A Clinical Study on Left Atrial Reverse Remodelling after Mitral Valvulo*p*lasty for Myxomatous Mitral Valve Disease in Dogs

(犬の粘液腫様僧帽弁疾患に対する僧帽弁形成術後の左房リバースリモデリングに関する臨床研究)

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CONTENTS

ABBREVIATIONS

2DSTE	two-dimensional speckle tracking echocardiography
A	peak velocity of late transmitral flow
Ao	peak velocity of left ventricular outflow tract
ACC	aortic cross clamp/aortic cross clamp time
ACE	angiotensin-converting enzyme
ACVIM	American College of Veterinary Internal Medicine
ACC	aortic cross clamp/aortic cross clamp time
AUC	area under the receiver-operating characteristic curve
CI	confidence interval
E	peak velocity of early diastolic transmitral flow
E/A	ratio of E to A
CPB	cardiopulmonary bypass/cardiopulmonary bypass time
LA	left atrial/atrium
LARR	left atrial reverse remodelling
LA/Ao	left atrial-to-aortic root ratio
LV	left ventricle
LVIDDN	left ventricular internal dimension at end-diastole normalized to body weight
LVIDDS	left ventricular internal dimension at end-systole normalized to body weight
MMVD	myxomatous mitral valve disease
MR	mitral regurgitation
MVP	mitral valvuloplasty
OR	odds ratio
PA	peak velocity of right ventricular out flow tract
PACS	peak atrial contraction strain
PALS	peak atrial longitudinal strain
R^2	coefficient of determination

ROC receiver-operating characteristic

NOTES (学位関連論文および各章との関連)

1. Kawamoto S, Nakamura K, Mori T, Wada T, Fujiwara A, Takiguchi M. Pre-operative left atrial size and functions are predictors of left atrial reverse remodelling after mitral valvuloplasty for myxomatous mitral valve disease in dogs. J Vet Cardiol 2024;57:47-57.

Relevance to Each Chapter: Corresponds to Chapters 1 and 2

GENERAL 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.

With the above background, we conducted two studies with the aim of clarifying the indications for MVP by observing the process of LARR in dogs after MVP and clarifying its predictive factors. In the first study, the postoperative changes in echocardiographic parameters such as left atrial size and functional indices was examined in dogs with MMVD after MVP. In the second study, I examined whether preoperative left atrial size and functional indices could be predictive factors for LARR after MVP.

CHAPTER 1

THREE MONTHS COURSE OF STRUCTUAL AND FUNCTIONAL REVERSE REMODELLING OF LEFT ATRIUM AFTER MITRAL VALVULOPLASTY FOR MYXOMATOUS MITRAL VALVE DISEASE IN DOGS

1. INTRODUCTION

Various factors that affect the left atrium, such as mitral regurgitation, atrial fibrillation, obesity, hypertension, and left ventricular diastolic dysfunction, can lead to left atrial enlargement and functional decline. These changes were referred to as left atrial remodelling. Conversely, reducing these factors can improve the structure and function of the left atrium. These changes were known as left atrial reverse remodelling. After Mitral valve surgery for human patients with mitral regurgitation, left atrial size and pressure are immediately decreased to some extent, leading to an improvement in left atrial fibrosis and myocardial remodelling. As a result, the size and function of the left atrium gradually improve further [13,14]. However, the left atrial size and function is not completely normalized in some patients. It is known that 16-34% of cases exhibit inadequate LARR after mitral valve surgery for mitral regurgitation in humans [11,14,15]. Furthermore, such inadequate LARR has been identified as a poor prognostic factor associated with the onset of stroke and atrial fibrillation. Therefore, predicting inadequate LARR is important for selecting appropriate cases for surgery.

In recent years, MVP for MMVD in dogs has been widely performed in Japan [16-18]. Although these reports have indicated that the left atrial size decreases after surgery, little is known about the process of LARR and the frequency of inadequate LARR.

The objective of Chapter 1 is to investigate early changes in left atrial size and function after MVP for MMVD in dogs, and to identify cases that exhibit insufficient LARR.

2. MATERIALS AND METHODS

2.1 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, history of pulmonary oedema, American College of Veterinary Internal Medicine (ACVIM) class, and treatment were collected from medical records.

