Preoperative left atrial size and functions are predictors of left atrial reverse remodelling after mitral valvuloplasty for myxomatous mitral valve disease in dogs

Short title: Predictors of left atrial size after mitral valvuloplasty in dogs

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Abstract

Objectives: The objective of this study was to determine alterations in left atrial size, function, and determinants of left atrial reverse remodelling (LARR) after mitral valvuloplasty (MVP) in dogs with myxomatous mitral valve disease (MMVD).

Animals: Thirty-seven dogs undergoing MVP.

Materials and Methods: Echocardiographic parameters, including left atrial (LA) strain, were evaluated at baseline, during the early postoperative period (within two weeks), and at one and three months postoperatively. Patients were divided into two groups based on the attainment of LARR, defined as a left atrial to aortic root ratio (LA:Ao) < 1.6 at three months. The predictors of LARR were analysed using univariate logistic regression analysis.

Results: LA:Ao significantly decreased in the early postoperative period (median 1.68; lower and upper quartile 1.54–1.92) compared to baseline (2.41; 2.00–2.80), with a further significant reduction observed at three months (1.46; 1.34–1.63). LARR was achieved in 27 (73%) patients. Baseline LA:Ao was higher, and peak atrial longitudinal strain (PALS) and peak atrial construction strain (PACS) were lower in the non-LARR group than in the LARR group. Among the baseline parameters, PACS was the strongest predictor of LARR (area under the curve, 0.837).

Conclusions: Following MVP, the LA size decreased in the early postoperative period and continued to decrease over three months of follow-up. A low PACS score was the most reliable predictor of inadequate LARR. Further studies are necessary to determine the relationship between LARR, prognosis, and the optimal timing for surgical intervention.

Keywords

Mitral regurgitation; Left atrial strain; Speckle tracking echocardiography; Booster pump function; Reservoir function

Abbreviations

2DSTE	two-dimensional speckle tracking echocardiography
LA	left atrium
LARR	left atrial reverse remodelling
LA:Ao	left atrial to aortic root ratio
LV	left ventricle
MMVD	myxomatous mitral valve disease
MR	mitral regurgitation
MVP	mitral valvuloplasty
PACS	peak atrial contraction strain
PALS	peak atrial longitudinal strain

Introduction

Myxomatous Mitral Valve Disease (MMVD) is the most common cardiac disease acquired in canines [1,2]. Mitral regurgitation (MR), resulting from myxomatous valve degeneration, induces volume overload in the left heart. Volume overload in the left atrium (LA) initiates a remodelling process, marked by the expansion of the LA chamber coupled with a corresponding decrease in its function. Two-dimensional echocardiographic parameters of the LA, including the left atrial-to-aortic root ratio (LA:Ao) and LA maximal volume, have been established as prognostic markers for canines with MMVD [3-5]. The LA plays a critical role in filling the left ventricle (LV) and maintaining the optimal cardiac output by functioning as a reservoir, conduit, and booster pump. During systole and isovolumic relaxation, the LA acts as a reservoir, receiving blood from the pulmonary veins, and storing energy in the form of pressure. In early diastole, it serves as a conduit, facilitating blood flow from the LA to the LV via a pressure gradient and enabling passive blood flow from the pulmonary veins into the LV. In late diastole, the LA functions as a booster pump and its active contraction increases the LV stroke volume by approximately 20–30% in healthy individuals [6,7]. LA function can be assessed by volumetric analysis and strain analysis using two-dimensional speckle tracking echocardiography (2DSTE) [8]. The previous studies have shown that indices of reservoir and booster pump function assessed by LA strain are more indicative of the prognosis of MMVD in canines than LA size [9,10].

After Mitral Valvuloplasty (MVP) in human patients with MR, the reduction in volume load owing to improved MR leads to an immediate decrease in LA size and pressure [11,12]. Furthermore, a decrease in LA wall stress contributes to improvements in LA fibrosis and myocardial remodelling, resulting in further improvements in LA size and function [13]. These postoperative structural and functional alterations of the LA are termed left atrial reverse remodelling (LARR). Several studies indicate that 16–34% patients experience inadequate LARR following mitral valve surgery [11,14,15]. Inadequate LARR is associated with poor outcomes, including a higher risk of stroke, atrial fibrillation, and shortened survival [15]. Preoperative indices of LA volume and function have proven to be predictors of LARR, underscoring the need for preoperative assessment of LA structure and function in patients with MR. In dogs, a decrease in LA size is observed in many cases after MVP for MMVD; however, inadequate LARR is also observed in some cases [16,17,18]. Nonetheless, studies focusing on LA function in dogs undergoing MVP are scarce, and clinical and echocardiographic indices that predict LARR remain undefined.

The primary objective of this study was to determine changes in LA size and function after MVP in dogs with MMVD. The secondary aim was to identify predictors of postoperative LARR. We hypothesised that preoperative LA strain indices, as determined using 2DSTE, could be predictors of LARR.

Animals, materials, and methods

Animals

Dogs that underwent MVP for severe chronic MR associated with MMVD by the Japan Animal Cardiovascular Care Team between November 2019 and August 2020 were included in this study. All dogs in this study underwent complete physical and echocardiographic examinations of adequate quality for 2DSTE analysis, ensuring no deficits during the follow-up period. Data concerning age, breed, sex, weight, echocardiographic indices, and treatment were collected from medical records. Dogs with early postoperative death, postoperative ischaemic myocardial damage, residual moderate or greater postoperative MR, or persistent atrial fibrillation, both pre- and post-surgery, were excluded. Ischemic myocardial injury was identified through a focal reduction in myocardial motility, accompanied by postoperative ST-segment elevation and progressive thinning of the myocardium over time. The severity of residual postoperative MR was determined by calculating the proportion of the regurgitant jet area to the left atrial area using color Doppler, with a ratio of 20% or more considered moderate or greater regurgitation.

