Effects of atenolol on left atrial and left ventricular function in healthy cats and in cats with hypertrophic cardiomyopathy

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Running head: EFFECTS OF ATENOLOL ON CARDIAC FUNCTION IN CATS
Abstract

This study aimed to assess the effects of atenolol on left ventricular (LV) and left atrial (LA) function in healthy cats and investigate the relationship between atenolol administration and LA enlargement (LAE) in cats with hypertrophic cardiomyopathy (HCM). In study 1, nine experimental cats were used to assess the effects of atenolol in healthy subjects. Cats were administered one of three medication protocols for 7 days: atenolol 6.25 mg/cat twice daily, 12.5 mg/cat twice daily, or placebo (biofermin) 1 tab/cat twice daily. In study 2, cats with HCM were retrospectively recruited and divided into four groups according to atenolol administration [(control group (Cont) or atenolol administration group (Ate)] and the presence or absence of LAE as follows: Cont LAE (-) group (n = 42), Cont LAE (+) group (n = 20), Ate LAE (-) group (n = 17), and Ate LAE (+) group (n = 12). LV and LA functions were compared in both studies. LV and LA functions were decreased by atenolol administration in study 1. In study 2, the peak myocardial velocity during early diastole (E’) was significantly decreased in the Cont LAE (+), Ate LAE (-), and Ate LAE (+) groups compared to that in the Cont LAE (-) group, but there were no significant differences between LAE (+) groups. Multivariate logistic analysis revealed that atenolol administration was not associated with LAE. Diastolic dysfunction may be associated with LAE; however, atenolol administration did not affect LAE in cats with HCM.

Key words: atenolol, cardiology, echocardiography, feline, hypertrophic cardiomyopathy.
Introduction

Hypertrophic cardiomyopathy (HCM) is the most common heart disease in cats and is characterized by concentric left ventricular (LV) hypertrophy and diastolic dysfunction [20, 27, 28]. Diastolic dysfunction is the primary abnormality of the disease and the key to assessing the progression of the disease [6, 15, 27]. Left atrial (LA) function was reportedly decreased with the progression of the disease [16], which potentially causes LA enlargement (LAE). LAE is considered to be a morphophysiological expression of LV diastolic dysfunction and is known to be one of the strong risk factors for atrial thromboembolism and congestive heart failure [16, 24]. As a result, it is important to identify the factors related to LAE.

Atenolol, an active beta-1 selective adrenergic antagonist, is a potential treatment option in humans and cats with asymptomatic HCM [1, 10]; although, its effects in cats remain controversial [11, 13, 22]. The presumed favorable effects of beta-blockers on HCM include an antiarrhythmic effect and reduction of LV outflow obstruction [11]. Its effects on diastolic function are primarily indirect and caused by its chronotropic action [7]; however, beta-blockers may impair the diastolic function and cause LAE [21]. Riesen et al. revealed that atenolol decreased both LV and LA functions; although, its effects on diastolic function were minimally assessed and the study was performed only on healthy cats [21].

There are few studies that report the effects of atenolol on cardiac function and the relationship between diastolic dysfunction and LAE in cats with HCM. Thus, in this investigation, it was hypothesized that atenolol affects diastolic function and is related to the progression of disease, particularly LAE in cats with HCM. The purpose of this study was to assess the effects of atenolol on cardiac function in healthy cats and in cats with HCM and to investigate whether the administration of atenolol affects LAE in cats with HCM.

Materials and Methods
Study 1. The effect of atenolol on LV and LA functions in healthy cats

Nine experimental cats (five male cats and four female cats), aged 38–50 months and weighing 2.62–4.35 kg, were included in the study. They were housed individually in cages and fed dry food in the morning and afternoon. Water was provided ad libitum. A complete clinical examination comprising of a physical examination, complete blood count (CBC), blood chemistry, thoracic radiography, electrocardiography, and echocardiography was performed in all cats to exclude diseases known to cause systemic hypertension. None of the cats demonstrated any abnormal findings. This experimental study protocol was approved by the Azabu University Animal Care and Use Committee (No. 1507200).

