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ORIGINAL ARTICLE

Reverse remodeling of mitral leaflets after medical treatment in recent-onset dilated cardiomyopathy

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Abstract

Background: *The growth of mitral leaflets (MLs) adaptive to left ventricluar (LV) remodeling has been observed. However, the elasticity of MLs upon mechanical stimuli would be supposed if it shrinks with LV reverse remodeling (LVRR).*

Material and methods: *Patients with idiopathic recent-onset dilated cardiomyopathy (RODCM) (n = 82) and 50 matched normal controls (NC) were prospectively enrolled. Echocardiography was performed at baseline and 6 months of follow-up for the anterior and posterior mitral leaflet (AML and PML) length, mitral annular dimension (MAD), and tenting height (TH). LVRR was measured as a ≥ 15% reduction in LV end-diastolic volume (LVEDV).*

Results: *After 6 months, LVRR was achieved in 69.5% of patients. The AML (28 ± 3 vs. 26 ± 3 mm, p = 0.004) and PML (19 ± 4 vs. 17 ± 3 mm, p < 0.001) decreased in length, as well as the MAD (31 ± 5 vs. 28 ± 5 mm, p = 0.001) and TH (10 ± 3 vs. 8 ± 2 mm, p < 0.001). Compared with the NC group, the AML and PML of the RODCM group were 16.7% and 35.7% longer at baseline and remained 8.3% and 21.2% longer at follow-up, respectively. The change in AML or PML correlated moderately with that in LVEDV (r = 0.487, p < 0.001; r = 0.516, p < 0.001, respectively). The AML and PML length decreased in the LVRR (+) subgroup (AML, 28 ± 3 vs. 26 ± 3 mm, p = 0.001; PML, 20 ± 4 vs. 16 ± 3 mm, p < 0.001), but remained the same in the LVRR (-) subgroup (27 ± 4 vs. 28 ± 4 mm, p = 0.318; 17 ± 3 vs. 17 ± 3 mm, p = 0.790).*

Conclusions: *Enlarged MLs could reverse accompanied by LV reverse remodeling. This study provided the other facet of ML plasticity adaptive to mechanical stretching.*

Keywords: Recent-onset dilated cardiomyopathy; reverse remodeling; mitral leaflets; left ventricular

Introduction

The growth of mitral leaflets (MLs) adaptive to mechanical stretch caused by a dilated left ventricle (LV) and mitral annulus has gained increasing attention in recent years. Several clinical and experimental studies in non-ischaemic [1] and ischaemic cardiomyopathy [2–8], aortic regurgitation, and lone atrial fibrillation [9, 10] have demonstrated adequate ML enlargement proportionate to the LV, and mitral annular remodelling could prevent significant secondary mitral regurgitation (SMR). In contrast, inadequate ML growth has been proposed to contribute to the complex mechanisms of SMR. This extensibility of the MLs is not fully understood, including their histology, pathophysiology, positive or negative stimuli, and changes that occur after stimulus withdrawal. Therefore, the current study was the first to investigate the change of MLs in patients with idiopathic recent-onset dilated cardiomyopathy (RODCM) who received guideline-directed medical therapy (GDMT) as well as its relationship with LV reverse remodelling (LVRR — left ventricular reverse remod) and SMR improvement.

Material and methods

This prospective cohort study was approved by the institutional review board and ethics committee of West China Hospital. Informed consent was obtained from all patients.

Patient enrolment

The study population (n = 90) was enrolled from the cohort of the patients with idiopathic RODCM (ChiCTR2000038869). The inclusion criteria were: (1) aged ≥ 18 years; (2) met

the criteria of DCM defined by the World Health Organization/International Society and Federation of Cardiology [11] and in the absence of volume overload or ischemic causes, including severe and uncontrolled hypertension, valvular heart disease, congenital heart disease, and coronary artery disease. Other identifiable non-genetic causes such as drugs, toxic endocrinology, infection or auto-immune diseases were also excluded [12]; (3) and < 6 months since the occurrence of heart failure (HF) symptoms. The exclusion criteria were: (1) reluctance to participate; (2) expected life span of < 1 year due to non-cardiac causes; and (3) follow-up duration of <6 months. A group of subjects who had no cardiovascular diseases and a normal heart on echocardiography were enrolled as the normal control (NC) group (n = 50).