Surgery

Surgery was performed through left fifth intercostal thoracotomy. Hypothermic cardiopulmonary bypass was established via cannulation of the left external jugular vein and left common carotid artery. Cardiac arrest was achieved by occluding the aorta proximal to the brachiocephalic artery using aortic clamping forceps and administering cardioplegia through a cannula positioned at the aortic root. Following cardiac arrest, the LA was incised to access the mitral valve. Artificial chordae tendineae reconstruction and mitral annuloplasty were performed in all cases, including resection of excess subvalvular tissue, resection of ruptured chordae tendineae, and cleft closure of the valve leaflet as necessary. The duration of cardiopulmonary bypass and aortic cross-clamp was documented.

Echocardiography

Echocardiographic examinations were performed utilizing a standard echocardiographic systems[d] equipped with a 2.9/5.8 MHz sector probe transducer. These assessments were performed at baseline, in the early postoperative period (within two weeks), and at one and three months postoperatively. All examinations were performed with the patients in a nonsedated state and manually positioned in both the right and left lateral recumbent positions on the examination table. The LA size was evaluated using the LA:Ao at the level of the aortic valve in the right parasternal short-axis cross-sectional view in early ventricular diastole using the first frame after aortic ejection [19]. Left ventricular end-diastolic and end-systolic diameters were measured using M-mode images at the level of the chordae tendineae in the right parasternal short-axis view. Left ventricular fractional shortening (FS) was recorded, and the end-diastolic and end-systolic LV internal diameters were standardised by body weight using the following formulas: LVIDDN = LV end-diastolic internal diameter / (body weight)$^{0.294}$, LVIDSN = LV end-systolic internal diameter / (body weight)$^{0.315}$. The criteria for LA and LV enlargement were LA:Ao >1.6 and LVIDDN >1.7 according to ACVIM guidelines [20]. Left ventricular inflow patterns were analysed using pulsed-wave Doppler to measure the maximum early diastolic inflow velocity (E), maximum late diastolic inflow velocity (A), and E:A from the apical four-chamber view. Left and right ventricular outflow tract blood flow velocities were also assessed using pulsed-wave Doppler from the apical five-chamber view and right parasternal short-axis view at the pulmonary artery valve level, respectively.

Speckle tracking echocardiography

Left atrial strain measurements were conducted offline by a sole examiner (S. K.) using vendor-independent 2D Speckle Tracking software[e]. The analysis was performed offline from 2D DICOM videos capturing three consecutive heartbeats. The LA endocardial border was traced as the region of interest in the end-systolic phase in the

LA-focused apical four-chamber view, ensuring the exclusion of the left auricle and pulmonary vein. Left atrial strain measurement throughout the cardiac cycle was set to start at the beginning of the QRS complex, and a global LA strain-time curve was generated. The strain at the end of the LA systole was set as the zero-reference value. Left atrial peak strain measured just before the mitral valve opening was defined as peak atrial longitudinal strain (PALS), and LA strain measured just before atrial contraction (coinciding with the onset of the P-wave on electrocardiography) was identified as peak atrial contraction strain (PACS) (Figure 1). All LA strain measurements were averaged over three consecutive cardiac cycles.

Statistical analyses

Measurements are presented as median and lower and upper quartile. Multiple comparisons of continuous variables at baseline, early postoperative period, one month, and three months were performed using the Steel-Dwass test. The relationships between different measurements were assessed using Spearman's correlation analysis. Simple linear logistic regression analyses were used to predict LA:Ao at three months after MVP from preoperative left atrial size and functional indices. Left atrial reverse remodelling was defined as achieving LA:Ao < 1.6 at three months after MVP, and the cases were divided into two groups (LARR and non-LARR groups). Variables were compared by The Kruskal-Wallis test for continuous variables and Fisher's exact test for categorical variables between the two groups. Predictors of LARR were assessed using binary logistic regression analysis. Echocardiographic variables with P < 0.05 in univariate analyses were included in the multivariate analysis, whitch was performed using a stepwise forward selection method with a threshold of P < 0.1 for variable inclusion. Receiver-operating characteristic curves and the area under each receiver-operating characteristic curves were calculated to assess the accuracy of each measure at baseline in discriminating between the LARR and non-LARR groups. Statistical analyses were performed using commercial software[f]. A two-sided P-value < 0.05 was considered significant.

Result

Mitral Valvuloplasty was performed in 61 patients with MMVD between November 2019 and August 2020. Of the 61 cases, 37 were enrolled for 2DSTE analysis, while six cases were excluded for poor echocardiographic window, six for death due to postoperative complications, six lost to follow-up, three for residual MR at one or three months, two for pre- and postoperative arrhythmias, and one for severe postoperative LV dysfunction. The 37 patients included 14 in stage B2, 14 in stage C, and nine in stage D. The most commonly represented breeds were Chihuahua (n = 19), followed by mixed breed (n = 7), Toy Poodle (n = 4), Maltese (n = 2), Cavalier King Charles Spaniel (n = 2), Miniature Dachshund (n = 2), and Miniature Schnauzer (n = 1). Dogs were treated with pimobendan (n = 36), ACE inhibitors (n = 29), torsemide (n = 29), amlodipine (n=28), spironolactone (n = 20), furosemide (n = 7), hydrochlorothiazide (n = 2), and tolvaptan (n = 2). Table 1 shows the demographic data, surgical dates, and echocardiographic characteristics of the patients.