2.2 Surgery

Surgery was performed through left fifth intercostal thoracotomy. Hypothermic cardiopulmonary bypass (CBP) 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.

2.3 Echocardiography

Echocardiographic examinations were conducted proficient sonographers utilizing a Vivid E95 (GE Healthcare Japan) 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 1, 3 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]. LV 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. LV 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]. LV 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.

2.4 Speckle tracking echocardiography

LA strain measurements were conducted offline by a sole examiner using vendor-independent 2D Speckle Tracking software (2D Cardiac Performance Analysis; TomTec Imaging System, Munich, Germany). 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. LA 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. LA 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.

2.5 Statistical analysis

Measurements are presented as median and lower and upper quartiles. Multiple comparisons of continuous variables at baseline, early postoperative period, 1, 3 months were performed using the Steel-Dwass test. Statistical analyses were performed using JMP version 13.0 (SAS Institute Inc., Cary, NC, USA). A two-sided P-value < 0.05 was considered significant.

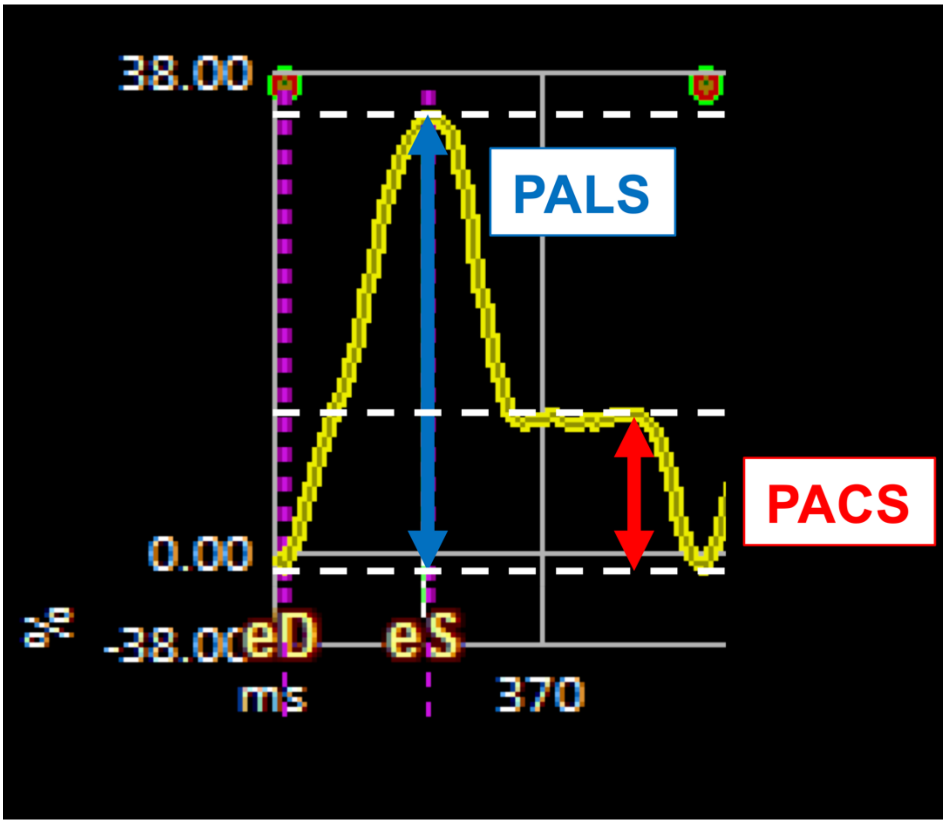

Figure 1: Left atrial strain curves from. Strain at the end of LA systole was established as the zero-reference value. The reservoir function of the left atrium is assessed with the first peak positive strain (PALS), and the contractile function is assessed with the second peak positive strain (PACS).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

3. RESULTS

<u>3.1 Animals</u>

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 lost to follow-up, six for poor echocardiographic window, six for death due to postoperative complications, three for residual MR at 1 or 3 months, two for pre- and postoperative arrhythmias, and one for severe postoperative LV dysfunction. The severity of residual MR was determined by calculating the proportion of the regurgitant jet area to the left atrial area using color Doppler, and moderate or greater regurgitation was defined as exceeding 20%. 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.

