Original manuscript

Reduction of tethering distance by papillary muscle tugging approximation with mitral valve replacement for non-ischemic functional mitral regurgitation induces left ventricular reverse remodeling

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Abstract

Background

Functional mitral regurgitation (FMR) is caused by left ventricular (LV) remodeling and subsequent tethering of the mitral valve (MV). If LV remodeling is irreversibly advanced, it could not be attenuated by the MV procedure alone, although the additional subvalvular procedure could induce LV reverse remodeling by forcibly reducing MV tethering. This study aimed to assess the anti-tethering effect of papillary muscle tugging approximation (PMTA) on LV reverse remodeling after mitral valve replacement (MVR) for non-ischemic FMR.

Methods

The study subjects were 19 patients who underwent MVR with and without PMTA (MVR+PMTA [n=11] and MVR alone [n=8], respectively) for non-ischemic FMR. The tethering distance (TD) and LV end-systolic volume (ESV) at the preoperative, postoperative, and follow-up periods were assessed in terms of their correlation and time-dependent changes. The intra-LV energy efficiency was also evaluated through vector flow mapping analysis.

Results

TD and ESV were comparable between both procedures preoperatively and did not change

after MVR alone. In MVR+PMTA, however, a significant decrease was identified in TD and ESV at the early postoperative and follow-up periods, respectively (TD = 48, 30, and 31 mm [P<0.001] and ESV = 159, 133, and 82 mL [P<0.001] at the preoperative, postoperative, and follow-up periods, respectively). Finally, at follow-up, the extent of change from the preoperative value in ESV significantly correlated with that in TD ($\rho = 0.81$, $P < 0.001$ for overall; $\rho = 0.93$, $P < 0.001$ for MVR+PMTA; $\rho = 0.86$, $P = 0.011$ for MVR alone). The ratio of TD to ESV was also significantly correlated with systolic energy loss to LV stroke work after MVR+PMTA ($\rho=0.81$, $P=0.015$).

Conclusions

PMTA for non-ischemic FMR could induce LV reverse remodeling depending on the extent of postoperative TD reduction. A smaller TD to ESV was associated with a higher intra-LV energy efficiency after PMTA+MVR.

(300 words)

Introduction

Functional mitral regurgitation (FMR) is a secondary valvular disease caused by left ventricular (LV) remodeling [1]. Although various mitral valve (MV) procedures, including MV replacement (MVR), MV repair, and even MitraClip, have been proposed to treat FMR, their benefits remain controversial [2-5]. These results suggest that MV procedure alone has limited effectiveness for FMR as a ventricular disease. Thus, additional procedures could be required depending on the extent of LV remodeling [6]. The subvalvular procedure is one of such procedures and includes various techniques: chordal cutting, papillary muscle approximation, and papillary muscle suspension [7]. Although its favorable results have been reported [8, 9], the precise mechanism of their effectiveness and the most effective technique remain unclear. Recently, we proposed papillary muscle tugging approximation (PMTA), a subvalvular procedure that combines papillary muscle approximation and suspension of the papillary muscles to the MV annulus, as an adjunctive procedure to MVR for FMR [10]. MVR+PMTA is characterized by the extent of the suspension. Further suspension can be achieved in MVR+PMTA compared to mitral valve repair with approximation and suspension of the papillary muscles because the extent of suspension in the repair is limited within a range where leaflet prolapse does not occur. Thus, the anti-tethering effect of MVR+PMTA could be greater than that of MVR alone or mitral valve repair with the approximation and suspension of the papillary muscles. Because of the early favorable results [11], we hypothesized that the

extent of suspension of the papillary muscles in MVR+PMTA is associated with a beneficial effect on LV remodeling. Therefore, this study aimed to assess the relationship between the anti-tethering effect of PMTA and LV reverse remodeling.