The echocardiographic indices from baseline to three months follow-up are presented in Table 2. Left atrial-to-aortic root ratio began to decrease in the early postoperative period and continued to decrease for three months (Figure 2A). Peak atrial longitudinal strain also decreased in the early postoperative period but tended to increase at three months (Figure 2B). Peak atrial construction strain showed a non-significant tendency to decrease in the early postoperative period, but then reversed and increased at three months (Figure 2C).

The correlations between LA size and function at three months and baseline echocardiographic indices are presented in Table 3. Left atrial-to-aortic root ratio at three months demonstrated a correlation with baseline LA:Ao ($\rho = 0.485$, $P = 0.002$), PALS ($\rho = -0.543$, $P < 0.001$) and PACS ($\rho = -0.546$, $P < 0.001$) respectively (Figure

3). Peak atrial longitudinal strain at three months correlated with baseline PALS (ρ = 0.504, P = 0.002) and PACS (ρ = 0.514, P = 0.001). Peak atrial construction strain at three months was correlated with baseline PALS (ρ = 0.563, P < 0.001), PACS (ρ = 0.529, P < 0.001). No correlation was found between the duration from surgery to the early postoperative period and LA:Ao (ρ < 0.001, P = 0.998), PALS (ρ = 0.127, P = 0.455) , or PACS (ρ = 0.108, P = 0.536) in the early postoperative period. Predictive equations for LA:Ao at three months after MVP derived from indices of preoperative left atrial size and function indices are presented in Table 4.

The clinical and echocardiographic indices of the LARR and non-LARR groups are presented in Table 5. Left atrial reverse remodelling was achieved in 73% (27/37) of cases at three months. Age, sex, weight, and history of pulmonary oedema were not significantly different between the two groups. Baseline LA:Ao was higher, and PALS and PACS were lower in the non-LARR group than in the LARR group (Figure 4). Receiver-operating characteristic curves analysis showed that the baseline PACS had the highest area under the curve for discriminating between the LARR and non-LARR groups (Table 6).

Univariate logistic regression analysis showed that LA:Ao, PALS, and PACS were significantly related to LARR at three months after MVP. Subsequently, multivariate logistic regression analysis identified PACS as the only independent correlate (P = 0.008, odds ratio 0.760 [95% Confidence Interval 0.595–0.970]) (Table 7).

Discussion

In the present study, 73% of the dogs with MMVD achieved LARR three months after MVP, and preoperative LA size and function were predictors.

In humans, inadequate LARR has been identified as a poor prognostic factor for atrial fibrillation, stroke, and all-cause mortality [15,21]. In humans, factors associated with LARR after mitral valve surgery include the preoperative LA volume index [22], preoperative reservoir function index [23], postoperative mitral stenosis, and postoperative MR severity [15]. In the present study, no patient developed post-surgical mitral stenosis, and patients with postoperative moderate MR were excluded. This study implies that the preoperative LA size and function indices, particularly the booster pump function index, are valuable in identifying cases of inadequate LARR and LA size at three months after MVP.

Reduced LA function has been identified as a better prognostic factor than LA size on primary human MR, suggesting that it is an important factor in assessing the suitability of surgical intervention [24-26]. Previous studies also demonstrated that LA function is more relevant than LA size to the severity and prognosis of MMVD in dogs than LA size [9,10]. Left atrial size is an important indicator of MR severity, whereas LA enlargement is a compensatory response to prevent MR-induced increases in LA pressure. In other words, in a highly compensated LA, LA pressure may remain within normal limits despite severe LA enlargement [27]. However, severe, long-lasting volume overload in the LA results in interstitial fibrosis, endocardial thickening, chronic inflammation, myocyte hypertrophy, and reduced matrix protease expression [28,29], ultimately leading to reduced LA function and increased LA pressure. Therefore, solely evaluating the LA size is inadequate for determining the severity of MR, and the assessment of LA function is crucial.

Left atrial reservoir function is influenced by LV contractility and LA compliance. In MMVD, LV contractility often increases in response to volume loading according to Frank-Starling's law [30]. Thus, in dogs with MMVD, decreased reservoir function is likely influenced by decreased LA compliance. It has been reported that patients with MR with impaired reservoir function have more LA fibrosis and endocardial thickening [31], and the fact that LARR was better in dogs with preserved reservoir function in the present study suggests that fibrosis is less prevalent and reversible in these dogs.

Booster pump function is influenced by preload, afterload, and intrinsic LA contractility. In chronic MR, booster pump function is increased or maintained in response to an increased preload, following the Frank–Starling law. However, in advanced MR, booster pump function is diminished due to excessive preload (beyond the optimal Frank-Starling curve), afterload mismatch resulting from increased LV end-diastolic pressure, and reduced intrinsic LA contractility resulting from fibrosis and other cellular damage [10,32]. Patients with impaired booster pump function are considered to have more advanced LA damage than those with impaired reservoir function [32-36]. The findings of the present study indicate that the booster pump function index is more effective than the reservoir function index in identifying severe cases characterised by irreversible and extensive changes in the LA.

An additional key finding of this study was the difference in post-operative changes between LA size and functional indices. In the present study, the LA size decreased after MVP, with a further significant reduction at three months follow-up. Such gradual changes were also observed in humans [15, 22]. The main reason for the early reduction in LA size could be the improvement in volume overload associated with the disappearance or reduction of MR. On the other hand, PALS and PACS declined after surgery, but then reversed to improve. The postoperative reduction in

PALS and PACS could be attributed to the reduced preload with improved MR. Indeed, previous studies showed that PALS and PACS tended to be higher in MMVD stage B1 cases (median PALS, 32.7%; median PACS, 19.1%) than in normal small dogs (median PALS, 25.2%; median PACS, 14.9%), and the presence of MR may increase PACS and PALS [10,37]. In addition, the restriction of left atrial movement around the annulus due to annuloplasty, along with surgical manipulations such as LA incision and suturing, may have contributed to the decline in left atrial function in the early postoperative period. Thus, this study demonstrates that morphological and functional remodelling occur differently.