Clinical assessment and follow-up

Demographics and clinical data were collected at baseline following the protocol. The initiation and titration of GDMT were performed in all patients. Comprehensive echocardiography was performed at baseline and 6-month follow-up in the RODCM group.

Transthoracic echocardiography

Standard transthoracic echocardiography was performed using a Philips iE33 scanner and a 5-MHz transducer (Philips Medical Systems, Andover, MA). Images were acquired for the LV and mitral apparatus assessment as previously reported[1]. Off-line analyses were performed by two independent observers who were blinded to the results. The mitral regurgitation (MR) jet area and left atrial (LA) area were measured in the apical four-chamber view where the MR severity was reflected by the ([MR jet area/LA area] × 100%)

ratio. Mild, moderate, and severe MR was indicated by a ratio of < 20%, 20–39%, and ≥ 40%, respectively. No MR was indicated by undetectable or untraceable trivial MR [13]. At the parasternal long-axis view, the anterior mitral leaflet (AML) or posterior mitral leaflet (PML) length was measured from the leaflet tip to its insertion point at a frame when it was fully stretched into a straight-line during diastole; the mitral annular dimension (MAD) or tenting height (TH) was measured at mid-systole. Interobserver and intraobserver variabilities for the AML, PML, TH, and MAD were obtained in 20 randomly selected images by two independent observers who performed the offline analysis twice on two different days. Good correlations were demonstrated for both intraobserver and interobserver reliabilities with intraclass correlation coefficients ranging from 0.750 to 0.926. The ratio of (AML + PML)/(MAD + TH) was calculated to reflect the ML length relative to mitral tenting size. LVRR was defined as a ≥ 15% reduction in LVEDV at 6-month follow-up.

Statistics

Continuous variables were checked for normality using the Shapiro-Wilk test and expressed as mean ± SD if normally distributed or median and interquartile range (IQR) otherwise. Categorical variables were reported as number and frequency (%). A paired t-test or signed Wilcoxon rank-sum test was used when appropriate to compare the parameters at baseline and 6-month follow-up. All tests were two-sided. The analyses were performed using SPSS software version 25.0. Statistical significance was set at $p < 0.05$.

Results

Baseline characteristics and clinical follow-up

A total of 90 patients with RODCM underwent the baseline assessment. None died, but eight did not undergo transthoracic echocardiography at the 6-month follow-up. Therefore, 82 patients with RODCM were included in the final analysis. In addition, 50 age, sex and body surface area matched NC were included. The RODCM group had a lower blood pressure and higher heart rate than the control group ($p < 0.05$).

Before enrolment, 50 out of 82 patients (61%) had initiated GDMT with a median duration of 1.3 ± 1.1 months. This proportion increased to 100% at the baseline visit. Baseline characteristics of the RODCM patients are listed in Table 1. At the end of 6 months, the New York Heart Association (NYHA) functional class was improved for at least one class in 21 (25.6%) patients. The *N*-terminal pro-brain natriuretic peptide level decreased to 159 (IQR, 62–389) pg/mL ($p < 0.001$). Fifty-one (62.2%) patients received the “four pillar” drugs. The median dose of angiotensin receptor-neprilysin inhibitor was 250 (IQR, 150–300) mg, while that of beta-blocker was 47.5 (IQR, 47.5–71.25) mg equivalent to metoprolol. Five patients underwent cardiac resynchronization therapy-defibrillator implantation, while another five underwent implantable cardioverter defibrillator implantation.

LV reverse remodelling and SMR reduction

At 6-month follow-up, LV size was reduced with an increase in systolic function, while LV wall thickness was unchanged. LVRR was achieved in 57 (69.5%) patients as defined. Those with LVRR (+) also had a greater improvement in left ventricular ejection fraction

(LVEF) than those with LVRR (-) (14 ± 11% vs. 6 ± 8%, $p < 0.001$). LA size and function also improved significantly. The DCM group showed larger LV and LA size, but a lower LVEF compared to the NC group, both at baseline and 6-month follow-up. (Table 2).

As shown in Table 2, SMR severity decreased significantly at 6-month follow-up. The proportion of patients with SMR decreased from 61% to 39%. SMR reduction of ≥ 1 grade was observed in 22 (26.9%) patients. Among the 16 (19.5%) patients with moderate or severe SMR at baseline, one patient had SMR relief from severe to moderate, one from severe to mild, and six from moderate to mild or none, while moderate SMR persisted in the other eight patients. Those with LVRR (+) had a higher percentage of SMR improvement of ≥ 1 grade than those with LVRR (-) (35.1% vs. 8.0%, $p = 0.014$).