The cats were administered one of three medication protocols for 7 days as follows: atenolol (Tenormin 25, AstraZeneca Inc., Osaka, Japan) 6.25 mg/cat (Ate 6.25 mg group) twice daily, 12.5 mg/cat (Ate 12.5 mg group) twice daily, or biofermin (Biofermin R, Biofermin Pharmaceutical Inc., Kobe, Japan) 1 tab/cat twice daily (placebo group). Each protocol had a randomized crossover design with a 14-day washout period in all cats (Fig. 1). After the administration of medications on day 7, an echocardiographic examination was performed, and systolic blood pressure (SBP) measurements were recorded. Each cat underwent an echocardiographic examination at baseline (pre-group) and after the administration of medication. In each group, echocardiography was performed 2 h after the administration of medication, to coincide with atenolol reaching its maximum concentration in the blood [14].

Study 2. The effect of atenolol on cardiac function in cats with hypertrophic cardiomyopathy

A retrospective study was performed. Cats that were presented to the Azabu University Veterinary Teaching Hospital for the screening of cardiac diseases from April 2012 to March 2019 were included. Cats that were diagnosed with asymptomatic HCM were recruited for this study. HCM was diagnosed when the interventricular septal thickness (IVSd) and/or the
LV free wall thickness (LVFWd) at end-diastole, measured using the right parasternal long-axis view and the short-axis view, was 6 mm or more in the absence of pressure overload and systemic diseases known to cause LV hypertrophy [8].

The cats were divided into four groups according to the presence or absence of LAE and the administration of atenolol (unmedicated cats with a left atrium within normal size parameters, Cont LAE (-); unmedicated cats with LAE, Cont LAE (+); cats treated with atenolol alone for 3 to 24 months with a left atrium within normal size parameters, Ate LAE (-); and cats treated with atenolol alone with LAE, Ate LAE (+) group). The data from each cat was included in the analysis only once. LAE was considered to be present if the left atrium-to-aortic diameter ratio (LA/Ao) was > 1.5 [8]. The cat whose atenolol dosage varied from 6.25 to 12.5 mg/cat once or twice daily was included in the Ate group following the results of study 1. Cats receiving a dose of atenolol < 6.25 mg/day were excluded from the study.

**Echocardiographic examination**

All echocardiographic images were acquired using an ultrasound unit equipped with a 7 or 10 MHz transducer (Vivid 7 and E9 system, GE Medical System, Tokyo, Japan). All echocardiographic examinations and measurements were performed by KS in study 1 and by KS, YF, or TA in study 2. Cats were gently restrained in lateral recumbency without sedation during the examination.

All conventional echocardiographic measurements were performed directly on the screen freeze-frame images, and three consecutive measurements were then averaged for each value.

The LV internal diameter at end-diastole (LVIDd), IVSd, and LVFWd were measured from M-mode images at the level of the chordae tendineae. Heart rate (HR) was calculated from the M-mode images.

The aortic and LA diameters at end-systole (AoD and LAD, respectively) and LA/Ao were measured from the right-sided parasternal short-axis view at the level of the aortic valve using a two-dimensional method as previously described and validated [4, 23].
Hypertrophic obstructive cardiomyopathy (HOCM) was diagnosed when dynamic left ventricular outflow tract obstruction was evident as an increased LV outflow tract velocity ($LVOTv; > 2 \text{ m/sec}$) with cranial motion of the mitral valve during systole. $LVOTv$ was assessed using the left apical 5-chamber view.

LV function was assessed using color tissue Doppler imaging (TDI). All color TDI examinations were performed as previously described [9]. Briefly, the lateral aspect of the mitral annulus was sampled using the left 4-chamber apical view. A $2 \times 2 \text{ mm}$ sample, without angle correction, was used. The peak myocardial velocity was measured during systole ($S'$) and early diastole ($E'$).

LA function was assessed by the complete function change as previously described [16]. LA diameter was assessed from the right parasternal long-axis 4-chamber view. Maximum and minimum diameters (LAD max and LAD min, respectively) were recorded, and changes in diameter were expressed as fractional shortening (LA-FS) using the following equation:

$$\text{LA-FS} = (\text{LAD max} - \text{LAD min}) / \text{LAD max} \times 100 \%.$$

LA volume was calculated from the same long-axis view using Simpson’s rule. Maximum and minimum volumes (LA volume max and LA volume min, respectively) were recorded, and changes in volume were expressed as ejection fraction (LA-EF) using the following equation:

$$\text{LA-EF} = (\text{LA volume max} - \text{LA volume min}) / \text{LA volume max} \times 100 \%.$$

Cats without merged E’ and A’ waves on all examinations were included in both studies. The mean value of three consecutive cardiac cycles in a single cine loop was used for statistical analysis.