Methods

Between 2015 and 2019, 50 patients with FMR due to dilated cardiomyopathy underwent MVR with and without PMTA (MVR+PMTA [n = 27] and MVR alone [n = 23], respectively) at Hokkaido University Hospital and the affiliated hospitals. Among them, 19 patients who underwent MVR for non-ischemic FMR were reviewed after exclusion of those with ischemic FMR, reoperation, active infective endocarditis, moderate or more aortic insufficiency at follow-up, and without follow-up echocardiographic data ≥1 year after surgery (Online Figure 1). The etiology of non-ischemic FMR was idiopathic dilated cardiomyopathy and dilated-phase hypertrophic cardiomyopathy in 18 patients and 1 patient, respectively. The Ethics Committees of Hokkaido University Hospital (no. 017-0433) and affiliated hospitals approved this study and waived informed consent for 11 patients, for whom data were retrospectively collected only from medical records and examination reports, and written informed consent was obtained from the other eight patients who agreed to undergo additional echocardiographic study using vector flow mapping (VFM) analysis.

Surgical procedures

All surgical procedures were selected based on the surgeons' preferences. MVR+PMTA was performed by two surgeons (Y.M. and S.W.), and its details have been described previously [10]. Briefly, under general anesthesia through a median sternotomy using standard cardiopulmonary bypass with aortic and bicaval cannulations, cardiac arrest was obtained by antegrade and retrograde cardioplegia with moderate hypothermia. The MV was exposed through a left atriotomy or transseptal approach. The anterior mitral leaflet was vertically divided into two parts, which were subsequently attached to both commissures using pledgeted 5-0 polypropylene sutures. Thereafter, the heads of the papillary muscles were approximated side by side using a single pledgeted 3-0 polypropylene mattress suture and then suspended in the middle of the anterior mitral annulus with an expanded polytetrafluoroethylene suture (CV-3). Finally, the MV was replaced. All mechanical prostheses used in both MVR+PMTA and MVR alone were implanted in the anti-anatomical position. No artificial chord was used in the MVR alone.

Echocardiography

To evaluate the extent of LV reverse remodeling and the relationship between LV size and tethering, the following data were collected for each patient from the echocardiographic

study at preoperative, postoperative, and follow-up periods: LV end-diastolic diameter, end-systolic volume (ESV), ejection fraction (EF), and tethering distance (TD). LV end-diastolic diameter was measured in the parasternal long-axis view. ESV and EF were obtained from apical two- and four-chamber views using the modified Simpson method, while TD was measured in an apical four-chamber view as the distance between MV annulus and the tip of the papillary muscles in mid-systole [12]. The ratio of TD to ESV (TD/ESV, TD divided by ESV) was also calculated to consider the standardized anti-tethering effect. The severity of MR was also evaluated considering vena contracta, regurgitant volume and fraction, and effective orifice area and graded as follows: 1+, mild; 2+, moderate; 3+, moderately severe; and 4+, severe [13]. In patients with atrial fibrillation, data were obtained from a single beat, where the preceding two R-R intervals were nearly equal [14].

Vector flow mapping

To assess the effect of PMTA from the aspect of intra-LV flow dynamics, de novo echocardiography for VFM examination was performed in eight patients who underwent MVR+PMTA and agreed with the test. The examinations were performed by experienced examiners at Hokkaido University Hospital, using ProSound F75 (Hitachi, Ltd., Tokyo, Japan) with a 2.5-MHz cardiac transducer (Hitachi, Ltd.) and a VFM workstation (DAR-RS1, Hitachi, Ltd.). The VFM principles and detailed algorithms have been previously reported [15], and the

following parameters were obtained: flow pattern, vortex size, circulation, vorticity magnitude, and energy loss (EL). EL was calculated automatically using the following equation after detecting the inflow and outflow borders of the LV:

$$Energy\ loss\ (J/[m \cdot s]) = \int \mu \left\{ 2\left(\frac{\partial u}{\partial x}\right)^2 + 2\left(\frac{\partial v}{\partial y}\right)^2 + \left(\frac{\partial u}{\partial y} + \frac{\partial v}{\partial x}\right)^2 \right\} dA$$

where μ is the blood viscosity, u and v are velocity components along the Cartesian axes (x and y), and A is the area increment of the integral. In addition, we also calculated the ratio of systolic EL to LV stroke work (LVSW) (sEL/LVSW, systolic EL divided by LVSW) as a parameter representing systolic energy efficiency in the LV [16]. LVSW was obtained from stroke volume, which was calculated from the LV outflow tract area and velocity time integral, multiplied by the mean blood pressure measured in the study.