<u>3.2 The 3 months course of LARR after MVP</u>

The echocardiographic indices from baseline to 3-month follow-up are presented in Table 2. LA/Ao began to decrease significantly in the early postoperative period and continued to decrease for 3 months (Figure 2A). PALS also decreased in the early postoperative period but tended to increase at 3 months (Figure 2B). PACS showed a non-significant tendency to decrease in the early postoperative period, but then reversed and showed a significant increase at 3 months (Figure 2C). Out of 37 cases, 27 (73.0%) showed a decrease in LA/Ao to less than 1.6.

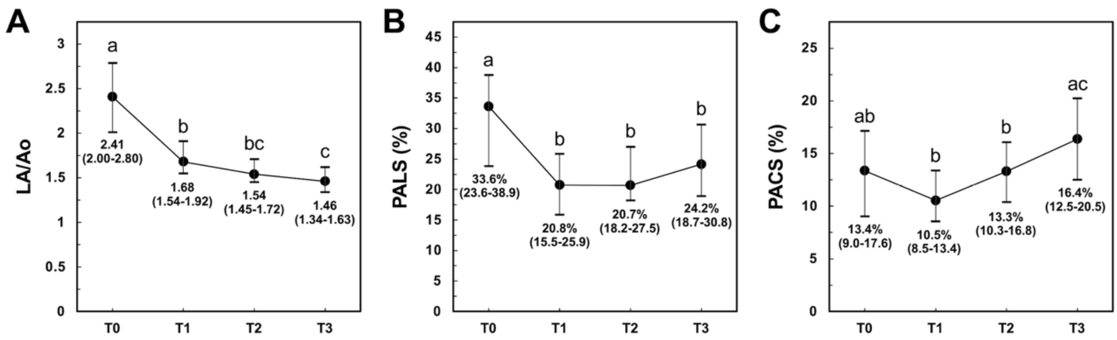

Figure 2: Time course change of LA/Ao (A), PALS (B), and PACS (C) at baseline (T0), in the early postoperative period (T1), and at 1 and 3 months (T2 and T3). Data are displayed as the median value, with 25th and 75th percentiles (whiskers). Different letters indicate statistically significant differences 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.

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.

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.

Value with different superscript letters indicate statistically significant differences according to the Steel-Dwass test ($P < 0.05$).

4. DISCUSSION

In the present study, 73% of the dogs with MMVD achieved LARR 3 months after MVP. In humans, inadequate LARR has been identified as a poor prognostic factor for atrial fibrillation, stroke, and all-cause mortality [15,21]. Factors associated with LARR after mitral valve surgery include the preoperative LA volume index, preoperative reservoir function index, postoperative mitral stenosis, and postoperative MR severity in humans [15, 22]. In the present study, no patient developed post-surgical mitral stenosis, and patients with postoperative moderate MR were excluded. Therefore, the LARR observed in this study is considered to purely reflect the process of improvement in left atrial volume overload.

In the present study, the LA/Ao decreased immediately after MVP, with a further significant reduction at 3 months follow-up. This sequential process of LARR has also been 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. The subsequent process of LARR was accompanied by improvement of left atrial function. Left atrial function has been reported to be associated with pathological changes, such as fibrosis and endocardial thickening in human [23]. In the present study, the improvement in left atrial functional indices observed during the three-month LARR process suggests the potential amelioration of these pathological changes.

On the other hand, PALS and PACS declined immediately after surgery, but then reversed to improve. The immediate 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 [10,24]. 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.

A few limitations were present in the current study. 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. The long-term course of LARR and its correlation with the long-term prognosis require extensive research. Third, 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.

5. SUMMARY

In this chapter, the 3 months course of LARR after MVP were investigated. In the process of LARR, the left atrial size shows a rapid reduction within the first two weeks postoperatively, with the reduction continuing over three months. On the other hand, the reservoir function and booster pump function decrease immediately after surgery, they tend to improve over the subsequent three months. After MVP for MMVD in dogs, structural and functional reverse remodelling follow different courses, with insufficient structural LARR observed in about 27% of cases.

