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Original article

B-type natriuretic peptide response and reverse left ventricular remodeling after surgical correction of functional mitral regurgitation in patients with advanced cardiomyopathy

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ABSTRACT

Background: Restrictive mitral annuloplasty (RMA) can reverse left ventricular (LV) remodeling and reduce plasma B-type natriuretic peptide (BNP), a surrogate biomarker of heart failure. However, the relationship between reverse LV remodeling and plasma BNP changes after RMA is poorly defined. We explored the main hemodynamic factors contributing to change in plasma BNP after RMA in patients with functional mitral regurgitation (MR).

Methods: Twenty-four patients with moderate to severe functional MR secondary to LV systolic dysfunction [ejection fraction (EF) <40%] underwent 64-row multidetector computed tomography (MDCT) before and 1.4 months after RMA. LV end-diastolic volume index (EDVI), end-systolic volume index (ESVI), LVEF, and regional and global end-systolic wall stress (ESS) were calculated from 3-dimensional MDCT images, with blood samples for plasma BNP measurement collected the same day.

Results: After RMA, LV volumes and global ESS were decreased, while LVEF improved (all $p < 0.01$). There were significant correlations between changes in LVEDVI and LVESVI ($r = 0.90$, $p < 0.0001$), LVESVI and global ESS ($r = 0.54$, $p = 0.006$), and global ESS and LVEF ($r = -0.60$, $p = 0.002$). The median value for the plasma BNP also decreased from 597 pg/ml [interquartile range (IQR), 360–934 pg/ml] to 207 pg/ml (IQR, 124–271 pg/ml), in association with changes in LVEDVI ($r = 0.47$, $p = 0.019$), LVESVI ($r = 0.56$, $p = 0.004$), LVEF ($r = -0.60$, $p = 0.002$), and global ESS ($r = 0.74$, $p < 0.0001$). Multivariate regression analysis showed that global ESS change was the strongest contributor to change in natural-log-transformed plasma BNP (standardized partial regression coefficient = 0.59, $p = 0.004$), indicating a strong association between decrease in LV afterload and reduction in plasma BNP level after RMA.

Conclusions: There may be a significant association between LV reverse remodeling and plasma BNP change after RMA. Furthermore, LV end-systolic myocardial stress may be the key mechanical stimulus influencing plasma BNP after surgical correction for functional MR. Whether these favorable BNP responses and reverse remodeling can predict improved survival requires further study.

Introduction

Heart failure is a major public health problem. Functional mitral regurgitation (MR) is a common complication of both ischemic and non-ischemic advanced cardiomyopathy, and the presence of

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functional MR in the setting of severe systolic left ventricular (LV) dysfunction (advanced cardiomyopathy) is strongly associated with poor outcome [1].

Restrictive mitral annuloplasty (RMA) using an undersized prosthetic ring is a preferred surgical option to treat moderate to severe functional MR. Previous observational studies demonstrated that surgical mitral annuloplasty [2–5] can effectively eliminate functional MR and promote LV reverse remodeling, thus yielding other hemodynamic changes and improvements in exercise capacity and New York Heart Association (NYHA) functional class. Other reports have also noted that plasma B-type natriuretic peptide (BNP) concentration, a strong predictor of prognosis in patients with heart failure, was significantly reduced after RMA [2,6]. Although these beneficial changes suggest the possible effectiveness of surgical treatment in modifying natural history of the disease, the impact of mitral valve annuloplasty on survival remains under discussion [2,7–9], highlighting the need for a comprehensive understanding of the neurohormonal response mechanism before and after surgical intervention for functional MR.

Systolic wall stress is a reasonable surrogate for LV afterload and the major determinant of LV systolic function [10], although it is considerably difficult to assess regional and global myocardial stress in left ventricles with different shapes. Multi-detector computed tomography (MDCT) is an emerging technique that enables more accurate and reproducible contour definition than echocardiography. We recently developed MDCT-based analysis software for computing global and regional circumferential myocardial stress [3,11]. In the present study, we hypothesized that change in systolic myocardial stress, an index of afterload, is a key factor that mainly contributes to LV reverse remodeling and neurohormonal response after surgical correction of MR. To test our hypothesis, we aimed to determine the association between response of plasma BNP and changes in LV function parameters (LV volume, performance and wall stress) in patients undergoing RMA for functional MR, utilizing the serial measurements with cardiac MDCT and our software.