In humans, postoperative LA function is important because prolonged LA dysfunction may be linked to poor prognostic outcomes, including the onset of postoperative atrial fibrillation after coronary artery bypass graft surgery [38]. In the current study, baseline PALS and PACS were correlated with PALS and PACS at three months, while the baseline LA:Ao was not correlated. This indicates that the preoperative LA function indices are associated with postoperative functional reverse remodelling.

Limitation

This study had several limitations. First, it involved a small cohort consisting primarily of small dogs with a median weight of 3.8 kg. Additional research is needed to investigate LARR in medium and large dogs across diverse case groups. Secondly, this study focused solely on predicting early postoperative LARR. While this finding suggests that early surgical intervention with preserved LA function is beneficial for LARR, the long-term course of LARR and its correlation with the long-term prognosis require extensive research. Third, this study did not evaluate the prognostic value of an LA:Ao < 1.6 at three months postoperatively. The cutoff value for LARR should be determined in future research based on its relationship with prognosis. Fourth, The influence of the duration of mitral valve insufficiency on LARR was not assessed in this study. Accurately determining the duration of the time in all cases was challenging due to the nature of being a referral hospital. Fifth, left atrial size was evaluated exclusively using the LA:Ao due to retrospective nature of this study. Evaluating postoperative changes in left atrial size using left atrial diameter or volumetric methods may enable a more precise assessment of LARR. Finally, although 2DSTE has the advantage of angle independence, it requires high-quality echocardiographic movies that completely delineate the LA endocardium throughout the cardiac cycle. In this study, 10% (n = 6) of the cases yielded echocardiographic images that were inadequate for 2DSTE analysis. However, this may be challenging to implement in all clinical settings because of the need for high-quality image data for analysis.

Conclusion

Following MVP, LA size decreased in the early postoperative period and continued to diminish over a three months follow-up. A low PACS score proved to be the most reliable predictor of insufficient LARR. Further studies are required to determine the relationship between LARR, prognosis, and the optimal timing for surgical intervention.

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Conflict of Interest Statement

The authors do not have any conflicts of interest to disclose.

Footnotes

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d. Vivid E95, GE Health Care, Tokyo, Japan

e. 2D Cardiac Performance Analysis, TomTec Imaging System, Unterschleissheim, Germany

f. JMP version 13.0, SAS Institute Inc., Cary, NC, USA

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Table

Table 1. Clinical and echocardiographic characteristics of study population.

Age (years)	10 (9–12)
Sex (male/female)	16/21
Body weight (kg)	3.8 (3.1–5.8)
Pulmonary oedema (y/n)	23/14
ACVIM class (B2/C/D)	14/14/9
LA:Ao	2.41 (2.00–2.80)
FS (%)	51.1 (46.5–54.9)
LVIDDN	2.03 (1.87–2.28)
LVIDSN	0.98 (0.86–1.08)
E (cm/s)	122 (99–139)
A (cm/s)	91 (67–104)
E:A	1.26 (1.08–1.66)
Ao (cm/s)	109 (94–131)
PA (cm/s)	76 (66–92)
PALS (%)	33.6 (23.6–38.9)
PACS (%)	13.4 (9.0–17.6)

A: peak velocity of late transmitral flow; ACVIM: American College of Veterinary Internal Medicine; Ao: peak velocity of left ventricular outflow tract; E: peak velocity of early diastolic transmitral flow; E:A: ratio of E to A; FS: fractional shortening; LA:Ao: left atrial to aortic root ratio; LVIDDN: left ventricular internal dimension at end-diastole normalized to body weight; LVIDSN: left ventricular internal dimension at end-systole normalized to body weight ; PA: peak velocity of right ventricular out flow tract; PACS: peak atrial contractile strain; PALS: peak atrial longitudinal strain.

Date are reported as median and lower and upper quartile.

Table 2. Changes in echocardiographic variables after MVP.

	baseline	early postoperative	one month	three months
LA:Ao	2.41 (2.00–2.80)^{a}	1.68 (1.54–1.92)^{b}	1.54 (1.45–1.72)^{bc}	1.46 (1.34–1.63)^{c}
FS (%)	51.1 (46.5–54.9)^{a}	31.3 (25.5–37.7)^{b}	31.8 (26.6–41.1)^{b}	32.7 (28.2–40.5)^{b}
LVIDDN	2.03 (1.87–2.28)^{a}	1.60 (1.37–1.78)^{b}	1.61 (1.40–1.75)^{b}	1.54 (1.43–1.65)^{b}
LVIDSN	0.98 (0.86–1.08)	1.09 (0.83–1.18)	1.00 (0.79–1.12)	1.03 (0.84–1.15)
E (cm/s)	122 (99–139)^{a}	82 (72–95)^{b}	81 (71–88)^{b}	73 (64–84)^{b}
A (cm/s)	91 (67–104)^{ab}	85 (69–108)^{a}	94 (82–108)^{ab}	104 (89–119)^{b}
E:A	1.26 (1.08–1.70)^{a}	0.90 (0.80–1.17)^{b}	0.82 (0.75–0.92)^{b}	0.73 (0.61–0.84)^{c}
Ao (cm/s)	109 (94–131)^{ab}	114 (102–138)^{a}	114 (103–124)^{ab}	101 (90–111)^{b}
PA (cm/s)	76 (66–92)^{a}	98 (81–118)^{b}	96 (84–116)^{b}	81 (70–95)^{ac}
PALS (%)	33.6 (23.6–38.9)^{a}	20.8 (15.5–25.9)^{b}	20.7 (18.2–27.5)^{b}	24.2 (18.7–30.8)^{b}
PACS (%)	13.4 (9.0–17.6)^{ab}	10.5 (8.5–13.4)^{b}	13.3 (10.3–16.8)^{b}	16.4 (12.5–20.5)^{ac}