CHAPTER 2

PREDICTORS OF LEFT ATRIAL REVERSE REMO DELLING AFTER MITRAL VALVULOPLASTY FOR MYXOMATOUS MITRAL VALVE DISEASE IN DOGS

1. INTRODUCTION

After mitral valvuloplasty, the reduction in left atrial volume and pressure overload leads to reverse remodelling of the left atrium, resulting in a decrease in left atrial size compared to preoperative measurements. In humans, postoperative inadequate LARR as a larger left atrial volume have been reported to be associated with postoperative outcomes such as atrial fibrillation (AF) and stroke [15]. Therefore, predicting postoperative LARR is considered clinically useful, and it has been reported that inadequate LARR is related to preoperative left atrial volume [22], left atrial function [25], residual mitral regurgitation (MR), and mitral valve stenosis postoperatively in human [15].

In the previous chapter, I have demonstrated the time course change of left atrial size and functions in dogs after MVP, and inadequate LARR was observed in 27% of the cases.

In Chapter 2, I aim to determine whether preoperative signalment and echocardiographic indices could predict LARR. I hypothesize that preoperative left atrial size and functional indices can predict postoperative LARR. Among these, I also hypothesize that left atrial functional indices, especially booster pump function, are excellent predictors.

2. MATERIALS AND METHODS

2.1 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, history of pulmonary oedema, ACVIM class, and treatment were collected from medical records.

2.2 Surgery

MVP was carried out in accordance with the methods described in Chapter 1. The duration of CBP and aortic cross-clamp (ACC) was documented.

2.3 Echocardiography

Echocardiography was carried out in accordance with the methods described in Chapter 1.

2.4 Speckle tracking echocardiography

Speckle tracking echocardiography was carried out in accordance with the methods described in Chapter 1.

2.5 Statistical analysis

Measurements are presented as median and lower and upper quartiles. The relationships between different measurements were assessed using Spearman's correlation analysis. Spearman's rank correlation coefficient, denoted by ρ, measures the strength and direction of an association between two variables. ρ can take values from +1 to -1. A ρ of +1 indicates a perfect association and -1 indicates a perfect negative association. The closer ρ approaches zero, the weaker the association becomes. Simple linear logistic regression analyses were used to predict LA/Ao at 3 months after MVP from preoperative left atrial size and functional indices. LARR was defined as achieving LA/Ao < 1.6 at 3 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 (ROC) curves and the area under each ROC curve (AUC) 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 JMP version 13.0 (SAS Institute Inc., Cary, NC, USA). A two-sided P-value < 0.05 was considered significant.

3. RESULTS

3.1 The relationship between left atrial size and function and preoperative indices

The correlations between LA size and function at 3 months and baseline echocardiographic indices are presented in Table 3. LA/Ao at 3 months demonstrated a significant correlation with baseline LA/Ao (ρ = 0.485, *P* = 0.002), PALS (ρ = -0.543, *P* < 0.001) and PACS (ρ = -0.546, *P* < 0.001) respectively (Figure 3). PALS at 3 months significantly correlated with baseline PALS (ρ = 0.504, *P* = 0.002) and PACS (ρ = 0.514, *P* = 0.001). PACS at 3 months was significantly 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.

3.2 Prediction of left atrial size

Predictive equations for LA/Ao at 3 month after MVP derived from indices of preoperative left atrial size and function indices are presented in Table 4.

3.3 Differences in preoperative indices based on the achievement of LARR at 3 months

The clinical and echocardiographic indices of the LARR and non-LARR groups are presented in Table 5. LARR was achieved in 73% (27/37) of cases at 3 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). ROC analysis showed that the baseline PACS had the highest AUC for discriminating between the LARR and non-LARR groups (Table 6).

3.4 Predictors for the achievement of LARR at 3 months

Univariate logistic regression analysis showed that LA/Ao, PALS, and PACS were significantly related to LARR at 3 months after MVP. Subsequently, multivariate logistic regression analysis identified PACS as the only independent correlate (P = 0.008, odds ratio 0.760 [95% CI 0.595–0.970]) (Table 7).

