Daily Rhythms of Left Atrial Pressure in Beagle Dogs with Mitral Valve Regurgitation

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Background: Mitral valve regurgitation (MR) causes increased left atrial pressure (LAP) and is associated with occurrence of clinical signs. It will be useful to understand diurnal variations of LAP for the management of MR.

Hypothesis: Circulatory parameters and diurnal rhythm are linked to clinical signs in cardiac diseases. LAP also exhibits a diurnal rhythm in dogs with MR.

Animals: Five healthy Beagle dogs weighing 9.8–12.8 kg (3 males and 2 females; aged 2 years) were used.

Methods: A radiotelemetry system for continuous measurement of LAP was used in this study. Rupture of the chordae tendineae was experimentally induced via left atriotomy, and a transmitter catheter was inserted into the left atrium. The body of the transmitter was implanted SC. After clinical condition was stabilized, the severity of MR was evaluated by echocardiography, and LAP was recorded for 72 consecutive hours for the analysis of diurnal variation.

Results: Abrupt increases in LAP, which averaged 16.7 mmHg, were observed at feeding periods. In contrast, strong diurnal LAP variations were found, with a significant but slight increase in daytime LAP compared with nighttime LAP.

Conclusions and Clinical Importance: Diurnal LAP is characterized by a slight but significant nocturnal decrease and abrupt increases in response to excitation. The latter seemed to be more important considering the relationship with clinical manifestations. The clinical relevance of exercise restriction in the management of MR was acknowledged.

Key words: Chronobiology; Circadian rhythm; Radiotelemetry.

M itral 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] MR is a progressive disease and despite medical treatment, death can result in dogs with severe MR.

Recently, surgical treatment for MR has been reported in the field of veterinary medicine.[2,3] However, surgical treatment is restricted to a few patients in a small number of facilities, and the majority of patients receive drug therapy for the management of MR.

In MR patients, cough is the most typical clinical manifestation and is one of the main complaints identified by owners.[4,5] Nighttime cough is characteristic and clinical signs worsen with time.[5] However, the relationship between increased left atrial pressure (LAP) and progression of clinical signs over time is not well known.

In human medicine, recent progress has been made in chronobiologic analysis. It is well known that ischemic cardiac events such as unstable angina and acute myocardial infarction occur within the first few hours after waking and becoming active.[6,7] This is because these events depend on a surge in a series of physiologic parameters, for example, heart rate,[8,9] blood pressure (BP),[8,9] platelet aggregability,[10,11] and blood concentrations of epinephrine, norepinephrine, and angiotensin II,[8,9] which are to some degree controlled by time-dependent proteins or gene expression.[12,13]

Abbreviations:

BP	blood pressure
LAP	left atrial pressure
MR	mitral regurgitation
TPR	total peripheral resistance

Circadian variations in circulatory functions have been reported in many mammals including dogs,[8,14,15] and LAP would be expected to have some variation because the left atrium works as a volume reservoir like the right atrium, in which the pressure is known to have circadian variations. In the veterinary field, chronobiologic analysis is described in only a few reports,[16,17] but cardiovascular events in dogs, as in humans, likely are related to time-dependent changes in cardiovascular function.

In the present study, we measured LAP in experimental dogs with MR under conscious, unrestrained, and no-stress conditions using a radiotelemetry system that enables the recording of pressure continuously for 72 hours. This monitoring system is expected to identify the diurnal rhythms of LAP and provide useful information for interpreting pathophysiologic conditions in MR.

Materials and Methods

Animals

In the present study, we used five 2-year-old Beagle dogs (3 males and 2 females) weighing 11.1 ± 1.0 kg (range, 9.8–12.8 kg). 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 available ad libitum and the dogs were fed commercial dry food[a] twice a day from 0800 to 0830 hours and 2000 to 2030 hours. Except for the 2 daily feeding periods, access to the room was restricted to avoid unnecessary stress. Before the present study, the health of the dogs was evaluated

by general clinical examination, blood and serum biochemical examinations, electrocardiography, thoracic radiography, and echocardiography. All dogs were acclimatized to the experimental environment and human handling. During all phases of the present 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." In addition, this study was approved by the animal experimental committee of TUAT (acceptance no. 20-70).