**Systolic blood pressure measurement**
SBP in study 1 was obtained noninvasively by Doppler sphygmomanometry (Doppler sphygmomanometer, Hadeco, Inc., Kawasaki, Japan). Hair distal to the cuff was clipped before placing the probe. An inflatable cuff of appropriate size was placed on the tail [2]. The cuff was manually inflated until the pulse signal was no longer audible and then gradually deflated. SBP was determined as the measurement where the Doppler signal became audible again. Several consecutive measurements were performed. After obtaining a stable set of five measurements, the mean values of the measurements were used for statistical analyses.

Statistical analyses
Statistical analyses were performed using a commercial computer software (IBM SPSS Subscription Service, IBM Corp., Armonk, NY, USA). All echocardiographic measurements and SBPs were visually inspected and tested for normality using the Kolmogorov-Smirnov test. Normally distributed data were expressed as mean ± standard deviation (SD). Non-normally distributed data were expressed as medians and interquartile ranges.

In study 1, all measurements among the groups were compared using repeated-measured ANOVA. When a significant difference was detected, multiple comparisons were evaluated using Bonferroni's multiple comparison or Friedman’s test. Intra-observer variability for TDI and LA function was assessed by calculating the coefficients of variation (CV) using the following formula: CV = (SD / arithmetic mean of measurements) × 100 [3]. CV was considered clinically acceptable if < 10% [9].

In study 2, all echocardiographic measurements, ages, and body weights were compared among the groups using a one-way ANOVA or a Kruskal-Wallis test. If significant differences were detected, multiple comparisons were performed using Bonferroni's multiple comparison test or a Steel-Dwass test. Sex differences were assessed using the $\chi^2$ test.

Multivariate logistic regression with the forward-backward stepwise method (likelihood ratio: $P$-value for entry < 0.10 and for exit > 0.20) were performed to estimate the risk of LAE associated with potential predictors, including: sex, age, body weight, M-mode values, LA
and LV function, and administration of atenolol. Odds ratios with 95% confidence intervals (CIs) were employed to measure the strength of association, and variables with $P < 0.05$ in the final model were considered factors associated with LAE. Goodness of fit was checked by using the Hosmer-Lemeshow test. A significant difference was defined as $P < 0.05$.

**Results**

In study 1, two out of nine cats were excluded due to the summation of E’ and A’ waves in the pre-group. No adverse effects were observed for any medications. Ninety-one client-owned cats were included in study 2 (Table 1). HOCM was diagnosed in 32 cats in the Cont LAE (-) group, 15 cats in the Cont LAE (+) group, and in all cats in both Ate groups. There were no significant differences in age, body weight, and sex between the groups in study 2. The cats received a minimum of 6.25 mg and a maximum of 12.5 mg of atenolol daily in both Ate groups. Twelve cats received atenolol once daily (6.25–12.5 mg/day), and 5 cats received atenolol twice daily (12.5 mg/day) in the Ate LAE (-) group. Nine cats received atenolol once daily (6.25–12.5 mg/day), and 3 cats received atenolol twice daily (12.5 mg/day) in the Ate LAE (+) group. The median time periods between the last administration of atenolol and the echocardiographic examination were 2 hours (2–4 hours) in the Ate LAE (-) group and 2 hours (2–5 hours) in the Ate LAE (+) group. There were no significant differences between the groups.

**Study 1. Echocardiographic examination**

The results of the echocardiographic examinations in study 1 are shown in Table 2. There were no significant differences in IVSd, LVIDd, LVFWd, LAD, AoD, and LA/Ao among the groups. Significant differences were observed in HR between the Ate 6.25 mg and the pre and placebo groups, the Ate 12.5 mg and the pre groups, and the placebo and the Ate 6.25 mg
The results of the TDI in study 1 are shown in Table 3. There were significant differences in S’ and E’ between the Ate 6.25 mg and the pre and placebo groups and between the Ate 12.5 mg and the pre and placebo groups. The intra-observer CVs were clinically insignificant in S’ and E’ (2.5% to 4.9%). The LA functions from study 1 is shown in Table 4. There were significant differences in LA-FS and LA-EF between the Ate 6.25 mg and the pre and the placebo groups, the Ate 12.5 mg and the pre and placebo groups, and the Ate 6.25 mg and the Ate 12.5 mg groups. The intra-observer CVs were clinically insignificant in LA-FS and LA-EF (4.5% to 9.8%).