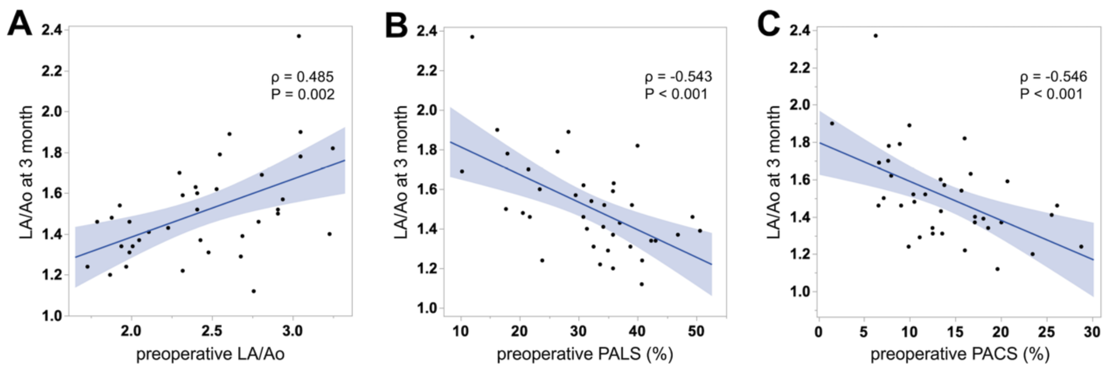

Figure 3: Scatter plots illustrating significant correlations between LA/Ao at 3 months after MVP and preoperative LA/Ao (A), PALS (B), PACS(C). LA/Ao: left atrial-to-aortic root ratio; MVP: mitral valvuloplasty; PACS: peak atrial contraction strain; PALS: peak atrial longitudinal strain.

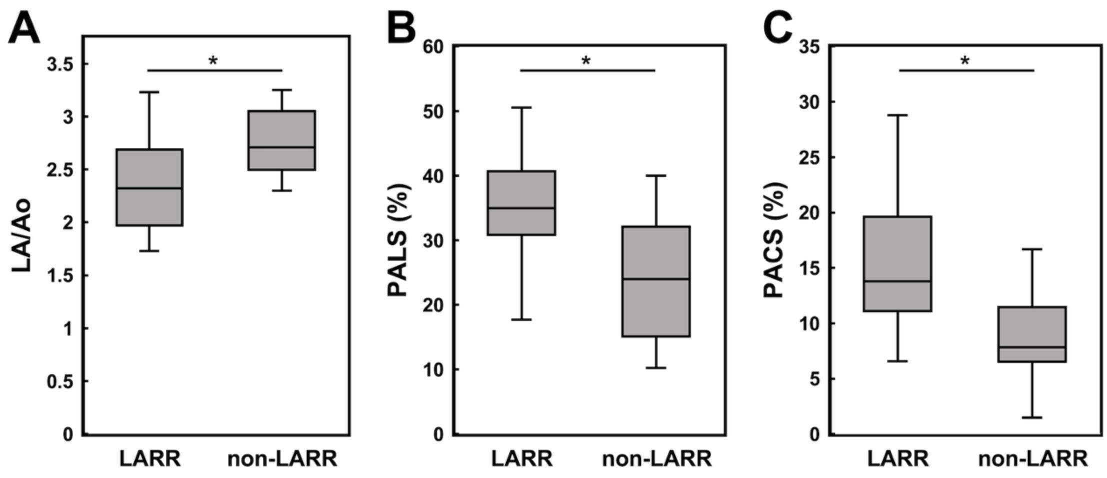

Figure 4: Box plot graphics representing LA/Ao (A), PALS (B), PACS (C) in the LARR and non-LARR groups at baseline. Box plot indicates the median value, and the 25th and 75th percentiles; whiskers depict the range of distribution. Asterisk represents a significant difference according to Kruskal Wallis 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.

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

	LA/Ao at 3 months		PALS at 3 months		PACS at 3 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	
CPB	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: left atrial; 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 contraction strain; PALS: peak atrial longitudinal strain.