Preparing MR and Transmitter Implantation

Dogs were premedicated with meloxicam[b] (0.2 mg/kg SC), atropine sulfate[c] (0.04 mg/kg SC), butorphanol tartrate[d] (0.2 mg/kg IV), and midazolam hydrochloride[e] (0.2 mg/kg IV). Induction was achieved with propofol[f] (4 mg/kg IV), after which the dog was intubated. General anesthesia was maintained with inhalation of isoflurane[g] mixed with oxygen. A left lateral thoracotomy was performed via the fifth 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 was then loosened and 5-in.-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 transesophageal echocardiography[h] and these procedures were repeated until visible MR was identified without any manual manipulation. The telemetry transmitter[i] catheter 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 evacuated by standard procedures. Postoperatively, 50 mg/kg/day of the antibiotic cefamedin[j] was administered IV or PO for 7 days and postoperative pain was treated with meloxicam SC for 3 days. Follow-up care included auscultation of pulmonary and cardiac sounds and blood testing, which routinely consisted of CBC and serum concentrations of blood urea nitrogen, creatinine, alkaline phosphatase, and electrolytes. Thoracic radiography and echocardiography were performed to evaluate pulmonary venous congestion and cardiac dilatation, when needed (Fig 1).

LAP Measurement Method

The digital signal from the transmitter was sensed by the receiver[k] and sent to a data exchange matrix.[l] An ambient pressure reference monitor[m] was also connected to the data exchange matrix to monitor correct atmospheric pressure and exclude all local environmental pressure fluctuations. Finally, the digital signal data was converted to an analog signal by the data exchange matrix and sent to a personal computer (Fig 2). Maximum, mean, and minimum LAP were obtained as the averages of 10-second recorded segments from continuous waveform recordings. These procedures were performed by analytical software.[n]

Diurnal LAP Variations Protocol

LAP measurement was not performed for at least 4 weeks after the telemetry transmitter implantations, until echocardiographic evaluations and LAP were confirmed to be free from major changes by twice-weekly examinations. Just before LAP measurement, the clinical condition was evaluated by general clinical examination, blood and serum biochemical examinations, electrocardiography, thoracic radiography, and echocardiography. Thoracic radiography indicated clear lung fields in dogs 1–3, whereas left atrial
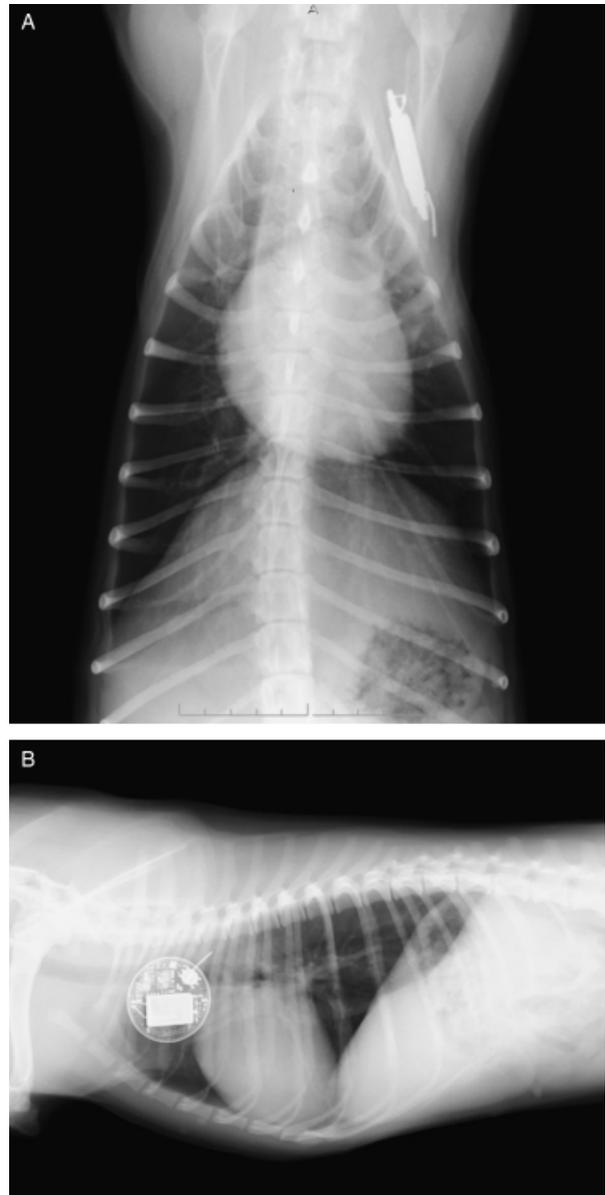

