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Original article

Perioperative Changes of the Slope in the Preload Recrutable Stroke Work Relationship by a Single-Beat Technique After Mitral Valve Surgery in Functional Mitral Regurgitation With Non-ischemic Dilated Cardiomyopathy

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Key words: Mitral regurgitation, dilated cardiomyopathy, preload recruitable stroke work relationship

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Abstract

Objectives: The slope in the preload recruitable stroke work relationship is a highly linear, load-insensitive contractile parameter. However, the perioperative change of the slope has not been reported before. We examined the perioperative slope from a steady-state single beat in patients with functional mitral regurgitation and assessed the correlation with brain natriuretic peptide (BNP) levels.

Methods: The study included 16 patients with non-ischemic dilated cardiomyopathy and refractory heart failure: 10 patients underwent mitral valve plasty and left ventricular plasty (MVP+LVP group) and 6 patients who underwent mitral valve replacement and papillary muscle tugging approximation (MVR+PMTA group). The left ventricular ejection fraction was assessed by the modified Simpson method; the slope was assessed by the single-beat technique using transthoracic echocardiography. BNP levels were measured by chemiluminescent immunoassay.

Results: The left ventricular ejection fraction and slope did not significantly change from pre- to early post-surgery in the MVP+LVP group. Both the left ventricular ejection fraction and slope significantly increased 6 months after surgery in the MVR+PMTA group. Postoperative BNP level was low in the MVR+PMTA group. While the postoperative left ventricular ejection fraction did not correlate with BNP levels, the postoperative slope significantly correlated with BNP level after surgery in the MVP+LVP group and in the total functional mitral regurgitation group.

Conclusions: The change of slope was dependent on surgical procedures. In functional mitral regurgitation, the slope may be a more sensitive parameter in reflecting the left ventricular contractile function than the left ventricular ejection fraction.

Introduction

It is difficult to precisely estimate the intrinsic left ventricular contractile function by left ventricular ejection fraction (LVEF) specially in patients with severely deteriorated heart. The LVEF is commonly used to reflect the cardiac systolic function because it can be measured easily and non-invasively using transthoracic echocardiography. However, the LVEF, as estimated by echocardiography, has some limitations. Firstly, the LVEF is strongly affected by afterload and the LVEF is under- and overestimated in high- (e.g. vasoconstriction) and low-afterload conditions (e.g. vasodilation or mitral regurgitation [MR]), respectively [1]. In functional MR (fMR) with low LVEF, the LVEF did not correlate with late outcomes after mitral valve repair, replacement, and catheter intervention using the MitraClip [2-4]. Furthermore, it is well known that patients who have normal LVEF can develop heart failure as a result of diastolic dysfunction (heart failure with preserved EF) [5].

The slope in the preload recruitable stroke work relationship (M_w) has been recognized as a load- and LV size-independent contractile functional parameter and an index of the overall ventricular function, reflecting not only systolic, but also diastolic properties. We have reported M_w , but not LVEF, can be a predictive ventricular functional parameter for survival after surgery on the dilated heart with MR [6, 7]. However, there have been no reports regarding the perioperative changes of M_w , and it is currently unknown how the LV function recovers from surgical interventions for MR. Therefore, we investigated the change in cardiac contractile parameters (LVEF and M_w) before and after mitral surgery and their correlation with serum brain natriuretic peptide (BNP) levels, the most common biomarker for heart failure, in patients with fMR.

Methods

Study population

This retrospective observational study was performed at a single center (Hokkaido University Hospital). The study included 16 patients who underwent mitral valve (MV) surgery for severe fMR with non-ischemic dilated cardiomyopathy (NIDCM) excluding the effect of bypass surgery for ischemic cardiomyopathy. From 2006 to 2015, 27 patients with NIDCM underwent left ventriculoplasty (LVP) with MV annuloplasty, papillary muscle approximation (PMA), and suspension (PMS). Ten patients were included for analysis (MVP+LVP group) (**Fig. 1**). We changed our surgical strategy and developed a new method, called “papillary muscle tugging approximation (PMTA),” which is a MV replacement (MVR) combined with single PMA and PMS without LVP [8]. Six patients with NIDCM who underwent MVR+PMTA from 2015 to 2017 were included for analysis (MVR+PMTA group). All patients had refractory heart failure and were not considered to be suitable candidates for heart transplantation due to old age and/or personal refusal.