Changes in the MLs

The AML and PML of the RODCM group decreased at 6-month follow-up (Figure 1). The AML tended to exhibit a lesser reduction than PML (-5% ± 14% vs. -10% ± 19%, $p = 0.076$); thus, the AML/PML ratio increased. Compared with the control group, the AML and PML of the DCM group were 16.7% and 35.7% longer at baseline, respectively, which remained 8.3% and 21.2% longer at follow-up. However, the AML/PML ratio was smaller at baseline and at 6 months (Table 3).

At both time points, MAD and TH were larger in the RODCM group than in the control group. MAD and TH were reduced in the RODCM group at 6-month follow-up. Since the

extent of decrease in the (AML+PML) tended to be less than that in the (MAD+TH) (-8% ± 13% vs. -12% ± 15%, p = 0.059), the ratio of (AML+PML)/(MAD + TH) was increased (1.14 ± 0.12 vs. 1.20 ± 0.16, p = 0.001) (Table 3).

Shortening of elongated leaflets and LV reverse remodelling

The change in AML (△AML) and PML (△PML) correlated moderately with the change in LVEDV (△LVEDV) (r = 0.487, p < 0.001; r = 0.516, p < 0.001, respectively). The correlation was weaker with the change in LVEF (△LVEF) (r = -0.279, p = 0.011 and r =-0.321, p = 0.003, respectively) (Figure 2). In addition, △AML and △PML were related to △MAD (r = 0.488, p < 0.001; r = 0.415, p < 0.001, respectively) and △TH (r = 0.528, p < 0.001; r = 0.529, p < 0.001, respectively).

Furthermore, the AML and PML decreased in those with LVRR (+) (AML, 28 ± 3 vs. 26 ± 3 mm, p = 0.001; PML, 20 ± 4 vs. 16 ± 3 mm, p < 0.001) but remained the same in those with LVRR (-) (AML, 27 ± 4 vs. 28 ± 4 mm, p = 0.318; PML, 17 ± 3 vs. 17 ± 3 mm, p = 0.790). The differences in △AML and △PML between the LVRR subgroups are shown in Figure 3.

Discussion

In this study, it was observed that the length of MLs in RODCM was elongated at baseline and, for the first time, was shortened (although not normalised) along with LV reverse remodelling after 6 months of GDMT. The PML demonstrated a greater stretching as well as a more contracting after treatment than the AML.

Histopathological basis of adaptive growth in the MLs

Mechanical stress induced specific cellular and molecular changes of the MLs contribute to morphological remodelling in SMR. In the transplant recipient heart of DCM and ischemic cardiomyopathy, the MLs showed increased cell proliferation and expanded extracellular matrix that contained more collagens and glycosaminoglycans compared to that of a normal heart, longer AML and PML were also observed by echocardiography before transplantation [14]. In an in vitro study, an additional fibrous layer was observed atop the original leaflet by exposure of cultured MLs to different haemodynamic conditions. The underlying mechanisms involve activation of the transforming growth factor-beta and bone morphogenetic protein signalling pathways as well as migration of valvular interstitial cells and macrophages through breakage of the endothelial cell lining [15]. In vivo studies that used volume overload [16], papillary muscle retraction [17, 18] and rapid pacing [19] models, LV remodelling was accompanied by ML growth over time by echocardiography. A larger ML was also demonstrated by gross pathology at sacrifice [17]. Histopathological changes in the stretched MLs included increased spongiosa layer thickness, decreased collagen alignment, and decreased α-smooth muscle actin+ staining in the atrial endothelium, with nests of α-smooth muscle actin+ cells penetrating the interstitium [17].

Reverse remodelling of MLs with LV reverse remodelling

If the changes in MLs after stretch force withdrawal was reversed, the proposed concept of mechanical stretch that induced ML growth could be more comprehensive. In the current study, it was confirmed that AML and PML shortening upon decreased tethering force and an increased closing force in terms of LVRR. It appeared to correlate more with △ left

ventricular end-diastolic dimension (LVEDD) than △LVEF, which supported the core role of mechanical stretching. Nishino et al. also demonstrated a significantly reduced ML surface area with LA reverse remodelling after successful catheter ablation for atrial fibrillation [20]. It was recently observed that chronic atrial fibrillation and diastolic heart failure induced LA enlargement was another stretch stimulus leading to adaptive ML growth [21].