Fig 1. Dorsoventral and right lateral radiographic images of a dog used in this experiment. The tip of the radiotelemetry transmitter catheter was inserted at the left atrial appendage, although the tip was not visible on films. The transmitter body was implanted under the triceps brachii muscle of the left foreleg.

dilatation and interstitial lung opacity, alveolar lung opacity, or both, indicating pulmonary edema, were identified in dogs 4–6. These thoracic radiography findings were in agreement with clinical signs and LAP measured during echocardiography. In addition, left atrial dilatation and MR jet area with 2 right parasternal projections were evaluated by echocardiography. On the basis of these examinations, dogs with MR were numbered and arranged in order of MR severity (Table 1).[18]

Measurements were carried out for a period of 72 consecutive hours (3 days) and the characteristics of circadian LAP variation were evaluated by the following 4 procedures:

(1) To observe the diurnal variations of LAP, the hourly means and standard deviations of LAP were calculated for each hour and plotted.
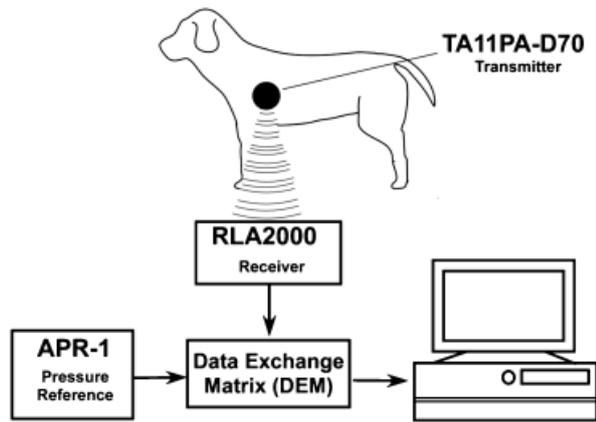
Fig 2. The scheme of left atrial pressure measurement by a radio-telemetry system in this experiment.

(2) To clarify LAP increase induced by feeding, maximum LAP before and after entering the breeding room were compared.

(3) To analyze the relationship between LAP and the dogs' activity, the hourly means and SD during the inactivity period (0100–0600 hours) and the activity period (1300–1800 hours) were calculated and compared for maximum, mean, and minimum LAP.

(4) To examine the strength of diurnal variations, the ratio of mean hourly SD during maximum LAP to mean daily SD during maximum LAP was calculated.

Statistical Methods

LAP values are expressed as mean ± SD. The Wilcoxon signed rank test was used to compare LAP before and after entry into the breeding room for feeding. Student's t-test with Welch correction was used for comparing LAP between daytime and nighttime. Statistical significance was set as $P < .05$. GraphPad Prism version 5.0a[o] and EXCEL 2003[p] were used to perform these statistical analyses.

Results

The operation to rupture mitral valvular chordae tendineae and implant transmitters was successful in every dog, and all the dogs recovered without any abnormalities in postoperative blood tests. The severity of the regurgitation jet varied among dogs. In dog 3, LAP increased suddenly more than 3 months after successful

data collection, and LAP was then remeasured as in dog 4. We thus obtained 6 LAP measurements from 5 dogs. Individual 24-hour LAP profiles were also calculated and are shown in Table 2.

Comparison of Diurnal LAP Variations

When the average values of maximum, mean, and minimum LAP were calculated for each hour, each LAP value showed a circadian rhythm, with twin peaks at 0800 and 2000 hours. The maximum and mean LAP at 0800 hours were higher than those at 2000 hours (Fig 3). The twin peaks were not clearly identified in dogs with higher LAP. The hourly SD of each LAP also showed circadian variation, with twin peaks at 0800 and 2000 hours in dogs with lower LAP, and less clearly identified twin peaks in dogs with higher LAP (Fig 4). BP fluctuation was more evident in the maximum and mean LAP and less evident in the minimum LAP.

Comparison of LAP before and after Feeding

Maximum LAP for 180 seconds after entering the breeding room at morning feeding periods is plotted in Figure 5. The 10 seconds of maximum LAP just before entering the room and the highest LAP after entering the room were compared. The peak of maximum LAP was observed within 20–60 seconds after entering the room. In Table 3, the averages of maximum LAP for 60 seconds just before entering the room were significantly lower than those for 60 seconds just after entering the room (32.5 ± 0.9 versus 49.2 ± 2.3 mmHg, $P < .0001$). In addition, dogs with severe MR tended to require a longer time to recover from increased maximum LAP.