A: peak velocity of late transmitral flow; Ao: peak velocity of left ventricular outflow tract; E: peak velocity of early diastolic transmitral flow; E:A: ratio of E to A; FS: fractional shortening; LA:Ao: left atrial to aortic root ratio; LVIDDN: left ventricular internal dimension at end-diastole normalized to body weight; LVIDSN: left ventricular internal dimension at end-systole normalized to body weight ; MVP: mitral valvuloplasty; PA: peak velocity of right ventricular out flow tract; PACS; peak atrial contractile strain; PALS: peak atrial longitudinal strain.

Date are reported as median and lower and upper quartile.

Different letters indicate statistically significant differences according to the Steel-Dwass test ($P < 0.05$).

Table 3. Correlation between baseline variables and LA size and function indices at three months.

	LA:Ao at three months		PALS at three months		PACS at three months	
	P	ρ	P	ρ	P	ρ
Age	0.602		0.534		0.342	
Body Weight	0.425		0.265		0.220	
ACC	0.856		0.784		0.538	
CBP	0.874		0.958		0.988	
LA:Ao	0.002	0.485	0.855		0.660	
FS	0.791		0.776		0.886	
LVIDDN	0.073		0.489		0.523	
LVIDSN	0.310		0.859		0.784	
E	0.339		0.576		0.512	
A	0.339		0.341		0.086	
E:A	0.560		0.803		0.493	
Ao	0.519		0.998		0.807	
PA	0.823		0.423		0.585	
PALS	< 0.001	-0.543	0.002	0.504	< 0.001	0.563
PACS	< 0.001	-0.546	0.001	0.514	< 0.001	0.529

A: peak velocity of late transmitral flow; ACC: aortic cross clamp time; Ao: peak velocity of left ventricular outflow tract; CBP: cardiopulmonary bypass time; E: peak velocity of early diastolic transmitral flow; E:A: ratio of E to A; FS: fractional shortening; LA:Ao: left atrial to the aortic root ratio; LVIDDN: left ventricular internal dimension at end-diastole normalized to body weight; LVIDSN: left ventricular internal dimension at end-systole normalized to body weight ; PA: peak velocity of right ventricular out flow tract; PACS: peak atrial contraction strain; PALS: peak atrial longitudinal strain.

Table 4 . Results of simple linear regression analyses for prediction of LA:Ao at three months from preoperative left atrial size and function indices in 37 dogs.

Variable	R^2	P	Regression Equation
preoperative LA:Ao	0.26	0.001	LA:Ao at three months = (0.2843 × preoperative LA:Ao) + 0.8156
preoperative PALS	0.32	< 0.001	LA:Ao at three months = (-0.014 × preoperative PALS) + 1.954
preoperative PACS	0.28	< 0.001	LA:Ao at three months = (-0.021 × preoperative PACS) + 1.799

LA:Ao: left atrial to the aortic root ratio; PACS: peak atrial contraction strain; PALS: peak atrial longitudinal strain; R^2: coefficient of determination

Table 5. Clinical and echocardiographic variable of LARR and non-LARR group at baseline.

	LARR (n=27)	non-LARR (n=10)	P
Age (years)	10 (9–12)	12 (9–12)	0.476
Sex (male/female)	12/15	4/6	1.000
Body weight (kg)	3.7 (3.1–5.2)	4.5 (3.1–6.5)	0.451
ACVIM class			0.245
B2	12 (44.4%)	2 (20%)	
C	9 (33.3%)	3 (30%)	
D	6 (22.2%)	5 (50%)	
Pulmonary oedema (yes/no)	15/12	8/2	0.260
Medicine (Preoperative)			
ACE inhibitor	20 (74.0%)	9 (90%)	0.404
Pimobendan	26 (96.3%)	10 (100%)	1.000
Loop Diuretics	20 (74%)	10 (100%)	0.155
Spironolactone	14 (51.8%)	6 (60%)	0.726
Amlodipine	18 (66.6%)	10 (100%)	0.079
Medication (three months after MVP)			
ACE inhibitor	0	0	1.000
Pimobendan	0	2	0.068
Loop diuretics	0	0	1.000
Spironolactone	0	0	1.000
Amlodipine	0	0	1.000
Surgery			1.000
ACC	106 (96–118)	111 (103–123)	0.374
CPB	150 (140–161)	155 (136–176)	0.533
Echocardiography			
LA:Ao*	2.32 (1.97–2.69)	2.71 (2.50–3.05)	0.008
FS (%)	50.9 (46.6–54.7)	51.9 (45.8–59.2)	0.694
LVIDDN	2.03 (1.82–2.17)	2.23 (1.96–2.40)	0.151
LVIDSN	0.97 (0.89–1.06)	1.02 (0.80–1.18)	0.707
E (cm/s)	123 (98–137)	119 (104–142)	0.837
A (cm/s)	93 (70–104)	91 (62–104)	0.701
E:A	1.25 (1.08–1.70)	1.28 (1.10–1.92)	0.927
Ao (cm/s)	109 (93–132)	108 (97–134)	0.959

PA (cm/s)	78 (66–91)	76 (65–105)	0.707
PALS (%)*	35.0 (30.8–40.7)	24.0 (15.1–32.1)	0.008
PACS (%)*	13.8 (11.1–19.6)	7.8 (6.5–11.5)	0.002

A: peak velocity of late transmitral flow; ACC: aortic cross clamp time; ACE: angiotensin-converting enzyme; ACVIM: American College of Veterinary Medicine; Ao: peak velocity of left ventricular outflow tract; CBP: cardiopulmonary bypass time; E: peak velocity of early diastolic transmitral flow; E:A: ratio of E to A; FS: fractional shortening; LAAR: left atrial reverse remodelling; LA:Ao: left atrial to aortic root ratio; LVIDDN: left ventricular internal dimension at end-diastole normalized to body weight; LVIDSN: left ventricular internal dimension at end-systole normalized to body weight ; MVP: mitral valvuloplasty; PA: peak velocity of right ventricular out flow tract; PACS: peak atrial contraction strain; PALS: peak atrial longitudinal strain.