Study 1. SBP

The SBP values in study 1 were 171.1 ± 21.1, 175.8 ± 27.3, 168.9 ± 24.0, and 151.7 ± 33.1 mmHg in the pre, placebo, Ate 6.25 mg, and Ate 12.5 mg groups, respectively. All of the measurements were within the reference range (124–210 mmHg) [26]. No significant differences were observed in the SBP among the groups.

Study 2. Echocardiographic examinations

The results of the echocardiographic examinations in study 2 are shown in Table 5. HR and LVOTv significantly decreased in both Ate groups as compared to those in both Cont groups. The results of the TDI in study 2 are shown in Fig. 2. S’ in both Ate groups was significantly decreased as compared to those in both Cont groups. E’ was significantly decreased in the Cont LAE (+) group and both Ate groups as compared to that in the Cont LAE (-) group and in the Cont LAE (+) and the Ate LAE (+) group as compared to that in the Ate LAE (-) group. The results of the LA function are shown in Fig. 3. LA-EF was significantly decreased in both LAE (+) groups as compared to that in both LAE (-) groups. There were no significant differences in LA-FS among the groups. Multivariate logistic analysis revealed that E’ (odds ratio: 17.0, 95% CI: 3.17–91.4, P < 0.01)
and LA-EF (odds ratio: 1.45, 95% CI: 1.14–1.85, P < 0.01) were associated with LAE. The administration of atenolol was not found to be associated with LAE. The Hosmer-Lemeshow test yielded a P-value of 0.892 without statistical significance; thus, the proposed model was consistent and adequate to explain the observed outcome.

**Discussion**

The current study investigated the effect of atenolol on healthy cats in the study 1. Riesen et al. reported that atenolol decreased both LV and LA functions. However, in their study, the number of cats whose diastolic function could be measured was small (2 of 10 cats), and echocardiography was performed with the cats under sedation [21]. The dosage range of atenolol is 6.25–12.5 mg/cat once or twice daily [19, 22]; however, the dose-dependent effect has been uncertain, making the effect of atenolol on diastolic function uncertain. Study 1 revealed that the diastolic parameter, E’, as well as systolic parameters decreased in healthy cats after atenolol administration, which supported the hypothesis that atenolol would decrease diastolic function. Dose-dependent decline was seen in HR and systolic parameters, but not in E’, in healthy cats.

Following the results of study 1, in study 2, the cat whose atenolol dosage varied from 6.25 to 12.5 mg/cat once or twice daily was included in the Ate group. In the cats with HCM, E’ decreased in both Ate groups, and E’ in both LAE (+) groups significantly decreased regardless of atenolol administration. Nagueh et al. [16, 18] reported that the progression of diastolic dysfunction was associated with an increased LA pressure and that the chronicity of diastolic dysfunction led to an increased LA volume. The results of this study suggest that atenolol decreased diastolic function, which is associated with LAE, but the administration of atenolol in HCM cats was not associated with LAE. Therefore, the assessment of diastolic function may be favorable for predicting LAE in cats with HCM.

Atenolol treatment is not recommended in heart failure patients due to HCM with systolic
dysfunction [10]. As a dose-dependent decrease in LV function was seen in normal cats in this 
study; the assessment of systolic function may be important when administering a high dose 
of atenolol.

LA-EF in both LAE (+) groups was decreased regardless of atenolol administration. Linney et 
al. [16] reported a significant decrease in LA-EF in cats with LAE and a significant negative 
association between LA-EF and LA volume max. Johns et al. [12] reported that LA function, 
assessed by the change in surface area, was reduced in cats with congestive heart failure as 
compared to that in healthy cats. The current study showed that LA-EF was significantly 
associated with LAE, as is described in other studies [16, 21]. Reduced LA systolic function 
was not due to the effect of atenolol, but rather as a result of LAE as LA-EF was not different 
between the Cont LAE (-) and Ate LAE (-) groups.