In order to compare perioperative changes in the LVEF and Mw, 10 patients with degenerative MR who underwent MVP and had adequate echocardiographic data to evaluate the Mw were included in this study as the degenerative group. The LVEF and Mw values in 10 patients (mean age, 60 ± 6 years; 5 men; LVEF, $62\% \pm 3\%$) without any echocardiographic abnormalities were also measured as a control. The University Ethics Committee approved the research protocol (No. 017-0433).

Surgical procedures of MVP and LVP

For the 8 patients with large LV diastolic dimension (≥ 70 mm) in the MVP+LVP group,

an overlapping LVP without a patch was performed, as previously described [9]. A Batista-type operation was performed for the 2 patients with myocardial fibrosis only in the posterior part of the LV. The MVP was conducted as a part of our original mitral complex reconstruction for all 10 patients. Briefly, papillary muscles were approximated side-by-side from the basis to the heads using three pledgeted mattress sutures (complete PMA) [10]. A CV-3 expanded polytetrafluoroethylene (ePTFE) suture was placed between the site of the chordal attachment of the approximated papillary muscles and the middle of the anterior mitral annulus. This suture was then passed through the true-sized semi-rigid total annuloplasty ring (PMS) [11].

Surgical procedures of MVR and PMTA

The PMTA was a combination of MVR with chordal preservation, single PMA, and PMS, without LVP [8]. After left atriotomy, the anterior MV leaflet was divided into two parts at the middle which were then attached to both commissures by pledgeted 5-0 polypropylene sutures. The papillary muscles were then approximated side-by-side using one pledgeted 3-0 polypropylene mattress suture (single PMA). The PMS was performed in the same manner as for the LVP group. The MV was then replaced using a mechanical valve in the intra-annular position. We used a low-profile mechanical valve (Abbott Park, Illinois, USA).

Assessment of cardiac function using echocardiography

Commercially available ultrasonic systems including Vivid 7 or Vivid E9 (GE Healthcare, Milwaukee, WI, USA), Aplio XG or Aplio Artida (Toshiba Medical Systems, Tochigi, Japan), and Sonos 5500 or iE33 (Philips Ultrasound, Bothell WA,

USA) were used for echocardiography. The examination was conducted by experienced examiners who were blinded to the study details. The following basic variables were measured from the parasternal long-axis view: LV end-diastolic dimension (LVDd) and end-systolic dimension (LVDs) (mm), interventricular septal thickness (IVST) (mm), and LV posterior wall thickness (LVPWT) (mm). On the apical long-axis image, the pulsed Doppler sample volume was located at the tip of MV leaflets in order to obtain the deceleration time (DcT) (ms) of the early transmitral flow. The LV end-diastolic volume (LVEDV), end-systolic volume (LVESV), and LVEF were measured using the modified Simpson method. The forward stroke and MR volumes were calculated by using pulsed wave Doppler at the LV outflow tract and MV annulus, respectively. Severe fMR was determined as follows: 1) an effective regurgitant orifice (ERO) ≥ 0.20 cm² and 2) a regurgitant volume ≥ 30 mL (ERO ≥ 0.40 cm², regurgitant volume ≥ 60 mL in degenerative MR) [12].

Estimation of the slope in the preload recruitable stroke work relationship

The Mw was estimated by using the formula described by Lee et al.: (total stroke work)/[EDV- κ ×EDV+(1- κ)×LV wall] (erg cm⁻³·10³) [13]. The EDV was derived from the total stroke volume divided by the LVEF. The LV wall was estimated by the echocardiography-derived LV mass. The constant, κ , was calculated as follows: $\kappa=0.004\times\text{LV mass}+0.6408$. We changed the method for calculating the stroke work from that we previously reported to calculate Mw both before and after surgery [6]. We calculated the total stroke work as follows: total stroke volume× mean blood pressure, which was previously calculated as follows: (total stroke volume)×(SBP-LAP), because of the disadvantage in that we could not calculate Mw after MR disappeared. The

previously reported cut-off value of 42 corresponds to about $35 \text{ erg cm}^{-3} \cdot 10^3$ in the current study. The blood pressure was measured by a manometer. The total stroke volume was calculated as follows: forward stroke volume + MR volume (mL).

Measurement of serum brain natriuretic peptide

Venous blood samples were collected in EDTA tubes after the patient had rested in the supine position. The BNP levels were measured immediately by using a chemiluminescent immunoassay method.