However, mechanical stretch might not be the only stimulus for the enlargement of MLs in DCM. In previous studies, there were patients with significant SMR who exhibited insufficient ML growth relative to atrioventricular orifice dilation. In this study, the extent of decrease in MLs was less than that in the (MAD+TH) even in the patients undergoing LVRR. Apart from a short duration of treatment, which might be attributed to non-stretching stimuli associated with pathophysiologies of DCM itself, particularly fibrosis, that hinder adequate elongation and return to a normal state in response to stretch on and off, respectively. For instance, an experimental model of apical acute myocardial infarction, where the imposed tethering force on MLs did not increase, it was demonstrated that ischemia alone could lead to excessive interstitial collagen deposition in the MLs [6]. Inhibiting these non-stretch-induced changes would perhaps promote proportional ML growth in response to stretch, thus offering a potential approach to treat or prevent SMR [22].

Different behaviours of AML and PML in SMR

In line with a previous publication that compared AML and PML in unselected DCM patients [1], the PML demonstrated greater elongation than the AML in this group of patients with RODCM; furthermore, at 6-month follow-up, the PML demonstrated a greater shortening than the AML. This finding was supported by previous studies of excised porcine mitral valves [24, 25] which found greater extensibility in the circumferential and radial directions of the PML as well as lower stiffness in the posterior aspect of the mitral annulus. More recently, a study that assessed ML strain by three-dimensional transoesophageal echocardiography in patients with SMR and primary MR found higher strain in the PML [26]. It is likely that the AML and PML could be treated differently when exploring the relationship between deformative changes in MLs and SMR.

Study limitations

This was a single-centre obervational study with a relatively modest size and short period of time, that could be reasonable as a hypothesis-generating pilot study. Measurements of the MLs relied on a single plane by two-dimensional transthoracic echocardiography, but standardised image acquisition and off-line analysis yielded good reproducibility and acceptance in several studies [1, 27]. Although the association between ML changes and

SMR was not the focus of this study, the low prevalence of moderate or severe SMR in the RODCM cohort made it inappropriate for further analysis.

Conclusions

The current study demonstrated that enlarged MLs could reverse along with LVRR after standardised therapy in patients RODCM. In this process, the PML showed a greater degree of changes than the AML. These findings support the hypothesis of ML plasticity adaptive to mechanical stress, though further studies are warranted.

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Statement of competing interests: None.