Comparison of LAP between Activity Period and Inactivity Period

LAP values were compared between the activity period and the inactivity period. As shown in Table 4, each LAP except for dog 1 in the activity period was significantly higher than in the inactivity period regardless of the severity of MR. Almost all of the coefficients of variation were approximately 0.2 regardless of MR severity.

Table 1. Mitral regurgitation (MR) dogs used in this experiment are numbered and arranged in order of MR severity.

Sample Number	Body Weight (kg)	Severity of MR	LA/Ao	LVIDd (cm)	Left Atrial Pressure (mmHg)	Clinical Signs
1	11.8	Mild	1.32	3.6	12.0/5.7/4.0	NP
2	10.4	Mild	1.46	4.1	16.5/10.9/8.9	NP
3[a]	10.7	Moderate	1.57	4.0	32.8/17.9/11.1	NP
4[a]	11.1	Severe	1.93	4.7	39.8/19.3/13.4	Cough
5	12.8	Severe	1.97	4.7	44.8/25.5/20.1	Cough
6	9.8	Severe	2.22	4.8	51.0/31.5/23.1	Cough

Severity of MR was determined on the basis of pre-experimental echocardiographic examination. Normal range: LA/Ao < 1.6 by use of short-axis projection, and LVIDd was calculated with the equation $LVIDd = 1.44 \times BW^{0.32}$.

[a]Sample numbers 3 and 4 were recorded from the same dog.

LA/Ao, the ratio of left atrial diameter in the diastolic period to aortic root diameter in the systolic period: LVIDd, left ventricular internal diameter in the diastolic period: LAP, left atrial pressure (maximum/mean/minimum) recorded during echocardiographic examinations just before diurnal LAP recordings. NP: none present.

Table 2. The average values and coefficients of variation of individual 24-hour LAP are shown separately as maximum, mean, and minimum.

Sample Number	Maximum LAP		Mean LAP		Minimum LAP	
	Mean Daily Values (mmHg)	Coefficient of Variation	Mean Daily Values (mmHg)	Coefficient of Variation	Mean Daily Values (mmHg)	Coefficient of Variation
1	11.02 ± 2.53	0.2298	4.92 ± 2.24	0.4562	2.13 ± 2.29	1.078
2	16.79 ± 3.32	0.1978	10.74 ± 2.27	0.2114	6.89 ± 1.97	0.2859
3[a]	27.53 ± 4.57	0.1661	19.52 ± 3.35	0.1714	14.65 ± 6.03	0.4118
4[a]	38.68 ± 7.89	0.2040	22.30 ± 3.79	0.1699	17.22 ± 4.04	0.2378
5	43.34 ± 8.53	0.1967	26.11 ± 4.45	0.1704	19.06 ± 4.54	0.2380
6	49.58 ± 11.40	0.2300	28.71 ± 6.15	0.2140	22.10 ± 9.19	0.4157
Mean	30.49± 14.65	0.4804	19.40 ± 8.63	0.4448	15.22 ± 7.05	0.4632

See Table 1 for the remainder of the key.

Comparisons of Mean Hourly SD and Mean Daily SD

In order to clarify the strength of diurnal variations of LAP, the ratios of mean hourly SD to mean daily SD were calculated (Table 5). The ratios were high regardless of the severity of MR during maximum LAP (average, 89.2 ± 3.5%; range, 84.5–93.0%), and similar results were also observed for mean (average, 86.5 ± 4.7%; range, 77.2–92.6%) and minimum LAP (average, 83.2 ± 8.6%; range, 64.6–88.8%).

Discussion

In human medicine, a pulmonary capillary wedge pressure (PCWP) catheter is used for monitoring PCWP, enabling indirect evaluation of LAP. However, there are some disadvantages in using PCWP catheters in dogs with MR. First, PCWP catheters are not intended for long-term use in dogs. It is difficult to prevent catheter-related infections and also to avoid interference with the catheter by the dog scratching or biting it. In addition, PCWP is not suitable for continuous recording of LAP, and the stress at the time of measurement makes the results inaccurate.

Moreover, PCWP can only measure mean LAP and not maximum and minimum LAP. Given these limitations, the radiotelemetry system used in the present study was more suitable for continuous measurement of LAP in conscious unrestrained dogs under no-stress conditions.