Statistical analysis

Echocardiography and BNP measurements were performed at 3 time points: baseline (before surgery), before discharge (early postoperative period), and 6 months after surgery (late postoperative period). Continuous variables are presented as means \pm standard deviation. For continuous variables, the unpaired t-test or Mann-Whitney's U test were used to compare groups, as appropriate. One-way repeated measured analysis of variance (ANOVA) was used to compare pre- and post-operative and 6-month postoperative values. For categorical data, group differences were evaluated using the χ^2 or Fisher's exact test. A p-value < 0.05 was considered statistically significant. Statistical analysis was performed with SPSS version 17.0 software (SPSS Inc., Chicago, IL, USA).

Results

Preoperative patient characteristics and echocardiographic parameters

Table 1 shows the baseline clinical characteristics and echocardiographic data of each group. There were no significant differences between the fMR groups, except for male sex and the preoperative MR volume.

Operative data

Table 2 shows the operative data in each group. The operative, cardiopulmonary bypass, and aortic cross-clamp times were significantly shorter in the MVR+PMTA group than in the MVP+LVP group; this was presumably due to the absence of LVP in the MVR+PMTA group.

Early outcomes

The mean follow-up duration was 17 ± 8 months and 30 ± 32 months in the MVR+PMTA and MVP+LVP group, respectively. There were no patients who had more than mild residual MR in the MVP+LVP group in the latest follow-up. There was no mortality in the MVR+PMTA group, whereas there were 4 hospital deaths (4, 5, 13, and 14 months after surgery) in the MVP+LVP group (cardiac, 3; necrosis of the intestine, 1). The 6-month survival rates were 100% and 80% in the MVR+PMTA and MVP+LVP groups, respectively (log-rank $p = 0.07$).

Perioperative changes of LVEF

Fig. 2A shows the change in LVEF in each group. The perioperative LVEF did not significantly change in the MVP+LVP group. On the other hand, in the MVR+PMTA

group, LVEF significantly increased at 6 months after surgery compared to baseline ($p = 0.022$) and early surgical period ($p = 0.003$). In the degenerative group, the LVEF was significantly decreased in the early surgical period compared to baseline ($p = 0.004$) and was increased at 6 months after surgery compared to the early surgical period ($p < 0.001$). Nonetheless, 6 months after surgery, the LVEF was comparable to that of the control group ($p = 0.41$).

Perioperative changes of Mw

Fig. 2B shows the change in the Mw in each group. The perioperative Mw did not significantly change in the MVP+LVP group. On the other hand, in the MVR+PMTA group, the Mw significantly decreased from baseline to the early surgical period ($p = 0.022$) and increased from the early surgical period until 6 months after surgery ($p = 0.038$). In the degenerative group, the Mw also significantly decreased at the early surgical period ($p = 0.020$) and at 6 months after surgery ($p = 0.017$) from baseline. Nonetheless, the Mw 6 months after surgery was comparable to that of the control group ($p = 0.12$).

Correlation between BNP and LV contractile functional parameters in fMR

The BNP values were only applicable in the fMR groups. The BNP levels did not significantly change in the MVP+LVP group ($p = 0.20$). On the other hand, in the MVR+PMTA group, the BNP levels tended to decrease consistently during the follow-up (522 ± 310 , 352 ± 247 , and 166 ± 147 pg/mL at baseline, early surgical period, and 6 months after surgery, respectively; $p = 0.08$). BNP level 6 months after operation was lower in the MVR+PMTA group than in the MVP+LVP group ($p < 0.01$).

Fig. 3A-C show correlation between the postoperative BNP levels and LVEF. The BNP levels did not correlate with the LVEF in any group. On the other hand, there was significant correlation between the postoperative BNP levels and the Mw in the MVP+LVP group (**Fig. 3D** $R^2 = 0.57$, $p = 0.005$) and in the total fMR groups (**Fig. 3F**, $R^2 = 0.40$, $p = 0.001$). The correlation between the Mw and the BNP levels in the MVR+PMTA group did not reach statistical significance (**Fig. 3E**) possibly due to the small number.

Discussion

In the current study, we demonstrated that the Mw, but not the LVEF, correlated with serum BNP levels after mitral surgery in fMR. Thus, the Mw may be a more sensitive parameter, reflecting LV contractile function and heart failure, than the LVEF.