Statistical analysis

Continuous variables are expressed as medians with interquartile ranges (IQRs). Categorical variables are expressed as numbers and percentages. Mann–Whitney U tests were performed to compare continuous data. Categorical data were compared using χ^2 or Fisher's exact tests, as appropriate. To assess time-dependent changes in the variables, the Friedman test was performed, followed by a post hoc test using Bonferroni's correction. Correlations between variables were assessed using Spearman's rank correlation coefficient (ρ). Statistical significance was set at $P < 0.05$. All analyses were performed using IBM SPSS Statistics

version 24 (IBM Corp, Armonk, NY, USA).

Results

Patients' baseline characteristics

Table 1 shows the patients' baseline characteristics. The median age was 66 years, and 12 patients (63%) were men. Fourteen patients (74%) presented with New York Heart Association functional class III or IV. MVR alone was associated with more hypertension than MVR+PMTA. Five patients (45%) with MVR+PMTA required preoperative inotropes. There was no statistical difference between the procedures in preoperative TD, LV end-diastolic diameter, and ESV, whereas EF tended to be lower in patients with MVR+PMTA.

Operative data

The operative data are presented in Table 2. A mechanical prosthesis was used in all patients with MVR+PMTA, whereas a bioprosthesis was used in most of those with MVR alone. In suspension of the papillary muscles, the prosthesis can interfere with the heads of the papillary muscles depending on the height of the prosthesis and the extent of suspension. Therefore, in MVR+PMTA, a mechanical prosthesis was preferably used to suspend the papillary muscles as much as possible without interference. Chordal preservation was

performed for the anterior leaflet in only one patient with MVR alone. Tricuspid annuloplasty was performed in all patients with MVR+PMTA, while half of patients with MVR alone underwent the procedure. In one patient with MVR+PMTA, concomitant coronary artery bypass grafting was performed for accidentally detected 50% stenosis in the left anterior descending artery, which was not considered to be the cause of cardiomyopathy.

Postoperative and follow-up data

Postoperative echocardiography was performed 16 days (IQR, 13–20 days) after MVR+PMTA and 18 days (IQR, 14–27 days) after MVR alone, while the follow-up study was conducted 29 months (IQR, 18–43 months) after MVR+PMTA and 43 months (IQR, 26–52 months) after MVR alone (P = 0.13 vs. MVR+PMTA). One patient died of heart failure 27 months after MVR+PMTA. Figure 1 and Supplemental Table 1 show the time-dependent changes in LV parameters. In MVR alone, no significant change was observed throughout the study period in any of the parameters. In MVR+PMTA, however, TD decreased early postoperatively and remained reduced during the follow-up period. In contrast, LV end-diastolic diameter, ESV, and EF significantly changed at follow-up, although no significant changes were found in any parameters early after surgery.

Correlations between tethering and LV size

There were significant correlations between TD and ESV in both procedures at each time point (Figure 2). Moreover, the extent of change in ESV from preoperative to follow-up values significantly correlated with that in TD ($\rho = 0.81$, $P < 0.001$ for overall; $\rho = 0.93$, $P < 0.001$ for MVR+PMTA; and $\rho = 0.86$, $P = 0.011$ for MVR alone, Figure 3).

Results of vector flow mapping analysis

VFM was performed at a median of 20 months (IQR, 15–30 months) after surgery. The results of the study and associated parameters are shown in Supplementary Table 2. TD did not correlate with any parameters in VFM analysis. However, TD/ESV significantly correlated with sEL/LVSW ($\rho = 0.81$, $P = 0.015$, Figure 4), while no significant correlation was found between TD/ESV and other parameters.

Discussion

As a result of myocardial disease, LV systolic dysfunction, LV dilatation, MV tethering, and subsequent FMR comprise a vicious cycle of LV remodeling [17]. Elimination of FMR by MV procedure could terminate this cycle and then contribute to LV reverse remodeling and relief of heart failure, although it could be too late if the LV remodeling progresses irreversibly. In fact, in the treatment of ischemic FMR, the extent of LV remodeling precludes LV reverse remodeling and survival after MV repair [18]. In this condition, surgically

induced anti-tethering could help terminate this cycle and result in LV reverse remodeling.