In this study, 3 variables of LAP (maximum, mean, and minimum) were obtained. In healthy dogs without cardiac disorders, the pressure curve of LAP shows bimodal peaks and the *a* wave is always higher than the *v* wave (Fig 6).[19] Atrial systole, which corresponds to the P wave of the electrocardiogram, forms the atrial *a* wave, and complete atrial relaxation corresponds to the *x* descent of the LAP waveform. Shortly afterward, because of the action of the atrioventricular conduction system, left atrial diastole, during which blood flows from pulmonary veins, is achieved during the ventricular end-systolic period. Subsequent left ventricular relaxation allows mitral inflow, leading to a passive decrease in LAP and descent from the top of the *v* wave. The time from *a* wave to *v* wave is consistent because of the atrioventricular conduction system, and we were able to identify the 2 obscured waves under the existence of certain interval variations derived from normal respiratory arrhythmia without simultaneous electrocardiogram recordings. In dogs with MR, however, the higher and lower bimodal peaks were reversed because congestion and regurgitant flow during the ventricular systolic period increased the *v* wave because of the atrial reservoir function. Therefore, maximum LAP corresponded to the value at the top of
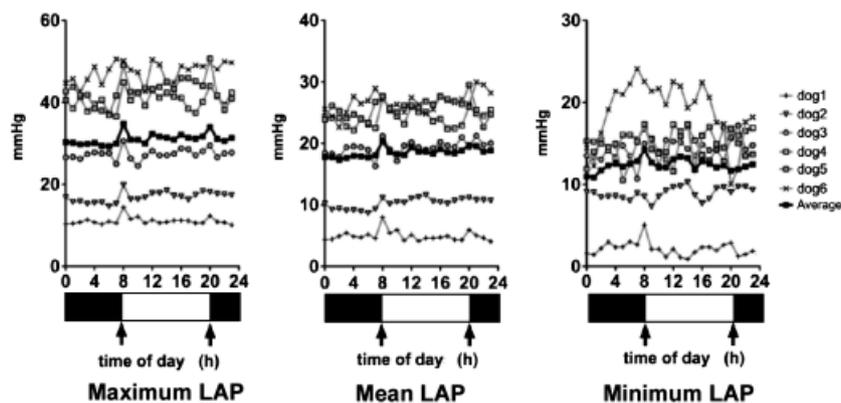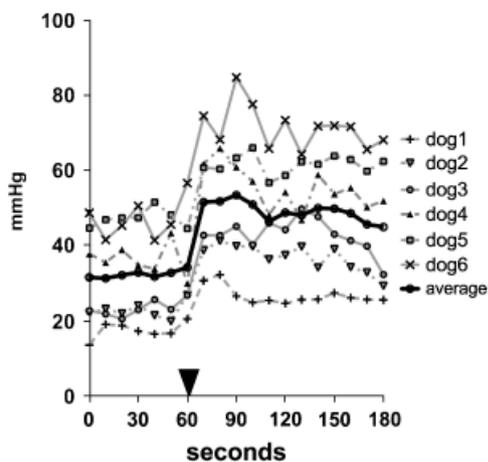

Fig 3. Twenty-four-hour variations of left atrial pressure in dogs with mitral regurgitation. White and dark horizontal bars at the bottom indicate the durations of the light and dark phases of the light-dark cycles, respectively. The dogs received 2 feedings (0800 and 2000 hours) represented by black arrows.
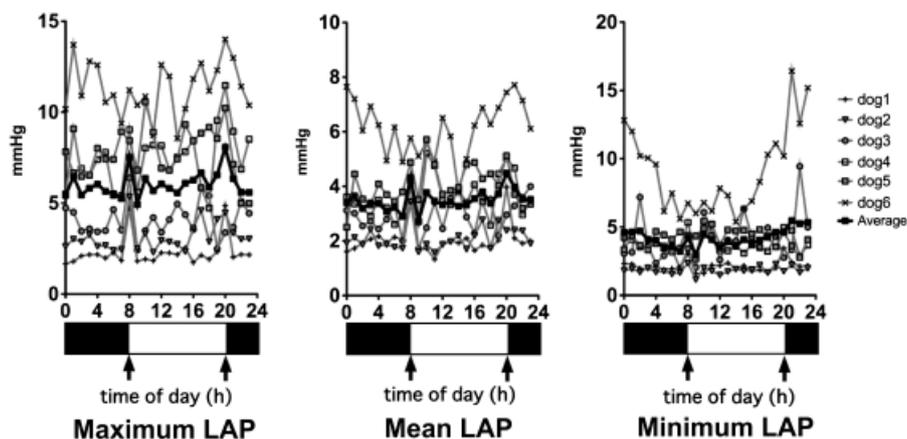
Fig 4. Twenty-four-hour variations of left atrial pressure hourly SD in dogs with mitral regurgitation. White and dark horizontal bars at the bottom and black arrows have the same meaning as in Figure 3.