The present study had several limitations. The main limitation of this study was the duration 
of atenolol administration. The duration was 7 days in study 1 and 3 months or more in study 
2. Chronic impairment of diastolic function caused by atenolol may contribute to LAE 
development. Therefore, further prospective long-term studies should be conducted. Secondly, 
the sample size was small. Scottish Fold was the most common breed in all groups, and the 
type of breed may influence the echocardiographic parameters [5, 17]. Different breeds may 
also carry different HCM-associated genes and cause different functional manifestations; 
although, this possibility has not been investigated. Thirdly, the echocardiographic 
examinations and analyses were not performed in a blinded manner, which may have incurred 
bias. Finally, the cats with HCM were at various stages of the disease, for example, congestive 
heart failure and the dilated phase [12, 25, 27-29]. Although the effects of atenolol on LAE 
were not clear in the current populations, further studies are warranted to investigate the effect 
of atenolol in cats with HCM at varying stages of disease.

In conclusion, the findings of this study indicated that diastolic dysfunction may be associated 
with LAE; however, the administration of atenolol did not affect LAE, and the effectiveness 
of atenolol administration was not confirmed in the population of cats with HCM. Further
prospective studies are warranted to investigate the effect of atenolol in cats with HCM.
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Figure 1. Experimental protocol in study 1

Nine experimental cats are used and dosed with one of three medication protocols for 7 days. The medication protocols were as follows: atenolol 6.25 mg/cat twice a daily (Ate 6.25 mg group), atenolol 12.5 mg/cat (Ate 12.5 mg group), and biofermin 1 tab twice a daily (Placebo group). Each protocol has a randomized crossover design with a 14-day washout period observed in all cats.
Figure 2. Results of tissue Doppler imaging in study 2

The peak myocardial velocity during systole (S’) in both Ate groups are significantly decreased as compared to those in both Cont groups. The peak myocardial velocity during early diastole (E’) is significantly decreased in the Cont LAE (+) group and both Ate groups as compared to that in the Cont LAE (-) group and in the Cont LAE (+) and the Ate LAE (+) group as compared to that in the Ate LAE (-) group.

*: Significant differences between the groups ($P < 0.05$).

**: Significant differences between the groups ($P < 0.01$).
Figure 3. Results of left atrial function in study 2

Left atrial ejection fraction (LA-EF) is significantly decreased in both LAE (+) groups as compared to that in both LAE (-) groups. There are no significant differences in left atrial fractional shortening (LA-FS).

**: Significant differences between the groups ($P < 0.01$).
Table 1. Characteristics of HCM cats in study 2.

|               | Cont LAE (-) | Cont LAE (+) | Ate LAE (-) | Ate LAE (+) |
|---------------|--------------|--------------|-------------|-------------|
| Age month     | 60.1±52.7    | 77.6±53.7    | 50.9±36.5   | 51.4±35.9   |
| Body Weight kg| 4.37±1.63    | 4.42±0.74    | 4.06±1.00   | 4.38±0.90   |
| Sex F/M       | 12/30        | 4/16         | 5/12        | 3/9         |
| Breed         | Scottish Fold 14 | Scottish Fold 8 | Scottish Fold 6 | Scottish Fold 2 |
|               | American Shorthair 9 | American Shorthair 3 | Norwegian Forest Cat 2 | Bengal 1 |
|               | Maine Coon 4 | Maine Coon 1 | American Shorthair 1 | American Shorthair 1 |
|               | Russian Blue 2 | Bengal 1 | Russian Blue 1 | Maine Coon 1 |
|               | Bengal 2 | Sphynx 1 | Maine Coon 1 | Ragamuffin 1 |
|               | Persian 1 | Munchkin 1 | Domestic Shorthair 6 | Domestic Shorthair 6 |
|               | Ragamuffin 1 | Norwegian Forest Cat 1 | Domestic Shorthair 6 | Domestic Shorthair 6 |
|               | Norwegian Forest Cat 1 | Domestic Shorthair 4 |                     |             |
|               | Domestic Shorthair 6 |                     |                     |             |
Table 2. Results of conventional echocardiographic parameters in study 1.