Mw as a contractile functional parameter

The concept of the preload recruitable stroke work (PRSW) relationship was first proposed by Glower et al. who used closed-chest dogs to demonstrate that the PRSW relationship was linear [14]. The Mw which was the slope of PRSW has been recognized as a load- and LV size-independent contractile functional parameter and an index of the overall ventricular function, reflecting not only systolic, but also diastolic properties. Although the PRSW was originally defined by invasive catheter examination, Lee et al. proposed a “single-beat technique” using transthoracic echocardiographic data and proved that the Mw could be estimated from a steady-state beat without alternation of the preload [13]. They further showed in subgroup analysis

that the Mw derived from the single-beat technique closely matched the data gathered from the conventional catheter method in patients with different LV sizes, LV mass, and regional wall motion abnormalities.

Correlation between BNP and Mw

In the present study, there was significant correlation between BNP levels and Mw in the post-operative phase, although there was no correlation between BNP levels and LVEF. While the LVEF is a load-sensitive parameter reflecting only systolic function, Mw reflects both systolic and diastolic function; this is likely to explain why the BNP levels correlated only with the Mw. Thus, the Mw might be a more sensitive parameter to reflect heart failure than the LVEF. The preoperative BNP levels did not correlate with the preoperative Mw. We speculate that higher rates of inotrope use (MVP+LVP group, 50%; MVR+PMTA group, 67%) might have influenced the correlation before surgery in this cohort.

Clinical implications of change in Mw

We previously reported that Mw, but not LVEF, predicted survival after MVP+LVP in patients with NIDCM [6]. However, we did not assess the Mw postoperatively routinely; thus, the benefit of surgical intervention was obscure. In the present study, the Mw significantly increased in the MVR+PMTA group, but not in the MVP+LVP group, 6 months after surgery. The LVP might have compromised LV function. Although long-term follow-up of more cases is required, the Mw may be used for the postoperative management of heart failure and the estimation of responders and non-responders for MVR+PMTA.

The Mw also significantly decreased in the degenerative MR group in the early postoperative period. In a dog model of MR, when MR was induced at a constant preload, although forward stroke volume decreased, peak circumferential fiber-shortening velocity and peak contractile element velocity as barometers of LV contraction were significantly increased compared to the model without MR [14]. They argue that reduction of impedance to ejection allows the ventricle to empty further, which reduces ventricular wall tension and increases in the velocity of shortening. We also argue that patients with severe MR are in a hyper-contractile state before surgery with over-preload, and Mw decreases temporarily after surgery due to the elimination of MR which normalizes the pre- and afterloads.

Changes of surgical strategy for NIDCM

We changed surgical strategy from MVP+LVP to MVR+PMTA in 2015 because of unacceptable results of MVP+LVP as we previously reported [6]. There were two changes in the surgical approach for non-ischemic DCM with MR in 2015: 1) withdrawal from LVP, and 2) prevention of MR recurrence by the modified MVR. Warwick R et al. showed by finite element analysis that LVP (LV volume reduction) decreases forward stroke volume unless LVEF dramatically improves [16]. We can expect the increase in LVEF by LVP in ischemic DCM, but not in NIDCM.

Furthermore, there has been little evidence showing that conventional chordal-sparing MVR improved symptoms and prolonged survival for a long time in NIDCM patients with severe MR. We expect additional effects of PM approximation and tugging to conventional chordal-sparing MVR, which needs to be validated in the future.

Limitations

This study has several limitations. First, the number of subjects was small and the number of subjects who were not candidates for transplantation was quite limited; thus, the analysis of correlation in the MVR+PMTA group may have been underestimated. Second, a selection bias may exist in the MVP+LVP group as this was only comprised of patients with adequate echocardiographic data before and after surgery. However, there were no significant differences in the evaluated characteristics and survival rate between the included and excluded patients (data not shown). Third, the change of abnormal wall motion area after LVP might relate to the inaccuracy of the estimation of LV volumes and Mw which were derived from the biplane Simpson's method. Fourth, we selected mechanical valve in MVR to avoid interference with the subvalvular apparatus, to maximize the effective orifice area during exercise, and to obtain smaller transvalvular central leakage. However, mechanical valve has a risk of thrombus formation and we need careful follow-up.