the *v* wave in dogs with MR, and mean LAP was also strongly influenced by the increased *v* wave. The maximum and mean LAP thus showed similarity to each other. However, minimum LAP showed a different waveform pattern. In healthy dogs, minimum LAP corresponds to the lowest value of the *x* descent, when complete atrial relaxation occurs at the end of the electrocardiogram P wave. However, in dogs with MR, regurgitant flow inhibited complete atrial relaxation, and a higher *x* descent was recorded. The lowest value of the *y* descent was lower than that of *x* descent and was thus recorded as minimum LAP. Minimum LAP occurred before atrial systole and was an indication of the blood remaining in the left atrium at that time. Recent analysis of human atrial volumes has indicated that the active and passive emptying effect is very important in the hemodynamics of the left atrium, especially in patients with an advanced MR.[q,r] This passive emptying effect is closely connected to ventricular diastolic function,[20] and minimum LAP, rather than the maximum and mean LAP, would be expected to reflect left ventricular function.[s]

In the present study, the steep peaks in maximum and mean LAP corresponded with feeding periods in most dogs. The increases in maximum LAP ranged from 15.6 to 39.0 mmHg, much higher than expected, and this markedly increased LAP was observed for a short period of time, 20–60 seconds after excitement. This observation emphasizes the need for adequate rest and avoidance of overexcitement in the management of MR. Excitation increases regurgitant flow and thereby directly increases blood volume in the left atrium. In addition, the shortened ventricular relaxation time resulting from the accelerated heart rate could also decrease mitral inflow, leading to retention of blood in the left atrium, especially with increased ventricular stiffness because of chronic heart failure.[21] Considering the reservoir function of the atrium, the increase in LAP would accelerate the increase in left ventricular filling pressure by contributing to an enhanced atrioventricular pressure gradient during the ventricular diastolic period. Left ventricular ejection would then increase according to the Frank-Starling mechanism, and the increased LAP would recover after a short period of time.[4] In dogs with severe MR, however, these compensatory mechanisms do not work effectively because systolic and diastolic function is insufficient.[4] Dogs with severe MR therefore take longer to recover from increases in LAP. In the present study, this

Fig 5. The steep elevations of maximum left atrial pressure recorded in the morning. The black arrow represents the time after entering the measuring room.

Table 3. For all dogs, the averages of maximum left atrial pressure for 60 seconds just before entering the room were significantly lower than those for 60 seconds just after entering the room.

Sample Number	Before Entering (mmHg)	After Entering (mmHg)	*P* Value
1	18.24 ± 1.43	27.51 ± 2.98	.0002
2	23.01 ± 2.20	39.00 ± 2.20	< .0001
3[a]	23.56 ± 2.16	43.58 ± 1.88	< .0001
4[a]	36.16 ± 4.19	58.06 ± 5.68	< .0001
5	47.72 ± 2.07	61.03 ± 3.00	< .0001
6	46.93 ± 5.32	74.05 ± 6.17	< .0001
Mean	32.51 ± 0.92	49.22 ± 2.32	< .0001

Student's *t*-test with Welch correction was used for this analysis. See Table 1 for the remainder of the key.

Table 4. Comparison of each left atrial pressure (LAP) between activity period (1300–1800 hours) and inactivity period (0100–0600 hours).

Sample Number	Maximum LAP (mmHg)		Mean LAP (mmHg)		Minimum LAP (mmHg)	
	Activity Time	Inactivity Time	Activity Time	Inactivity Time	Activity Time	Inactivity Time
1	10.97 ± 2.20	10.71 ± 2.08	4.61 ± 1.93	4.88 ± 2.00	1.70 ± 2.12	2.27 ± 2.10
2	17.53 ± 3.14	15.51 ± 2.89***	11.49 ± 2.10	9.65 ± 2.02***	7.20 ± 1.96	6.42 ± 1.83***
3[a]	28.61 ± 4.63	27.14 ± 3.73***	20.31 ± 3.40	18.89 ± 2.79***	15.26 ± 4.77	14.09 ± 4.34***
4[a]	40.28 ± 7.63	37.59 ± 7.19***	22.97 ± 3.84	21.47 ± 3.33***	17.92 ± 3.85	16.55 ± 3.81***
5	44.39 ± 8.28	42.35 ± 7.53***	27.34 ± 4.44	25.03 ± 3.92***	20.19 ± 4.82	17.82 ± 4.01***
6	49.17 ± 11.30	47.61 ± 12.03**	28.30 ± 5.73	27.79 ± 6.28*	22.98 ± 6.96	21.22 ± 9.55***
Mean	29.71 ± 22.13	27.75 ± 19.89***	18.99 ± 9.52	16.35 ± 8.93***	14.17 ± 7.23	13.98 ± 12.11**

