kg) q12h PO in eight dogs with MR. The box and whiskers plot demonstrates the mean (+), the median (line), 5 and 95% confidence limits (box), and range (bars). * $P < .05$, ** $P < .01$.

Left Atrial Pressure

Mean LAP decreased significantly after the administration of 0.25 mg/kg pimobendan (15.81 ± 5.44 mmHg to 12.67 ± 5.71 mmHg, $P < .001$), as shown in Figure 1. Similarly, mean LAP significantly decreased after the administration of 0.50 mg/kg (15.76 ± 5.45 mmHg to 10.77 ± 5.23 mmHg, $P < .001$). Also, the 0.50 mg/kg group had significantly lower LAP ($P < .01$) after 7 days compared with the 0.25 mg/kg group.

Statistically significant reduction was first observed 4 days after the administration of 0.25 mg/kg, as shown in Figure 2. In contrast, significant reduction was first observed 1 day after the administration of 0.50 mg/kg.

Echocardiography and Hemodynamic Parameters

SV of the 0.50 mg/kg group and CO of both the 0.25 and the 0.50 mg/kg groups increased significantly compared with baseline, as shown in Figure 3. LVEDD, left ventricular internal diameter in the systolic period (LVESD), Peak E, E/Ea, and ARJ/LAA of both the 0.25 and the 0.50 mg/kg groups decreased significantly compared with baseline. Also, ARJ/LAA of the 0.50 mg/kg group was significantly lower ($P < .05$) after 7 days compared with the 0.25 mg/kg group as shown in Figure 4. Sa of the 0.25 mg/kg group was increased significantly compared with baseline. As shown in Table 1, other parameters did not change significantly.

SBP and MBP did not decrease significantly compared with baseline. In addition, HR of both the 0.25 and the 0.50 mg/kg groups did not change significantly. SVR decreased significantly compared with baseline, as shown in Figure 5.

Discussion

This study had a number of important findings. First, LAP was decreased with pimobendan in a dose-dependent manner in dogs with MR. Secondly, stroke volume and cardiac output increased and systemic vascular resistance decreased, whereas HR and systolic blood pressure remained unchanged. Finally, left ventricular dimensions decreased, and the severity of

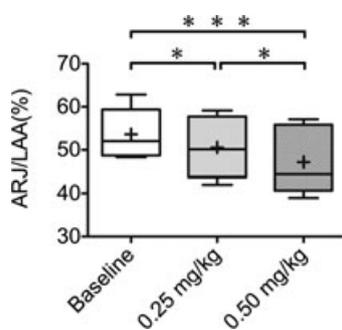


Fig 4. The ratio of the maximum area of the regurgitant jet signals to the left atrium area (ARJ/LAA) 7 days after administration of pimobendan (0.25 and 0.50 mg/kg) q12h PO in 8 dogs with MR. The box and whiskers plot demonstrates the mean (+), the median (line), 5 and 95% confidence limits (box), and range (bars). * $P < .05$, ** $P < .01$, *** $P < .001$.

mitral regurgitation appeared to decrease according to the reduction in ARJ/LAA and E wave velocity.

In humans with chronic congestive heart failure, pimobendan decreases morbidity, improves physical activity, and decreases pulmonary capillary wedge pressure (measured as a surrogate for LAP).^{24–26} However, there are few studies in dogs with MR because LAP cannot be measured by cardiac catheterization without general anesthesia. The positive inotropic effects of pimobendan potentially could increase MR severity.^{12,13} However, in the present study, LAP was significantly decreased by pimobendan in dogs with MR. A significant dose–effect relationship was observed on LAP (Fig 1). Although additional studies are required to fully assess the clinical usefulness of high doses of pimobendan, our results suggest it will be beneficial at least as short-term MR therapy. In the present study, adverse effects of pimobendan were not observed, but we feel this warrants further examination.

In our previous report, an ACE inhibitor did not significantly decrease LAP despite a reduction in afterload. Conversely, pimobendan significantly decreased LAP, as well as ARJ/LAA (Fig 4). Systemic vascular resistance in this study cannot be directly compared with systemic vascular resistance recorded in our previously reported ACE inhibitor study, particularly using relatively insensitive echocardiographic techniques. Nevertheless, the reduction in systemic vascular resistance with both drugs suggests that the decrease in LAP with pimobendan was associated with its positive inotropic effects and not just with a decrease in afterload.