Table 4. Results of simple linear regression analyses for prediction of LA/Ao at 3 month 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 3 months = (0.2843 × preoperative LA/Ao) + 0.8156
preoperative PALS	0.32	< 0.001	LA/Ao at 3 months = (-0.014 × preoperative PALS) + 1.954
preoperative PACS	0.28	< 0.001	LA/Ao at 3 months = (-0.021 × preoperative PACS) + 1.799

LA/Ao: left atrial-to-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 groups at the 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	1.00
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
Medication (Preoperative)			
ACE inhibitor	20 (74.0%)	9 (90%)	0.404
Pimobendan	26 (96.3%)	10 (100%)	1.00
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 (3 months after MVP)			
ACE inhibitor	0	0	1.00
Pimobendan	0	2	0.068
Loop diuretics	0	0	1.00
Spironolactone	0	0	1.00
Amlodipine	0	0	1.00
Surgery			1.00
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.

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

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

	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 3 month after MVP.

	Univariate analysis			Multivariate analysis		
	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.

4. DISCUSSION

Inadequate LARR has been identified as a poor prognostic factor for atrial fibrillation, stroke, and all-cause mortality in humans [15,21]. Therefore, predicting postoperative LARR from preoperative indices holds clinical significance. Factors associated with LARR after mitral valve surgery include the preoperative LA volume index [22], preoperative reservoir function index [25], 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. Therefore, it was possible to evaluate the relationship between preoperative echocardiographic indices and LARR without being influenced by surgical confounding factors. 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 3 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 [26-28]. 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]. LA 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 [29]. However, severe, long-lasting volume overload in the LA results in interstitial fibrosis, endocardial thickening, chronic inflammation, myocyte hypertrophy, and reduced matrix protease expression [30, 31], 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 [32]. 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 [33], 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 [10,34]. Patients with impaired booster pump function are considered to have more advanced LA damage than those with impaired reservoir function [34-38]. 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.

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 [39]. In the current study, baseline PALS and PACS were correlated with PALS and PACS at 3 months, while the baseline LA/Ao was not correlated.

This study had several limitations. Firstly, the sample was obtained from a single facility, and the sample size is small. Secondly, the most cases included in this study were small-breed dogs. Further studies are needed to identify the predictors of LARR in medium and large-breed dogs. Thirdly, 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. Forthly, 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. However, it is important to note that LA/Ao, which is widely used clinically, can capture structural reverse remodelling. Lastly, this study lacks pathological confirmation. While there are reports suggesting that mild fibrosis can improve, it may also be irreversible. Further research is needed to confirm the histological changes that occur during the structural and functional reverse remodelling process observed in this study.

In conclusion, preoperative left atrial size and functional indices obtained by 2DSTE were useful indicators associated with LARR after MVP. Among these, PACS, an indicator of booster pump function, was particularly useful for detecting LARR with high accuracy. Additional research is needed to investigate the impact of LARR on prognosis after MVP.

5. SUMMARY

In this chapter, I investigated the predictors of LARR at three months postoperatively. It was revealed that LA/Ao, PALS, and PACS were all associated with LARR and were effective in predicting left atrial size and identifying inadequate LARR at three months postoperatively. Furthermore, PACS, a marker of booster pump function, is strongly correlated with LARR after MVP in dogs. Assessing the left atrial function can provide further insights into the detecting LARR after MVP.

GENERAL CONCLUSION

In Chapter 1, I evaluated the changes in echocardiographic indices after MVP in dogs with MMVD. In addition to traditional echocardiographic indices, I assessed left atrial function using LA strain evaluated by 2DSTE. The study revealed that LA/Ao, the left atrial size index, rapidly decreased during the early postoperative period and continued to gradually decrease over the subsequent 3 months. However, in approximately 27% of the cases, LA/Ao remained outside the normal range at 3 months postoperatively. Regarding the functional change of LA, the reservoir function index (PALS) and booster pump function index (PACS) showed a tendency to decrease in the early postoperative period, followed by an improvement trend over the subsequent 3 months. This study clarified the short-term left atrial reverse remodelling process after the improvement of volume overload and highlighted the presence of cases with inadequate LARR.