Materials and methods

Study patients

The study population consisted of 24 patients who underwent 64-row MDCT and plasma BNP measurements before and after RMA between 2007 and 2010 (Table 1). All had a diagnosis of advanced cardiomyopathy [LV ejection fraction (EF) <40%] and congestive heart failure symptoms despite receiving maximal medical treatment. Each had clinically important functional MR (moderate to severe MR or regurgitant volume ≥30 ml/beat) secondary to LV remodeling and systolic restrictive motion of mitral leaflets in echocardiography findings. Patients with recent myocardial infarction (<3 months), organic MR, or rheumatic mitral disease, and those who underwent concomitant surgical ventricular reconstruction were excluded from analysis. The study protocol was approved by an institutional review board and all patients provided informed consent.

Table 1
Patient characteristics.

Variables	Entire cases ($n=24$)
Demographics	
Age (years)	64 ± 10
Males	22 (91.7%)
Body surface area (m^2)	1.72 ± 0.18
Ischemic etiology	17 (70.8%)
NYHA class	
II	5 (20.8%)
III	18 (75.0%)
IV	1 (4.2%)
Medications	
Beta-blockers	16 (66.7%)
ACE inhibitors	6 (25.0%)
Angiotensin II receptor blockers	12 (50.0%)
Diuretics	19 (79.2%)

NYHA, New York Heart Association; ACE, angiotensin-converting enzyme.

Surgical procedures

All operations were performed through a median sternotomy under a mild hypothermic cardiopulmonary bypass, with antegrade and retrograde intermittent cold blood cardioplegia. Ring size was determined after careful intraoperative measurements of anterior leaflet height and intertrigonal distance and then downsizing by 2 to 3 sizes. No other adjunct procedures were performed on the valve itself. Consequently, the annuloplasty ring implanted was 24 mm in 14 (58%), 26 mm in 7 (29%), and 28 mm in 3 (13%), respectively. Simultaneous procedures included coronary artery bypass grafting (CABG) in 15 (63%) and tricuspid annuloplasty in 20 (83%).

Cine-MDCT angiography

The protocol of cine-MDCT angiography was described in detail previously [3,11]. LV end-diastolic volume (LVEDV) and end-systolic volume (LVESV) were obtained from the largest and smallest LV chamber MDCT images, respectively. LVEF was calculated as [(LVEDV − LVESV)/LVEDV] × 100. LV volumes were indexed for body surface area (LVEDVI and LVESVI, respectively). All image processing was verified by well-experienced radiologists (S.H. and K.K.).

Left ventricular end-systolic pressure estimation

Blood pressure was obtained non-invasively by a digital sphygmomanometer (cuff) before each MDCT examination. In this study, LV end-systolic pressure was calculated with the following equation: $P = 0.98 \times$ (systolic blood pressure + 2 × diastolic blood pressure)/3 + 11 mmHg [12].

Regional and global myocardial wall stress

Regional and global myocardial stresses were determined using a personal computer with dedicated analysis software (Osaka University-OSCAR STRESS tool, Osaka, Japan; YD, Ltd, Ikoma, Nara, Japan) [3,11]. Regional end-systolic stress (ESS) was calculated on the basis of Janz's method [13] as follows: Regional ESS = $1.332 \times P \times \Delta A_C/\Delta A_W$, where P is LV end-systolic pressure, ΔA_C and ΔA_W are local cross-sectional area of the LV cavity and the cross-sectional area of the LV wall at end-systole, respectively. In the present study, to simplify the display and analysis of regional ESS, 3 LV levels (base, mid, and apex) were determined with reference to long axis and 3 perpendicular short axes at equal intervals. The global ESS was defined as the average values of regional ESS for each element, e.g. basal, mid, or apex-LV short-axis slice, calculated for each patient. All measurements were repeated 2 times, and the average value was used as a final one.