Conclusions

The change of the Mw, which can be derived easily by the single-beat method, was dependent on the surgical procedures for fMR. The Mw, but not the LVEF, correlated with the serum BNP levels after surgery. Thus, in fMR, the Mw may be a more sensitive parameter reflecting LV contractile function than the LVEF.

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Conflict of interest

The authors declare that there is no conflict of interest.

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Figure legends

Figure 1. Flow chart for the inclusion process of the study. AVR, aortic valve replacement; LVP, left ventriculoplasty; MV, mitral valve; MVP, mitral valve plasty; MVR, mitral valve replacement; PMTA, papillary muscle tugging approximation.

Figure 2. Changes of the LVEF (A) and Mw (B) in the control, degenerative, MVP+LVP, and MVR+PMTA groups. 6Mo, 6 months after the operation; LVEF, left ventricular ejection fraction; LVP, Left ventriculoplasty; MVP, mitral valve plasty; MVR, mitral valve replacement; PMTA, papillary muscle tugging approximation; Pre-OP, before the operation; Post-OP, before discharge.

Figure 3. Correlations between postoperative BNP and LVEF (A-C), postoperative BNP and Mw (D-F) in MVP+LVP (A, D), MVR+PMTA (B, E), and total functional MR group (C, F). BNP, brain natriuretic peptide; fMR, functional mitral regurgitation; LVEF, left ventricular ejection fraction; LVP, Left ventriculoplasty; MR, mitral regurgitation; MVP, mitral valve plasty; MVR, mitral valve replacement; PMTA, papillary muscle tugging approximation.

Table 1. Preoperative characteristics and echocardiographic data in each group

Variables	Degenerative	Functional MR		p value [†]
	MR (n=10)	MVP+LVP (n=10)	MVR+PMTA (n=6)	
Demographic data				
Age (y)	59±15	60±10	60±12	0.95
Male	6 (60%)	9 (90%)	2 (33%)	0.036
Atrial fibrillation	3 (30%)	7 (70%)	1 (17%)	0.12
Diabetes mellitus	0 (0%)	4 (40%)	0 (0%)	0.23
Renal failure (Cr>2.0mg/dL)	0 (0%)	1 (10%)	0 (0%)	1.00
Catecholamine dependent	0 (0%)	5 (50%)	4 (67%)	0.63
NYHA class III/IV	0/0	8/2	2/4	0.12
BNP (pg/mL)	48±58	1041±671	522±310	0.10
CRT device implantation	0 (0%)	5 (50%)	1 (17%)	0.31
Echocardiographic data				
LVDd (mm)	56±5	78±8	71±11	0.15
LVDs (mm)	37±6	69±9	64±12	0.30
LVEF (%)	63±12	26±6	23±8	0.40
DcT (ms)	186±35	169±77	166±19	0.92
IVST (mm)	9±2	9.5±0.8	7.8±2.3	0.06
PWT (mm)	8±2	8.4±1.3	7.7±1.6	0.33
MR grade (3/4) ^{‡‡}	3/7	0/10	2/4	0.13
Forward stroke volume (mL)	61.6±16.2	46.3 ± 13.6	35.4 ± 12.1	0.12
MR volume (mL)	58.7±20.8	34.5 ± 14.9	59.9 ± 23.1	0.017
Mw (erg·cm ⁻³ ·10 ³)	106±31	35±7	35±7	0.98
Cardiac index (L/min/m ²)	2.5±0.5	1.9±0.5	1.8±0.4	0.68
LVEDV (ml)	114±34	283±97	225±72	0.23
LVEDVI (ml/m ²)	72±14	169±53	146±43	0.40
LVESV (ml)	47±25	210±84	176±67	0.42
LVESVI (ml/m ²)	30±16	125±14	115±18	0.67

Values±standard deviation. [†] MVR+PMTA group vs MVP+LVP group. ^{‡‡}Severe MR was defined as: effective regurgitant orifice (ERO) ≥ 0.20 cm², regurgitant volume ≥ 30 mL in functional MR; ERO ≥ 0.40 cm², regurgitant volume ≥ 60 mL in degenerative MR. ACE-I, angiotensin-converting enzyme inhibitors; ARB, angiotensin receptor blockers; BNP, brain natriuretic peptide; CRT, cardiac resynchronization therapy; DcT, deceleration time; IVST, interventricular septal thickness; LVDd, left ventricular end-diastolic dimension; LVDs, left ventricular end-systolic dimension; LVEF, left

ventricular ejection fraction; LVEDV(I), left ventricular end diastolic volume (index); LVESV(I), left ventricular end-systolic volume (index); LVP, LV plasty; MR, mitral regurgitant; MVP, mitral valve plasty; MVR, mitral valve replacement; Mw, the slope in the preload recruitable stroke work relationship; NYHA, New York Heart Association; PMTA; papillary muscle tugging approximation; PWT, posterior wall thickness.