Pimobendan has increased CO in previous reports.^{27,28} Similarly, in the present study, pimobendan increased CO, but did not affect BP, presumably as a result of the combination of pimobendan's positive inotropic and arterial dilatory effects. These effects potentially could be valuable in cases of low output heart failure with severe MR.

There are reports on echocardiographic values of MR dogs after administration of pimobendan.^{28–30} However, there have been few reports evaluating

Table 1. Comparison of left atrial pressure (LAP), echocardiographic and hemodynamic parameters after the pimobendan administration. See materials and methods section for the technique of measuring echocardiographic parameters.

Variable	Before Pimobendan	Pimobendan 0.25 mg/kg	Pimobendan 0.5 mg/kg
LAP (mmHg)	15.81 ± 5.44	12.67 ± 5.71***	10.77 ± 5.23****†
LVEDD (cm)	4.05 ± 0.61	3.85 ± 0.54*	3.84 ± 0.60*
LVESD (cm)	2.43 ± 0.11	2.27 ± 0.22*	2.26 ± 0.40*
%FS	39.5 ± 4.25	41.9 ± 4.25	41.1 ± 6.34
LA/Ao	1.68 ± 0.33	1.61 ± 0.24	1.58 ± 0.22
E wave (m/s)	0.98 ± 0.23	0.91 ± 0.18*	0.86 ± 0.18*
E/Ea	7.93 ± 2.03	7.03 ± 1.36*	6.93 ± 1.49*
Sa (cm/s)	9.64 ± 1.12	12.35 ± 2.12*	11.63 ± 2.31
MRPG (mmHg)	123.3 ± 15.2	124.3 ± 16.3	130.2 ± 20.2
ARJ/LAA (%)	53.6 ± 5.73	50.5 ± 6.62*	47.1 ± 7.48***†
SBP (mmHg)	128.0 ± 8.6	124.4 ± 10.2	122.8 ± 9.4
MBP (mmHg)	97.6 ± 7.8	93.3 ± 8.0	90.0 ± 10.4
HR (bpm)	123.1 ± 14.7	121.8 ± 9.2	124.9 ± 12.3
SV (mL)	13.4 ± 2.60	14.4 ± 3.03	16.3 ± 3.03*
CO (mL/min)	1684.1 ± 421.4	1970.9 ± 372.2*	2007.1 ± 376.6**
SVR (dyne*sec/cm ²)	4737.7 ± 1445.2	3722.7 ± 967.3*	3419.3 ± 520.4**

LVEDD, left ventricular internal diameter in the diastolic period; LVESD, left ventricular internal diameter in the systolic period; %FS, fractional shortening; LA/Ao, the ratio of left atrial diameter to aortic root diameter; E wave, transmitral early diastolic wave velocity; E/Ea, the ratio of transmitral early diastolic wave velocity to lateral mitral annulus velocity in the early diastolic period; Sa, lateral mitral annulus velocity in the systolic period; MRPG, mitral regurgitation pressure gradient; ARJ/LAA, the ratio of the maximum area of the regurgitant jet signals to the left atrium area; SBP, systolic blood pressure; MBP, mean blood pressure; HR, heart rate; SV, stroke volume; CO, cardiac output; SVR, systemic vascular resistance.

* $P < .05$, ** $P < .01$ and *** $P < .001$ compared with before administration of pimobendan. † $P < .05$ and †† $P < .01$ differences between 0.25 and 0.50 mg/kg.

preload after administration of pimobendan. We previously have reported that E wave and E/Ea can be used for the evaluation of preload after administration of high doses of furosemide, and have monitored the reduction of LAP in the short term.¹⁶ Also, reports have shown that E/Ea is a good index for the estimation of LAP and left ventricular filling pressure.^{31–33} E/Ea might not be a particularly good indicator of