Date are reported as median and lower and upper quartile.

*Value between LARR and non-LARR differed significantly (P < 0.05).

Table 6. AUC and optimal diagnostic cutoffs between LARR and non-LARR.

	Cutoff	AUC	Sensitivity	Specificity
PACS	10.0	0.837	0.80	0.85
PALS	30.8	0.789	0.80	0.74
LA:Ao	2.53	0.789	0.80	0.70

AUC: area under the receiver operating characteristic curve; LA:Ao: left atrial-to-aortic root ratio; LAAR: left atrial reverse remodelling; PACS: peak atrial contraction strain; PALS: peak atrial longitudinal strain.

Table 7. Binary logistic regression analysis of LARR three months after MVP

	Univariate analysis			Multivariate analysis		
Variable	OR	95%CI	P	OR	95% CI	P
LA:Ao	15.824	2.190-200.8	0.014			
PALS	0.877	0.794-0.967	0.009			
PACS	0.740	0.585-0.935	0.012	0.760	0.595-0.970	0.008

CI: confidence interval; LAAR: left atrial reverse remodelling; LA:Ao: left atrial to aortic root ratio; MVP: mitral valvuloplasty; OR: odds ratio; PACS: peak atrial contraction strain; PALS: peak atrial longitudinal strain.

Figure legends

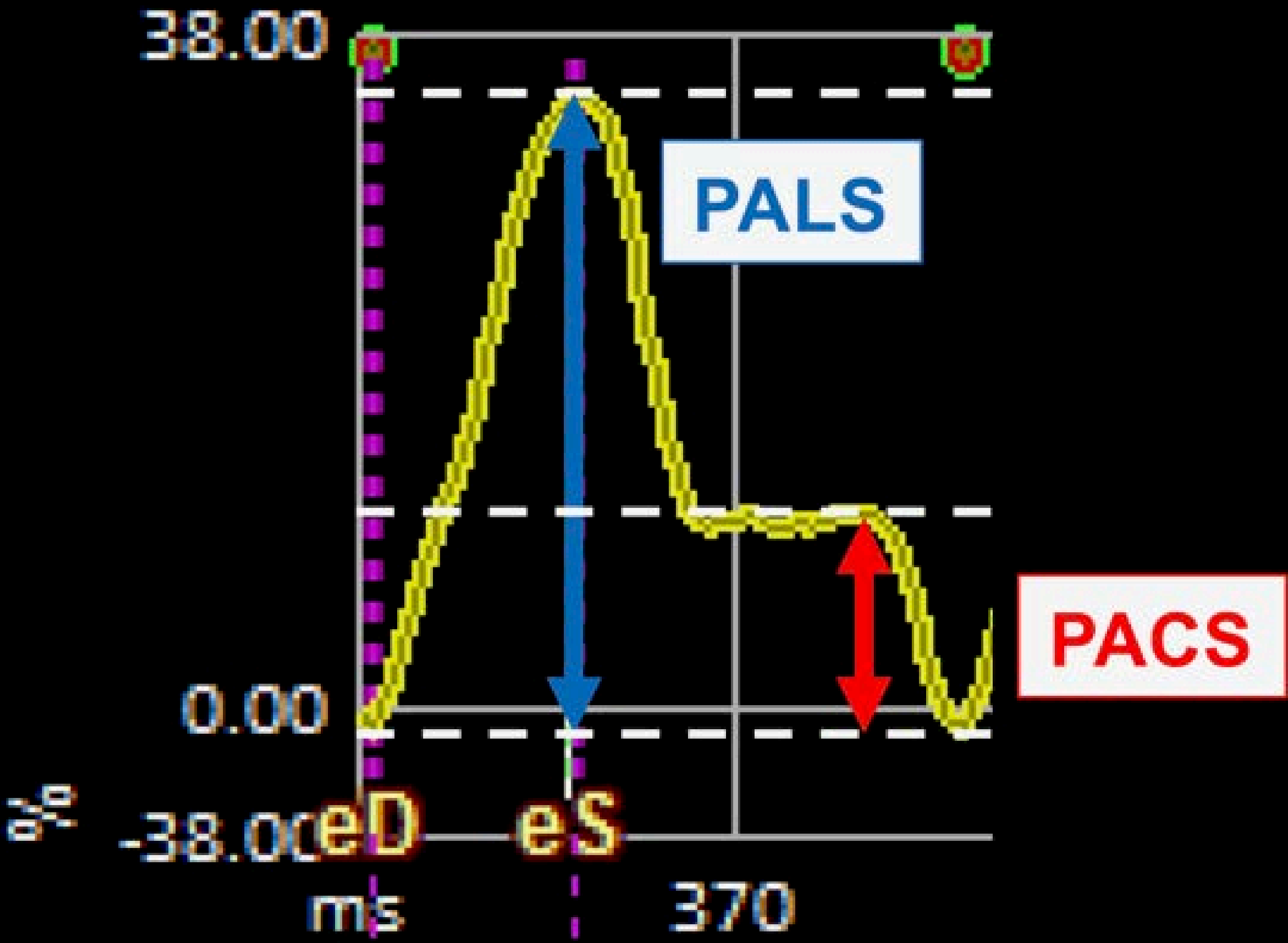
Figure 1: Left atrial strain curves from. Strain at the end of LA systole was established as the zero-reference value. The reservoir function of the left atrium is assessed with the first peak positive strain (PALS), and the contractile function is assessed with the second peak positive strain (PACS). PACS: peak atrial contraction strain; PALS: peak atrial longitudinal strain.