|       | index | Pre    | Placebo | Ate 6.25mg | Ate 12.5mg |
|-------|-------|--------|---------|------------|------------|
| LVFWd | cm    | 3.78±0.34 | 3.59±0.38 | 3.84±0.23 | 3.70±0.59  |
| LVIDd | cm    | 16.0±1.1  | 15.8±0.8  | 16.1±0.5  | 16.0±1.5   |
| IVSd  | cm    | 3.43±0.37 | 3.66±0.33 | 3.47±0.23 | 3.42±0.29  |
| HR    | bpm   | 174.1±16.3| 179.3±24.9| 145.7±12.1*| 125.7±18.8†|
| LAD   | cm    | 1.26±0.09 | 1.27±0.05 | 1.24±0.11 | 1.27±0.07  |
| AoD   | cm    | 1.04±0.09 | 1.07±0.12 | 1.05±0.09 | 1.08±0.08  |
| LA/Ao |       | 1.21±0.11 | 1.21±0.15 | 1.19±0.10 | 1.18±0.10  |

LVFWd: Left ventricular free wall thickness at end-diastole; LVIDd: Left ventricular internal diameter at end-diastole; IVSd: Interventricular septum wall diameters at end-diastole; HR: heart rate; LAD: Left atrial diameter at end-systole; AoD: Aortic diameter at end-systole; LA/Ao: Left atrium-to-aorta ratio.

*: Significant differences compared with the pre and placebo groups (P < 0.05). †: Significant differences compared with the pre, placebo, and Ate 6.25 mg groups (P < 0.05).
### Table 3. Results of TDI parameters in study 1

| index | Pre       | Placebo  | Ate 6.25mg | Ate 12.5mg |
|-------|-----------|----------|------------|------------|
| S'    | cm/sec    | 5.37±0.71| 5.46±1.14  | 4.03±0.86* | 3.76±0.54**|
| E'    | cm/sec    | 9.49±1.72| 9.61±1.73  | 7.63±1.94* | 7.78±2.02* |

S’: Peak myocardial velocity during systole; E’: Peak myocardial velocity during early diastole. *: Significant differences compared with the pre and placebo groups (P < 0.05). **: Significant differences compared with the pre and placebo groups (P < 0.01).
Table 4. Results of left atrial function in study 1.

| Index | Pre   | Placebo | Ate 6.25mg | Ate 12.5mg |
|-------|-------|---------|------------|------------|
| LA-FS | %     | 31.3±3.5| 31.0±4.2   | 26.5±3.8*  | 22.4±4.1** †  |
| LA-EF | %     | 48.9±7.8| 47.9±8.8   | 42.6±4.5*  | 37.1±4.6** †  |

LA-FS: Left atrial fractional shortening; LA-EF: Left atrial ejection fraction.
*: Significant differences compared with the pre and placebo groups (P < 0.05).
**: Significant differences compared with the pre and placebo groups (P < 0.01).
†: Significant differences compared with the Ate 6.25 mg group (P < 0.05).
Table 5. Results of conventional echocardiographic parameters in study 2.

| Parameter | Cont LAE (-) | Cont LAE (+) | Ate LAE (-) | Ate LAE (+) |
|-----------|--------------|--------------|-------------|-------------|
| LVFWd mm  | 5.20±0.95    | 5.26±1.12    | 5.01±1.13   | 5.78±1.33   |
| LVIDd mm  | 14.7±2.4     | 14.3±1.7     | 14.6±1.9    | 15.3±2.0    |
| IVSd mm   | 6.02±0.90    | 6.02±0.84    | 6.00±0.88   | 5.83±1.21   |
| HR bpm    | 168.1±19.9   | 169.8±14.0   | 152.8±21.0* | 155.1±20.8* |
| LAD mm    | 12.14±1.74   | 17.65±1.46** | 11.98±1.71  | 17.90±1.66**|
| AoD mm    | 9.90±1.08    | 9.65±0.74    | 9.83±0.74   | 9.66±0.60   |
| LA/Ao     | 1.23±0.10    | 1.83±0.20**  | 1.24±0.10   | 1.76±0.09** |
| LVOTO m/sec| 3.61±0.89    | 3.27±1.04    | 3.28±0.68   | 3.23±0.86   |
| n         | 32           | 15           | 17          | 12          |

LVFWd: Left ventricular free wall thickness at end-diastole; LVIDd: Left ventricular internal diameter at end-diastole; IVSd: Interventricular septum wall diameters at end-diastole; HR: heart rate; LAD: Left atrial diameter at end-systole; AoD: Aortic diameter at end-systole; LA/Ao: Left atrium-to-aorta ratio; LVOTO: left ventricular outflow tract obstruction.

*: P < 0.05 compared with both Cont groups, **: P < 0.01 compared with each LAE (-) groups.