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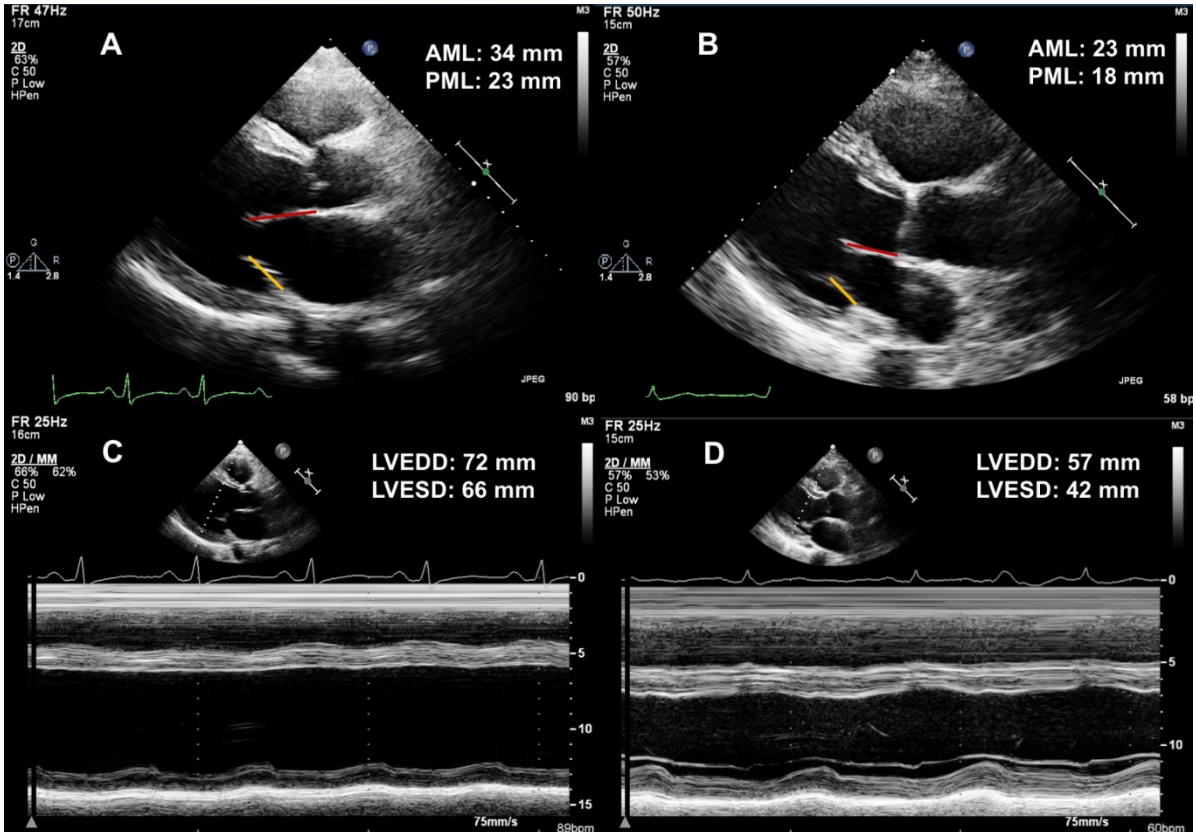
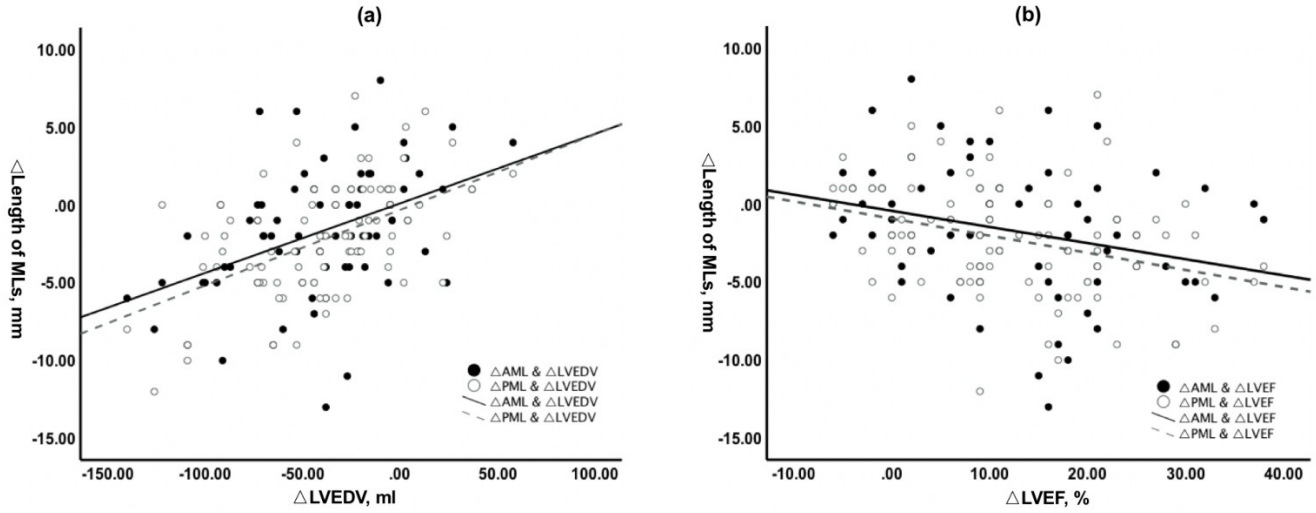
Figure 1. An example of a patient with RODCM who showed reverse remodelling in MLs and left ventricle. Compared with baseline (A and C), the length of AML and PML measured at the parasternal long axis view decreased (B), and the left ventricular dilation and systolic dysfunction measured by M-mode echocardiography improvement (D) at 6-month follow-up.



LVEDD — left ventricular end-diastolic dimension, LVESV — left ventricular end-systolic dimension; LVRR — left ventricular reverse remodeling; PML — posterior mitral leaflet.

Figure 2. Correlations between changes in ML length and LVEDV (a) and LVEF (b).



LVEDV — left ventricular end-diastolic volume; LVEF — left ventricular ejection fraction; ACEI — The rest of the abbreviations are as shown in Figure 1.

Figure 3. Changes in ML length by LVRR subgroup. The remaining abbreviations are as shown in Figure 1.