Figure 2: Time course change of LA:Ao (A), PALS (B), and PACS (C) at baseline (T0), in the early postoperative period (T1), and at one and three months (T2 and T3). Data are displayed as the median and lower and upper quartile (whiskers). Different letters indicate statistically significant differences according to Steel-Dwass test ($P < 0.05$). LA:Ao: left atrial to aortic root ratio; PACS: peak atrial contraction strain; PALS: peak atrial longitudinal strain.

Figure 3: Scatter plots illustrating significant correlations between LA:Ao at three months after MVP and preoperative LA:Ao (A), PALS (B), PACS(C). LA:Ao: left atrial to aortic root ratio; MVP: mitral valvuloplasty; PACS: peak atrial contraction strain; PALS: peak atrial longitudinal strain.

Figure 4: Box plot graphics representing LA:Ao (A), PALS (B), PACS (C) in the LARR and non-LARR groups at baseline. Box plot indicates the median and lower and upper quartile; whiskers depict the range of distribution. Asterisk represents a significant difference according to Kruskal Wallis test ($P < 0.05$). LA:Ao: left atrial to aortic root ratio; LARR: left

atrial reverse remodelling; PACS: peak atrial contraction strain; PALS: peak atrial longitudinal strain.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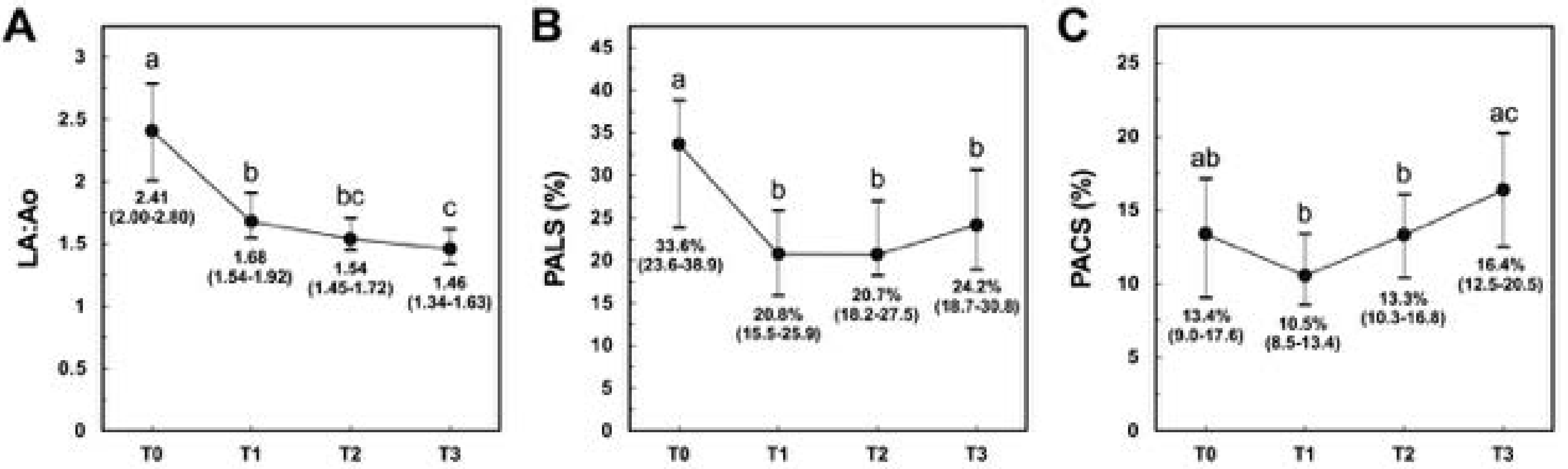
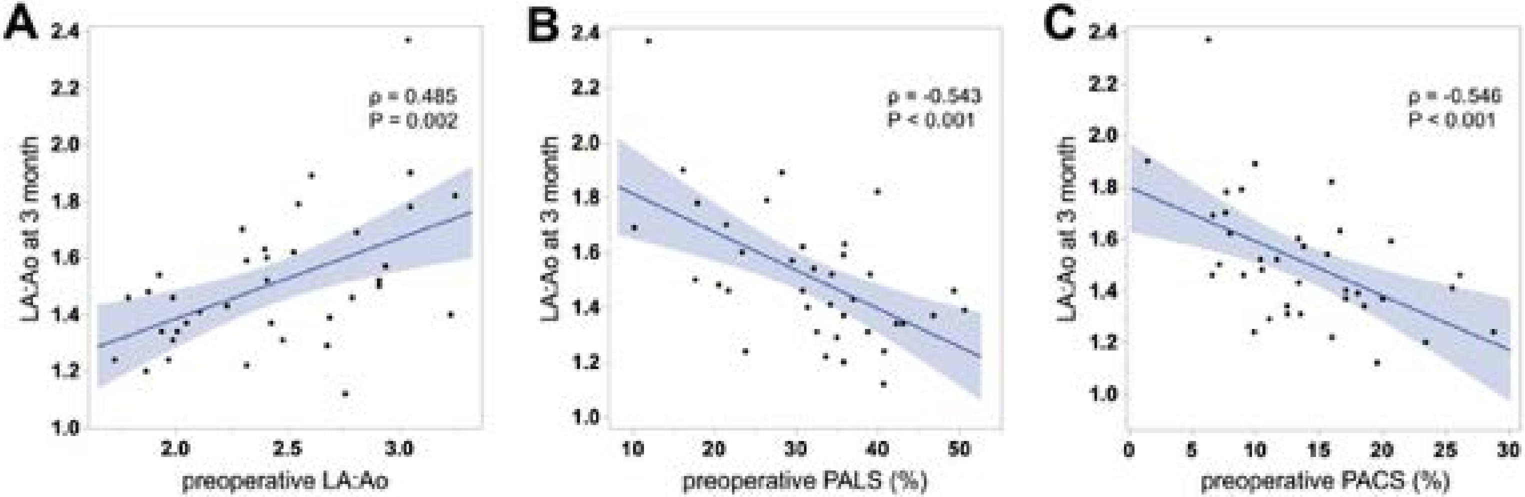
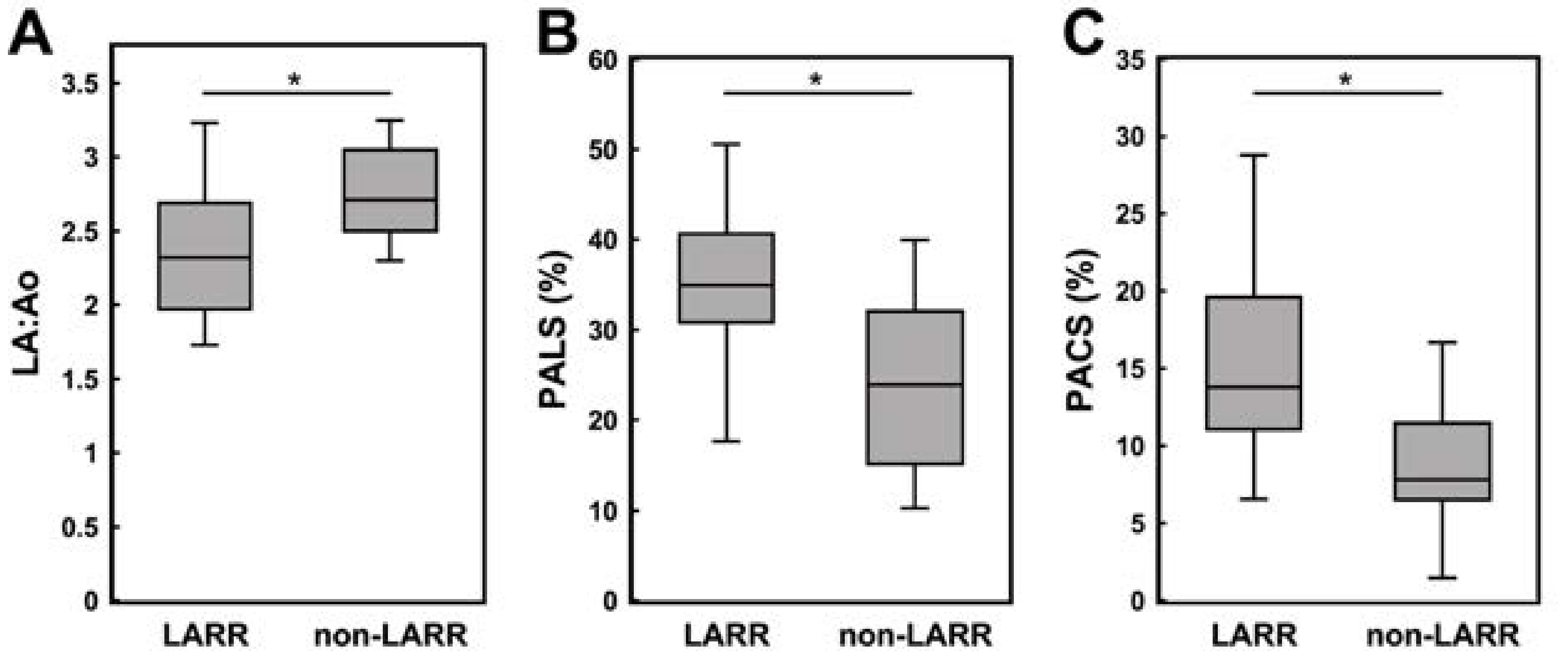
PACS
0.00
%
-38.00
eD
eS
ms
370


A
LA:Ao
a
2.41
(2.00-2.80)
b
1.68
(1.54-1.92)
bc
1.54
(1.45-1.72)
c
1.46
(1.34-1.63)
T0
T1
T2
T3
B
PALS (%)
a
33.6%
(23.6-38.9)
b
20.8%
(15.5-25.9)
b
20.7%
(18.2-27.5)
b
24.2%
(18.7-30.8)
C
PACS (%)
ab
13.4%
(9.0-17.6)
b
10.5%
(8.5-13.4)
b
13.3%
(10.3-16.8)
ac
16.4%
(12.5-20.5)


A
B
C
ρ = 0.485
P = 0.002
ρ = -0.543
P < 0.001
ρ = -0.546
P < 0.001
LA:Ao at 3 month
preoperative LA:Ao
preoperative PALS (%)
preoperative PACS (%)


A
B
C
LA:Ao
PALS (%)
PACS (%)
*
0
0.5
1
1.5
2
2.5
3
3.5
0
10
20
30
40
50
60
0
5
10
15
20
25
30
35
LARR
non-LARR
LARR
non-LARR
LARR
non-LARR