We used TD, one of the parameters of tethering [19], to evaluate the anti-tethering effect of papillary muscle suspension because it appropriately represents the effect of the procedure. As shown in Figure 2, where significant correlations between TD and ESV were found in every condition, TD can increase depending on the LV size as LV remodeling progresses. Conversely, we hypothesized that ESV could decrease in accordance with the surgical reduction of TD by PMTA and assessed the relationship between TD and ESV. As a result, the postoperative changes in TD and ESV occurred at different time points (TD decreased before ESV); this difference in timing and the relationship between the parameters at follow-up (the extent of change from preoperative value in ESV significantly correlated with that in TD) support our hypothesis that the surgical anti-tethering by PMTA induced LV reverse remodeling.

The anti-tethering effect could also be attributed to isolated MV procedures or LV volume reduction procedures such as surgical ventricular reconstruction. In ischemic etiology, surgical ventricular reconstruction could be effective for highly selected patients [20, 21]. However, LV volume reduction with an LV incision for non-ischemic etiology was not as effective as that for an ischemic one [22, 23]. In the failing heart, the Frank–Starling mechanism no longer works properly, and further LV preload inversely reduces the LV pressure [24]. To maximize the function of the myocardium, extensive distension of myocardial fibers should be

prevented. Thus, we also hypothesized that surgical anti-tethering by PMTA is a feasible concept in this aspect because the strongly suspended papillary muscles can work as anchors to prevent extensive distension of the myocardial fibers (lower TD/ESV). Conversely, after surgical ventricular reconstruction, a lack of such anchors could cause deteriorated myocardial fibers to continue to work with nearly maximum preload, resulting in spoiled myocardial function even after successful anti-tethering by LV volume reduction (higher TD/ESV). In addition, an excess LV preload considering the ability of the myocardium raises the neurohormonal activity and subsequently promotes a vicious cycle of LV remodeling [25]. In this study, VFM was performed to evaluate intra-LV hemodynamics after PMTA. Finally, our results supported the hypothesis and showed that surgical reduction of TD in the dilated LV (lower TD/ESV) can relieve myocardial burden, resulting in the improvement of LV energy efficiency in systole. In contrast, excessively short intra-LV anchors could affect diastolic function and result in a loss of the necessary preload. Although our results suggest that the anchoring effect would be in a beneficial range after PMTA, the negative effect of PMTA on LV diastolic function could not be denied, and further studies are required to address this issue.

The primary reason for selecting mechanical valves in MVR+PMTA was their lower height than bioprosthesis, although there were reports regarding other advantages in the use of mechanical prostheses: larger effective orifice area, lower transvalvular leakage, and superior opening and closing function [26, 27]. In contrast, anticoagulation is an issue regarding the use

of mechanical valves, especially in patients with advanced age, bleeding complications, and heart failure with congestive liver dysfunction [28]. This potential drawback of MVR+PMTA could be mitigated by the use of a low-profile bioprosthesis: a possibility which will require further research in the future.

Limitations

This study had several limitations. First, the number of subjects was small because of the rarity of the disease and the indication of the procedures limited to patients without candidacy of heart transplantation. Second, differences in prosthesis types and preservation of mitral leaflets between procedures could affect postoperative LV reverse remodeling. However, these differences did not affect our conclusion because the key result of this study was that the extent of surgically induced reduction in TD was related to the extent of LV reverse remodeling. In fact, TD did not decrease during the early postoperative and follow-up periods after MVR alone with total chordal preservation and was similar between those with and without anterior chordal preservation, although the number of patients with anterior chord preservation in MVR alone was too small for statistical analysis. This also applies to the types of prostheses. Third, the difference in the timing of follow-up evaluation between the procedures could bias the results because LV reverse remodeling occurs in a time-dependent fashion. However, previous studies regarding MV surgery for ischemic FMR and aortic valve replacement for aortic

insufficiency showed that LV reverse remodeling had almost occurred within 1 year after surgery [29-32]. Finally, this study did not assess the outward anti-tethering effect of papillary muscle approximation due to a lack of data. However, because the effect of the suspension of the approximated papillary muscles was clearly shown, we believe that the effect of the approximation does not affect the conclusions of this study. A future study with a larger number of subjects with further integrity in the procedures and background conditions will be required for further clarification of our results.