Table 1. Patient baseline characteristics

	RODCM (N = 82)
Age, years	49 ± 12
Male sex, n (%)	59 (72)
Systolic blood pressure, mmHg	107 ± 17
Diastolic blood pressure, mmHg	73 ± 12
Heart rate, bpm	78 ± 14
Hypertension, n (%)	16 (19.5)
Diabetes, n (%)	7 (8.5)
Atrial fibrillation, n (%)	11 (13.4)
NYHA class, n (%)	
I/II	78 (95.1)
III/IV	4 (4.9)
NT-proBNP, pg/mL	549 (228 – 943)
ARNI/ACEI/ARB/, n (%)	81 (98.8)
Beta-blocker, n (%)	68 (82.9)
SGLT2i, n (%)	45 (54.9)
MRA, n (%)	65 (79.3)
Diuretic, n (%)	69 (84.1)

angiotensin-converting enzyme inhibitors; ARB — angiotensin receptor blockers; ARNI — angiotensin receptor-neprilysin inhibitor; MRA — mineralocorticoid receptor antagonists; NT-proBNP — *N*-terminal pro-brain natriuretic peptide; NYHA — New York Heart Association; RODCM — recent-onset dilated cardiomyopathy; SGLT2i — sodium glucose cotransporter 2 inhibiton.

Table 2. Post-treatment changes in the left heart

	RODCM (N = 82)			**NC (n = 50)**
	Baseline	**6-Month Follow-up**	**P value**	
LV				
LVD, mm	64 ± 7*	58 ± 8*	< 0.001	47 ± 3
IVS, mm	9 ± 2	10 ± 2	0.320	9 ± 2
LVPW, mm	8 ± 2	8 ± 2*	0.644	8 ± 2
LVEDV, mL	171 ± 61*	131 ± 50*	< 0.001	86 ± 16
LVESV, mL	123 ± 56*	79 ± 41*	< 0.001	34 ± 9
LVEF	30 ± 9*	42 ± 9*	< 0.001	60 ± 5
LVSI	1.5 ± 0.2*	1.6 ± 0.2*	< 0.001	2.0 ± 0.2
LA				
LAEDV, mL	71 ± 30*	56 ± 26*	0.007	36 ± 12
LAESV, mL	41 ±2 7*	25 ± 21*	0.001	12 ± 6
LAEF	46 ± 16*	59 ± 15*	< 0.001	67 ± 7

IVS — interventricular septum; LAEDV — left atrial end-diastolic volume; LAEF — left atrial ejection fraction; LAESV — left atrial end-systolic volume; LVD — left ventricular dimension; LVEDV — left ventricular end-diastolic volume; LVEF — left ventricular ejection fraction; LVESV — left ventricular end-systolic volume; LVPW — left ventricular post-wall; LVSI — left ventricular sphericity index; RODCM — recent-onset dilated cardiomyopathy.
*$p < 0.05$ compared to the NC group

Table 3. Changes in the mitral apparatus.

	RODCM (n = 82)			NC (n = 50)
	Baseline	**6-Month Follow-up**	**P value**	
AML, mm	28 ± 3*	26 ± 3*	0.004	24 ± 3
PML, mm	19 ± 4*	17 ± 3*	< 0.001	14 ± 3
MAD, mm	31 ± 5*	28 ± 5*	0.001	26 ± 4
TH, mm	10 ± 3*	8 ± 2*	< 0.001	7 ± 2
AML+PML, mm	47 ± 6*	43 ± 6*	< 0.001	38 ± 4
MAD+TH, mm	42 ± 6*	36 ± 6*	< 0.001	33 ± 5
(AML+PML)/ (MAD+TH)	1.1 ± 0.1	1.2 ± 0.2	< 0.001	1.2 ± 0.2
AML/PML	1.5 ± 0.2*	1.6 ± 0.3*	< 0.001	1.9 ± 0.5
SMR, n (%)			< 0.001	
Absence	33 (40.2)	50 (61.0)		47 (94.0)
Mild	33 (40.2)	22 (26.8)		3 (6.0)
Moderate	14 (17.1)	10 (12.2)		0
Severe	2 (2.5)	0		0

AML — anterior mitral leaflet; MAD — mitral annular dimension; NC — normal controls; PML — posterior mitral leaflet; TH — tenting height. The remaining abbreviations are as shown in Table 1.

*p < 0.05 compared to the NC group