Excluding sample 1, each LAP in the activity period was significantly higher than in the inactivity period. Student's *t*-test with Welch correction was used for this analysis. See Table 1 for the remainder of the key.

*$P < .05$.

**$P < .001$.

***$P < .0001$.

was observed as the obscuring of the twin pressure peaks at feeding periods. This means that if increased LAP is suspected in dogs with severe MR given inadequate medical treatment, further medical interventions such as diuresis and vasodilatation with nitrates should be attempted to decrease LAP temporarily and improve the insufficient compensatory mechanisms as soon as possible. Excessive use of diuretics, however, even if restricted to a short period of time, may activate the renin-angiotensin-aldosterone system.

The increases in LAP at 0800 hours were higher than those at 2000 hours. This finding suggests that stressful stimuli may present a greater risk in the morning for dogs with MR. At night, total peripheral resistance (TPR) is higher than during the day in order to keep BP within a narrow range despite the loss of water during sleep and the decreases in cardiac output associated with nocturnal decreases in HR.[15,22–24] Therefore, increased nocturnal TPR would inhibit the compensatory mechanisms induced by increasing forward stroke volume in the morning. We did in fact observe higher LAP at 0800 hours than at 2000 hours in this study, and this effect may explain the commonly observed morning coughing in dogs with clinical MR, although comparison of clinical signs including coughing was not performed in this study.

When comparing LAP between the activity period and inactivity period, LAP during the activity period was significantly higher than during the inactivity period and there was no nocturnal increase, as expected. The strength of the diurnal patterns was quantified and compared by calculating the ratio of mean hourly SD to mean daily SD. In the present study, the averaged ratio in each LAP was higher (maximum LAP: 89.2 ± 3.5%, mean LAP: 86.5 ± 4.7%, minimum LAP: 83.2 ± 8.6%) than in a past report in rats,[22] which indicated a weaker diurnal pattern of LAP variation. This discrepancy may reflect a species difference. Unfortunately, to our knowledge, comparisons of diurnal patterns of hemodynamic parameters in dogs have not been reported fully, and we could not perform simultaneous recordings of LAP and BP because we used only 1 radiotelemetry transmitter in each dog, which was necessitated by the problem of cross talk among transmitters.

CVP variations resemble LAP variations in terms of weak diurnal variations and decreased function of the atrium as a volume reservoir, and the nocturnal decrease in LAP would be induced by the same mechanisms as those for CVP. CVP is influenced by body fluid volume, and many reports describe circadian variations in body fluid homeostasis from the point of view of urine production, circulatory profiles, and hormonal excretion (eg, natriuretic peptides,[25,26] vasopressin,[27] and aldosterone[28]). These factors induce nocturnal decreases in CVP.[29] Medical interventions such as diuresis (eg, furosemide and thiazide) decrease LAP and improve

Table 5. Comparison of mean hourly SD with mean daily SD of maximum left atrial pressure (LAP).

Sample Number	Maximum LAP			Mean LAP			Minimum LAP		
	Mean Hourly SD (mmHg)	Mean Daily SD (mmHg)	Percent of 24-h SD	Mean Hourly SD (mmHg)	Mean Daily SD (mmHg)	Percent of 24-h SD	Mean Hourly SD (mmHg)	Mean Daily SD (mmHg)	Percent of 24-h SD
1	2.21	2.53	87.4	1.97	2.24	87.9	1.99	2.28	86.8
2	3.10	3.33	93.0	1.98	2.27	87.2	1.74	1.96	88.8
3[a]	3.67	4.29	85.5	2.57	3.33	77.2	3.07	4.75	64.6
4[a]	6.62	7.83	84.5	3.49	3.77	92.6	3.52	4.02	87.6
5	7.89	8.49	92.9	3.76	4.44	84.7	3.78	4.53	83.4
6	10.31	11.20	92.1	5.32	6.03	88.2	7.98	9.00	88.7
Mean	5.63	6.28	89.7	3.18	3.68	86.5	3.68	4.42	83.2