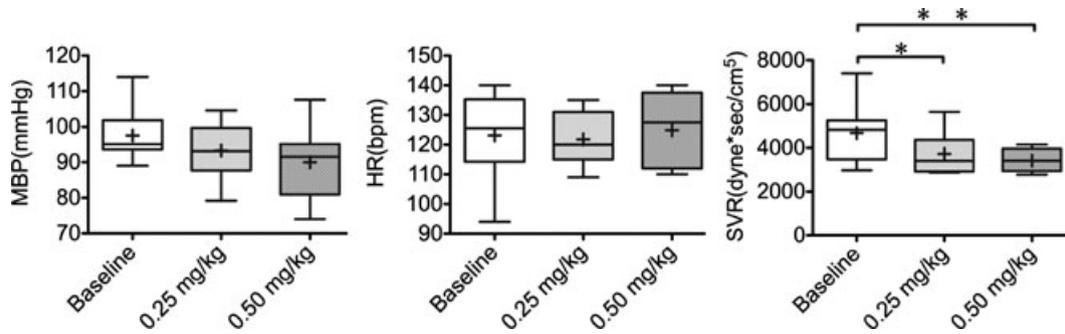


Fig 5. Mean blood pressure (MBP), heart rate (HR), and systemic vascular resistance (SVR) 7 days after administration of pimobendan (0.25 and 0.50 mg/kg) q12h PO in 8 dogs with MR. No medication values were those obtained before drug administration. The box and whiskers plot demonstrates the mean (+), the median (line), 5 and 95% confidence limits (box), and range (bars). * $P < .05$, ** $P < .01$.

congestive heart failure in dogs with MR.³⁴ However, in the present study, E wave and E/Ea of the 0.50 mg/kg group decreased significantly after administration of pimobendan (Table 1). This result suggests that E wave and E/Ea can be used for the evaluation of pimobendan treatment and short-term monitoring of the reduction of LAP.

Limitations

Pimobendan is recommended at dosages of 0.1–0.25 mg/kg q12h for dogs with MR.⁴ This study was not designed to evaluate potential adverse effects of long-term administration of pimobendan at a dosage of 0.50 mg/kg q12h. Toxic effects may occur with long-term administration of pimobendan at high dosages in asymptomatic dogs. In the present study, five 2-year-old Beagle dogs were used and a 5-week period was defined as a subchronic period for experimentally induced MR. In clinical situations, dogs with MR and cardiac dysfunction and myocardial tissue damage might differ from the model dogs in this study. Therefore, our model may more closely resemble acute MR and differ from naturally occurring chronic MR.

Conclusion

LAP was significantly decreased with pimobendan treatment in dogs with surgically induced MR. In addition, pimobendan caused a dose-dependent decrease in LAP. A significant dose-effect of 0.25 and 0.50 mg/kg was observed in LAP. Although this study did not focus on adverse effects, we conclude that high-dose administration of pimobendan could be useful for treating severe MR in dogs with substantially increased LAP. Additional studies in clinical patients with degenerative mitral valve disease and acute chordal rupture are warranted.

Footnotes

^aMetacam 0.5% injectable; Boehringer Ingelheim Vetmedica Japan, Hyogo, Japan

^bAtropine sulfate; Tanabe Seiyaku Co., Ltd, Osaka, Japan

^cVetorphale; Meiji Seika Kaisha Ltd, Tokyo, Japan

^dDormicum; Astellas Pharma Inc, Tokyo, Japan

^eRapinivet; Schering-Plough, Tokyo, Japan

^fIsoflu; Dainippon Sumitomo Pharma Co, Ltd, Osaka, Japan

^gTA11PA-D70; Data Sciences International, St Paul, MN

^hCefamezin; Astellas Pharma Inc, Tokyo, Japan

ⁱLasix; sanofi-aventis K., Tokyo, Japan

^jVetmedin; Nippon Boehringer Ingelheim Co, Ltd, Tokyo, Japan

^kDSI Dataquest; A.R.T. 4.1, Data Sciences International, St Paul, MN

^l α -10; Aloka Co, Ltd, Tokyo, Japan

^mDICOM server; ImageONE Co, Ltd, Tokyo, Japan

ⁿBP-100D; Fukuda ME, Tokyo, Japan

^oGraphPad Prism version 5.0a; GraphPad, San Diego, CA

^pEXCEL 2008 for Macintosh; Microsoft, Redmond, WA

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Supporting Information

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

Fig S1. Dorsoventral and right radiographic images of a dog used in this experiment. The tip of the radio-telemetry 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.

Fig S2. The scheme of left atrial pressure measurement by a radio telemetry system in this experiment.

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