In Chapter 2, I investigated the relationship between preoperative echocardiographic indices and post operative LARR. A significant correlation was found between LA/Ao at 3 months after MVP and preoperative LA/Ao, PALS, and PACS. Next, I divided the cases into two groups based on the presence of postoperative LARR and evaluated the relationship between LARR and the preoperative indices. It was found that cases with inadequate LARR had higher preoperative LA/Ao and lower PALS and PACS. Univariate logistic regression analysis revealed that these factors were predictive of inadequate LARR. Among them, PACS was independently significant and had the highest predictive accuracy for inadequate LARR (AUC 0.837, sensitivity 80%, specificity 85%).

In conclusion, this study clarified the process of LARR and the factors related to LARR after MVP in dogs with MMVD. Both left atrial size and functional indices were associated with postoperative LARR and were predictors of LARR. Among them, PACS was the best predictor of LARR. Additional research is needed to investigate the impact of LARR on prognosis after MVP.

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JAPANESE SUMMARY

本研究の目的は、犬の MMVD に対する MVP 後の LARR に術前の心疾患の重症度が関連するという仮説のもと、術前の心エコー図検査指標と LARR との関連を明らかにすることであった。そこで、MMVD に対する MVP を実施した臨床犬を用いて、第 1 章では MMVD に対する MVP 後の構造的・機能的 LARR の過程について、第 2 章では術前の各指標が LARR に与える影響について検討した。

第 1 章では、 犬の MMVD に対する MVP 後の各心エコー図検査指標の変化を評価した。従来の心エコー図検査指標に加えて、2DSTE を用いて評価した LA strain をもとに左心房機能解析を実施した。構造的 LARR の過程についての検討において、左心房サイズ指標である LA/Ao は、術後早期に迅速に低下し、その後 3 ヶ月かけて緩やかに低下することが明らかとなったが、約 27%の症例において術後 3 ヶ月の LA/Ao は正常値を逸脱した。機能的 LARR の過程についての検討において、リザーバー機能指標である PALS およびブースターポンプ機能指標である PACS は術後早期に低下傾向を認め、その後 3 ヶ月かけて改善傾向を示すことが明らかとなった。このように、容量過負荷が改善した後の短期的な LARR を明らかにしたと同時に、不十分な LARR を呈する症例の存在が明らかとなった。

第 2 章では、術前のシグナルメントや心エコー図検査指標と LARR が関

連するかどうかを検討した。術後３ヶ月後の LA/Ao と術前の LA/Ao、 PALS、PACS との相関が認められ、直線的な関連を示すことが明らかとなった。次に、MVP 後３ヶ月の時点において LA/Ao が正常値まで改善したかどうかで 2 群に分け、不十分な LARR と術前の心疾患の重症度との関連を評価した。まず、不十分な LARR を呈した症例において、術前の LA/Ao が高く、PALS および PACS が低いことが明らかとなり、単変量ロジスティック回帰分析の結果これらの因子は全て不十分な LARR の予測因子であることが明らかとなった。なかでもブースターポンプ機能指標である PACS は、他の指標と独立して有意に不十分な LARR を予測することが可能であり、その予測精度が最も高いことが明らかとなった (AUC 0.837、感度 80%、特異度 85%）。

今後の研究課題としては、より多くの症例において、より長期的な LARR の過程を評価すべきと考えられた。また、今回用いた単純な左房径のみの評価ではなく、２次元または３次元的な volumetric な指標や機能指標を用いてより正確に術前の重症度を評価していく必要があると考えられた。さらに今後は、線維化や心内膜肥厚といった組織学的変化と術前の構造的・機能的リモデリングとの関連や、組織学的変化の重症度と LARR との関連の評価を行っていく予定である。

本研究を通して、犬の MMVD に対する MVP 後の LARR の過程と、LARR に関連する因子が明らかとなった。左心房サイズ指標および機能指標はいずれ

も術後 LARR と関連し、不十分な LARR の予測因子であることが明らかとなった。特に PACS は、他の因子と独立して、最も高い精度で不十分な LARR を検出することができる優れた指標であった。本研究より、MMVD に対する MVP 前の検査指標として２DSTE による左房機能評価が有用である可能性が示唆された。