See Table 1 for the remainder of the key.
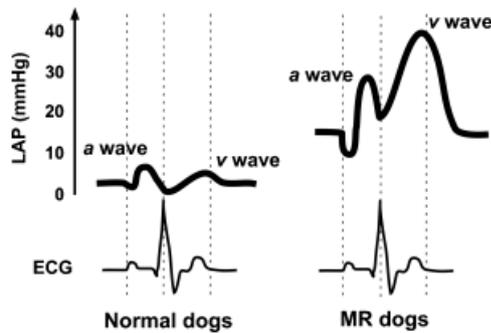
Fig 6. LAP curves during one cardiac cycle. The waveforms of LAP in normal dogs and mitral regurgitation dogs show inverse bimodal peaks each other. The waveform on the left was recorded with a multipurpose catheter in normal Beagle dogs in our laboratory, simultaneously with ECG. The other waveform was recorded without synchronizing it with ECG in this study, and thus the time phase of ECG might not precisely correspond with the waveform of LAP.

clinical signs, which supports the important relationship between body fluid volume and LAP variations. However, there are some differences between LAP variations and CVP variations. The increase in morning CVP is delayed by a few hours after getting up because it takes a few hours to redistribute body fluid volume after drinking in the morning.[29] In the present study, the delay in LAP elevation was not observed. Diurnal LAP variations are also linked to systemic BP variations, and decreased BP during the night could contribute to decreased LAP.

Limitations

The present study had some limitations. LAP measurements were conducted after the function of the heart had stabilized. However, the course of disease was shorter than observed in clinical dogs with chronic mitral valve endocardiosis. Although the hemodynamics of the MR model dogs are quite similar to those of clinical dogs, myocardial involvement might not be as advanced as in clinical cases. In addition, the relationship between cough and LAP was not monitored in the present study. If the time of onset of cough had been monitored by video camera, more detailed information between cough and LAP could have been obtained. Even allowing for these limitations, continuous observation of LAP with this experimental system was able to provide valuable data on hemodynamics in dogs with MR.

Conclusion

The major characteristics of LAP variation in dogs with MR were identified by continuous LAP observation. These characteristics are a slight nocturnal decrease and abrupt increases when excited. The latter seemed to have a stronger relationship with clinical manifestations. It is important to recognize the need for rest and restriction of physical activity in the management of MR. In addition, the minimum LAP was expected to have some association with diastolic function. Additional research is needed to determine the clinical implications of the

minimum LAP, and a method of correlating minimum LAP by noninvasive methods such as echocardiographic examination will be necessary for clinical use. With this experimental system, continuous observation of LAP in dogs with MR could provide valuable information for dosage and dose intervals for various medications used to treat MR.

Footnotes

[a] Healthy Label, Nisshin Pet Food Inc, Tokyo, Japan
[b] Metacam 0.5% injectable, Boeheringer-Ingelheim Vetmedica Japan, Hyogo, Japan
[c] Atropine sulfate, Tanabe Seiyaku Co Ltd, Osaka, Japan
[d] Vetorphale, Meiji Seika kaisha Ltd, Tokyo, Japan
[e] Dormicum, Astellas Pharma Inc, Tokyo, Japan
[f] Rapinovet, Schering-Plough, Tokyo, Japan
[g] Isoflu, Dainippon Sumitomo Pharma Co Ltd, Osaka, Japan
[h] ProSound α 10, Aloka Co Ltd, Tokyo, Japan
[i] TA11PA-D70, Data Sciences International, St Paul, MN
[j] Cefamezin α, Astellas Pharma Inc
[k] RLA-2000, Data Sciences International
[l] DEM, Data Sciences International
[m] APR-1, Data Sciences International
[n] DSI Dataquest A.R.T. 4.1, Data Sciences International
[o] GraphPad Prism version 5.0a, GraphPad, San Diego, CA
[p] EXCEL 2003 for MAC, Microsoft, Redmond, WA
[q] Thomas L, Foster E, Ross DL, Schiller NB. Does left atrial size and volume variation correlate with pulmonary venous flow and mitral regurgitation severity? In: 48th Annual Scientific Meeting of The Cardiac Society Of Australia and New Zealand, The Melbourne Exhibition and Congress Centre 2000 (abstract 158)
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