Conclusions

Surgical anti-tethering by PMTA added to MVR for non-ischemic FMR could induce LV reverse remodeling depending on the extent of TD reduction. Moreover, a smaller TD/ESV was associated with higher energy efficiency in the LV after MVR+PMTA. In the treatment of FMR with advanced LV remodeling, adding a procedure that could provide an anti-tethering effect would be recommended.

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The authors declare that there is no conflicts of interest.

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Figure legends

Graphical abstract

Surgical anti-tethering by PMTA could induce LV reverse remodeling after MVR for non-ischemic FMR, depending on the extent of reduction of the tethering distance. FMR, functional mitral regurgitation; LV, left ventricle; MVR, mitral valve replacement; PMTA, papillary muscle tugging approximation

Figure 1. Time-dependent changes in tethering distance, left ventricular end-diastolic diameter, end-systolic volume, and ejection fraction. LV, left ventricle; MVR, mitral valve replacement; PMTA, papillary muscle tugging approximation

*Bonferroni corrected $P < 0.05$ compared with preoperative value, †Bonferroni corrected $P < 0.05$ compared with postoperative value

Figure 2. Correlations between tethering distance and left ventricular end-systolic volume in both procedures at each time point. EF, left ventricular ejection fraction; ESV, left ventricular end-systolic volume; MVR, mitral valve replacement; PMTA, papillary muscle tugging approximation, TD, tethering distance

Figure 3. Correlation between the extent of change in ESV, from preoperative to follow-up values, and TD. Δ ESV% = 100 (preoperative ESV – follow-up ESV) / preoperative ESV; Δ TD = preoperative TD – follow-up TD; ESV, left ventricular end-systolic volume; MVR, mitral valve replacement; PMTA, papillary muscle tugging approximation; TD, tethering distance

Figure 4. Correlation between the ratio of TD to ESV and that of sEL to LVSW after MVR+PMTA. ESV, left ventricular end-systolic volume; LVSW, left ventricular stroke work; MVR, mitral valve replacement; PMTA, papillary muscle tugging approximation, sEL, systolic energy loss; TD, tethering distance

Online Figure 1. Flow diagram for patient enrollment. AI, aortic insufficiency; FMR, functional mitral regurgitation; MVR, mitral valve replacement; PMTA, papillary muscle tugging approximation

Table 1. Patients' baseline characteristics

Variables	MVR+PMTA (N=11)	MVR alone (N=8)	P values
Age, years	66 (56, 78)	63 (47, 73)	0.72
Male, n (%)	5 (45)	7 (88)	0.15
Diabetes mellitus, n (%)	1 (9)	3 (38)	0.26
Hypertension, n (%)	0 (0)	4 (50)	0.018
Dyslipidemia, n (%)	1 (9)	4 (50)	0.11
Renal failure (creatinine >1.3), n (%)	2 (18)	3 (38)	0.60
Dialysis, n (%)	0 (0)	1 (13)	0.42
Atrial fibrillation, n (%)	4 (36)	2 (25)	1.00
History of ventricular tachycardia	2 (18)	3 (38)	0.60
Cardiac resynchronization therapy	1 (9)	0 (0)	1.00
Medications, n (%)			
Beta-blocker	8 (73)	4 (50)	0.38
RAAS blockers	7 (64)	3 (38)	0.37
Spironolactone	8 (73)	3 (38)	0.18
NYHA functional class, n (%)			0.14