Table 2. Operative data

Variables	Degenerative	Functional MR		p value [†]
	MR (n=10)	MVP+LVP (n=10)	MVR+PMTA (n=6)	
Operation time (min)	309 ±65	440 ± 22	308 ± 29	0.003
Cardiopulmonary bypass time (min)	168 ±40	251 ± 67	160 ± 11	0.006
Aortic cross-clamp time (min)	116 ±30	129 ± 21	84 ± 14	<0.001
MAP ring size (mm)	30 ± 2.9	29 ± 2.3	-	-
MVR valve size (mm)	-	-	28 ± 1.6	-
Left ventriculoplasty (%)				
Overlapping <u>left</u> ventriculoplasty	-	8 (80%)	-	-
Batista type	-	2 (20%)	-	-
Total blood transfusion volume (mL)	825 ± 962	2844 ± 1005	1852 ± 1504	0.13
Concomitant procedures (%)				
Tricuspid annuloplasty	1 (10%)	9 (90%)	6 (100%)	1.00
Maze / Pulmonary vein isolation	1 (10%)	7 (70%)	2 (33%)	0.30
CRT device implantation	0 (0%)	5 (50%)	1 (17%)	0.31
Mechanical circulatory support (%)				
IABP <u>pre-OP</u>	0 (0%)	0 (0%)	0 (0%)	-
IABP <u>post-OP</u>	0 (0%)	3 (30%)	0 (0%)	0.16
PCPS <u>pre-OP</u>	0 (0%)	0 (0%)	0 (0%)	-
PCPS <u>post-OP</u>	0 (0%)	0 (0%)	0 (0%)	-

Values±standard deviation. [†] MVR+PMTA group vs MVP+LVP group. CRT, cardiac resynchronization therapy; IABP, intra-aortic balloon pumping; LVP, LV plasty; MR, mitral regurgitation; MAP, mitral annuloplasty; MVR, mitral valve replacement; OP, operation; PCPS, percutaneous cardiopulmonary support; PMTA; papillary muscle tugging approximation

Fig. 1

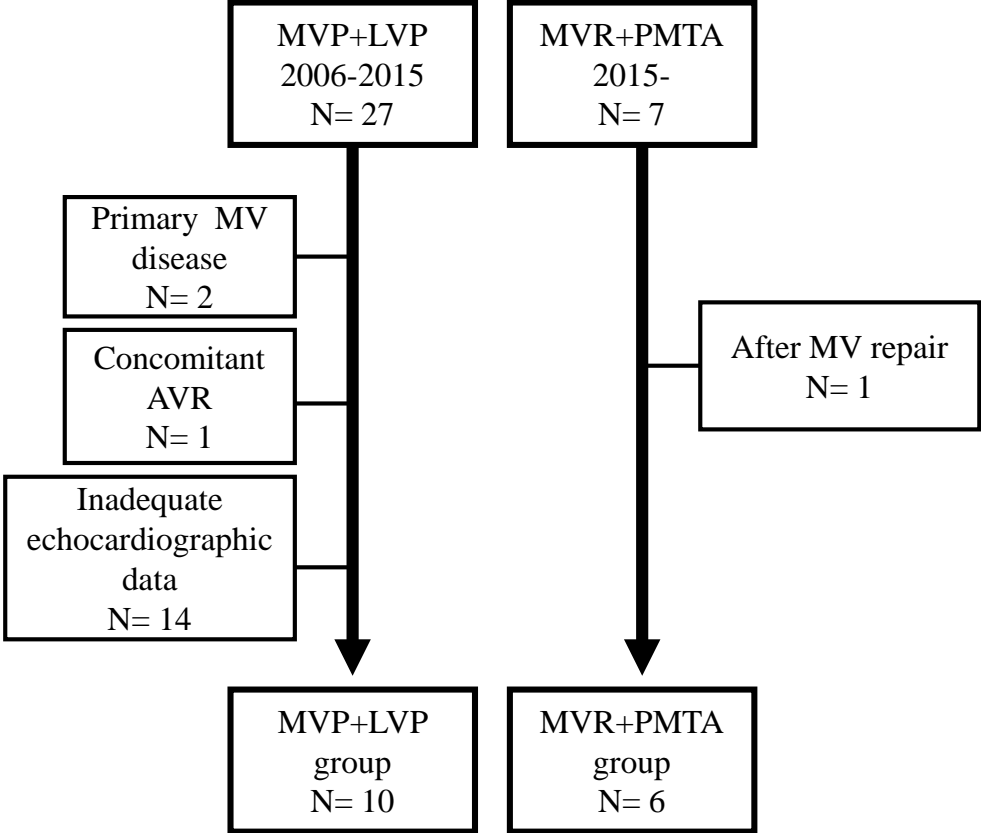
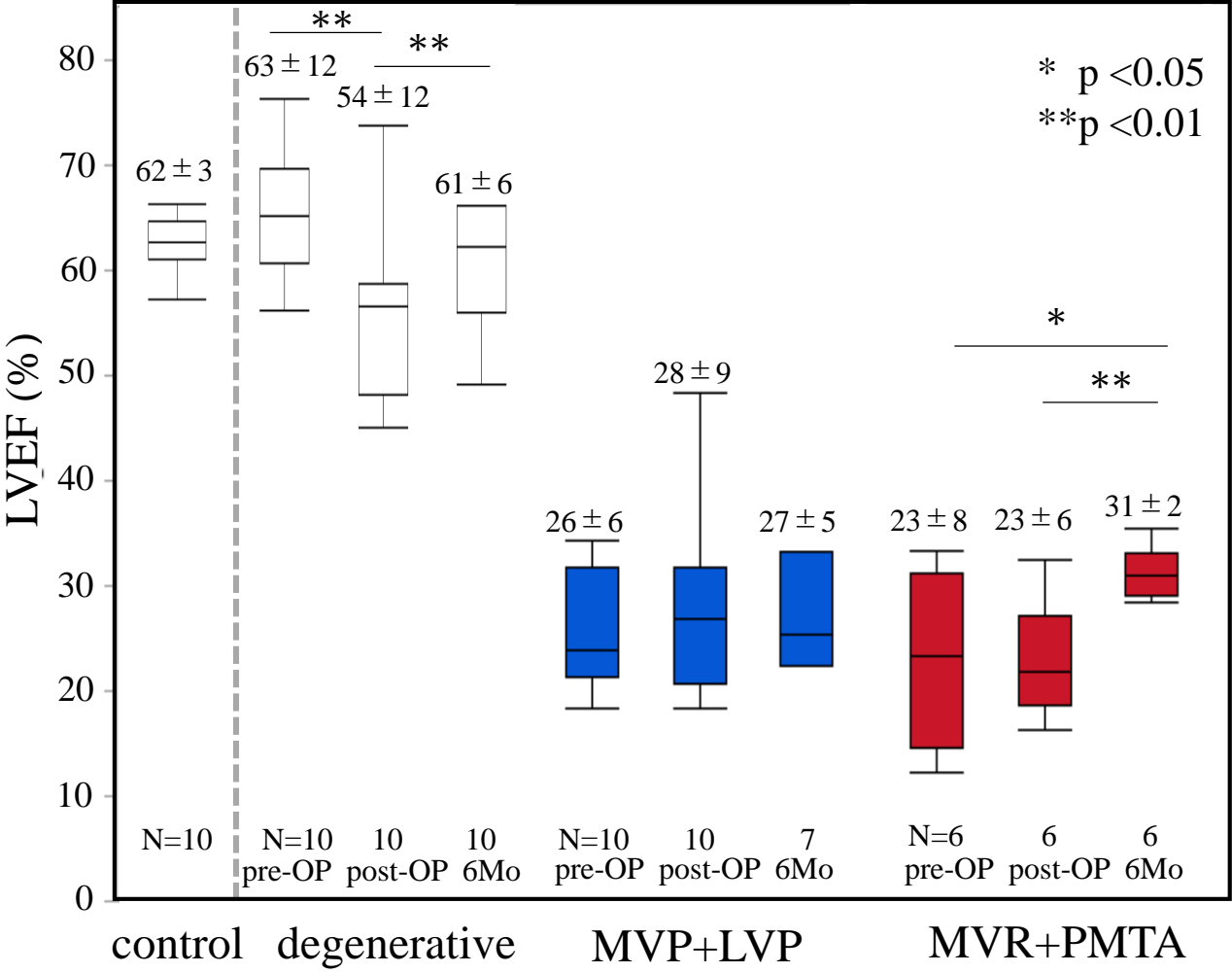