I	0 (0)	0 (0)	
II	1 (9)	4 (50)	
III	5 (45.5)	3 (37.5)	
IV	5 (45.5)	1 (12.5)	
Inotrope use, n (%)	5 (45)	0 (0)	0.045
Mitral regurgitation grade, n (%)			0.46
1+ or less	0 (0)	0 (0)	
2+	1 (9)	2 (25)	
3+	1 (9)	2 (25)	
4+	9 (82)	4 (50)	
Tethering distance, mm	48 (46, 50)	50 (43, 56)	0.49
LV end-diastolic diameter, mm	67 (63, 73)	68 (63, 70)	0.84
LV end-systolic volume, mL	159 (144, 210)	152 (98, 210)	0.66
LV ejection fraction, %	24 (20, 29)	34 (23, 36)	0.06

LV, left ventricle; MVR, mitral valve replacement; NYHA, New York Heart Association; PMTA, papillary muscle tugging approximation; RAAS blockers, renin–angiotensin–aldosterone blockers

Table 2. Operative data

Variables	MVR+PMTA (N=11)	MVR alone (N=8)	P values
Types of prosthesis, n (%)			0.001
Biological	0 (0)	6 (75)	
Mechanical	11 (100)	2 (25)	
Prosthesis size, mm	27 (27, 31)	27 (27, 30)	0.90
Chordal preservation, n (%)			
Anterior leaflet	11 (100)	1 (13)	<0.001
Posterior leaflet	11 (100)	8 (100)	NA
Concomitant procedures, n (%)			
Tricuspid annuloplasty	11 (100)	4 (50)	0.018
Maze/pulmonary vein isolation	4 (36)	2 (25)	1.0
CRT implantation	2 (18)	3 (38)	0.60
CABG	1 (9)	0 (0)	1.0
Operation time, min	335 (290, 384)	327 (298, 543)	0.90
Cardiopulmonary bypass time, min	166 (151, 193)	173 (145, 290)	0.84
Cross-clamp time, min	92 (70, 105)	124 (95, 218)	0.051

CABG, coronary artery bypass grafting; CRT, cardiac resynchronization therapy; MVR, mitral valve replacement; PMTA, papillary muscle tugging approximation

Supplementary Table 1. Time-dependent changes in LV parameters

Variables	MVR+PMTA (N=11)	MVR alone (N=8)	P values
Tethering distance			
Preoperative	48 (46, 50)	50 (43, 56)	0.49
Postoperative	30 (30, 35)*	48 (42, 54)	<0.001
Follow-up	31 (26, 34)*	49 (44, 54)	0.004
LV end-diastolic diameter, mm			
Preoperative	67 (63, 73)	68 (34, 70)	0.84
Postoperative	66 (62, 68)	65 (58, 69)	0.35
Follow-up	58 (51, 67)*	63 (57, 67)	0.54
LV end-systolic volume, mL			
Preoperative	159 (144, 210)	152 (98, 210)	0.66
Postoperative	133 (130, 179)	145 (96, 204)	0.78
Follow-up	82 (52, 107)*†	117 (83, 166)	0.16
LV ejection fraction, %			
Preoperative	24 (20, 29)	34 (23, 36)	0.06
Postoperative	24 (19, 29)	32 (25, 38)	0.06

Follow-up	41 (32, 51) *†	36 (27, 48)	0.93

LV, left ventricle; MVR, mitral valve replacement; PMTA, papillary muscle tugging approximation. *Bonferroni corrected $P < 0.05$ compared with baseline parameter, †Bonferroni corrected $P < 0.05$ compared with postoperative parameter

Supplementary Table 2. Results of vector flow mapping study and associated parameters

Variables	Values
Heart rate, bpm	67 (52, 80)
Mean blood pressure, mmHg	78 (66, 82)
LV stroke work, mL·mmHg	4471 (4209, 5717)
Flow pattern, n (%)	
Clockwise	2 (25)
Counterclockwise	6 (75)
Vortex size, mm^2	
Diastole	1104 (822, 1403)
Systole	969 (741, 1412)
Circulation, m^2/s	
Diastole	26 (17, 36)
Systole	16 (11, 28)
Vorticity magnitude, $10^{-1} \cdot s^{-1}$	
Diastole	0.23 (0.17, 0.27)
Systole	0.22 (0.14, 0.22)

Energy loss, J/(m·s)	
Diastole	0.25 (0.22, 0.51)
Systole	0.04 (0.03, 0.06)

LV, left ventricle