Fig. 2

A



B

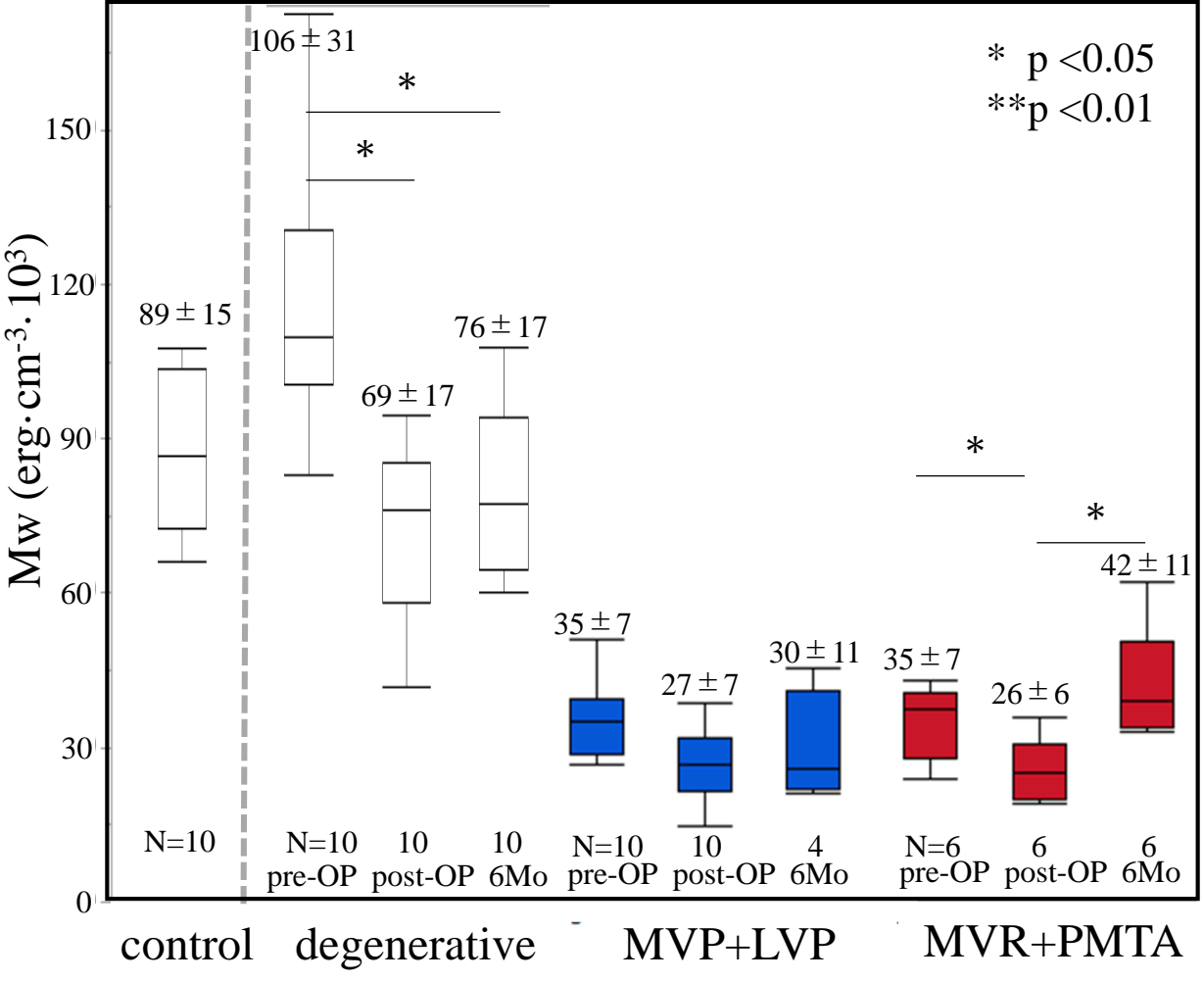


Fig. 3