Measurements of plasma B-type natriuretic peptide

Blood samples were drawn from the antecubital vein earlier in the day of MDCT assessment. Plasma BNP levels were measured directly with validated and commercially available

immunoassay kits (Shionogi, Florham Park, NJ, USA and TOSOH, Tokyo, Japan).

Follow-up examinations

Every 6 months to 1 year, each patient was assessed in the department as well as by their primary cardiologist. Functional status was assessed according to NYHA criteria for symptoms of heart failure and plasma BNP level. Clinical follow-up examinations were completed for all patients (100%) with a mean duration of 33 ± 11 months.

Statistical analysis

Categorical data are shown as frequencies and proportions, and were compared using chi-square analysis or Fisher's exact test, as appropriate. Continuous data are presented as the mean ± standard deviation or median with interquartile ranges (IQR), and were compared using Student's *t* test or Mann–Whitney *U* test, as appropriate. Preoperative and postoperative variables were assessed by Wilcoxon signed rank test or repeated-measures analysis of variance (ANOVA), with group, time, and group–time interaction effects. Non-normally distributed variables tested in the repeated ANOVA were natural log-transformed to satisfy normality of the used models, as appropriate. The plasma BNP level was natural log-transformed (*Ln*) to satisfy the normality of the used models, and correlations between *Ln* BNP and hemodynamic variables were tested with Pearson's correlation coefficient (*r*).

Multiple linear regression analysis was used to define the independent determinants for change in *Ln* BNP. Factors obtaining a *p*-value less than 0.1 in the univariate analysis were then entered appropriately into multivariate analysis. The results are summarized as correlation coefficients (*r*) and standardized partial regression coefficients (SPRCs). All *p*-values are 2-sided and values of $p < 0.05$ were considered to indicate statistical significance. Statistical analyses were performed using JMP 7.0 (SAS Institute, Cary, NC, USA), SAS (version 9.2, SAS Institute), and SPSS (version 17.0, SPSS Inc.) statistical software.

Results

Symptoms and plasma BNP before and late after RMA

MR degree was less than grade 2+ in all patients immediately after surgery and significantly decreased from 3.5 ± 0.6 at baseline to 0.5 ± 0.8 ($p < 0.0001$) at 1 month after surgery. The proportion of patients with NYHA class I (no symptoms) or II heart failure increased, while that of those with class III or IV heart failure decreased from baseline to the last follow-up visit (Fig. 1). The symptoms improved by an average NYHA class score of 1.1. The median value for plasma BNP decreased from 597 pg/ml (IQR, 360–935 pg/ml) at baseline to 207 pg/ml (IQR, 124–271 pg/ml) at 1.4 months (IQR, 1.0–2.4 months) after surgery (mean reduction, 48%). The proportion of patients with plasma BNP <100 pg/ml or 100–299 pg/ml increased, while that of those with BNP at 300–500 pg/ml or >500 pg/ml decreased from baseline to the last follow-up visit (Fig. 1).

Change in *Ln* plasma BNP was positively correlated with that in NYHA functional class ($r = 0.50$, $p = 0.011$).

Changes in LV ejection performance and wall stress before and after RMA

All patients underwent 64-row MDCT (SOMATOM Definition Dual Source CT, Siemens, Erlangen, Germany) within 1 month before (at baseline) and 1.4 months (IQR, 1.0–2.4 months) after RMA. Heart rate and blood pressure at the time of image acquisition were not significantly changed in postoperative examinations (Table 2). LVEDVI and LVESVI were decreased and LVEF increased significantly after surgery (Fig. 2). Regional ESS was significantly reduced at the basal, mid, and apex-ventricular levels. Consequently, global ESS was significantly decreased (Fig. 2).

There were significant correlations between ΔLVEDVI and ΔLVESVI ($r = 0.90$, $p < 0.0001$), ΔLVESVI and Δglobal ESS ($r = 0.54$, $p = 0.006$), and Δglobal ESS and ΔLVEF ($r = -0.60$, $p = 0.002$), indicating a strong association between decrease in afterload and improvement in ejection performance after RMA.

Relationship between LV reverse remodeling and BNP response after RMA

There was a substantial correlation between *Ln* BNP value and those for LVEDVI ($r = 0.25$, $p = 0.083$), LVESVI ($r = 0.32$, $p = 0.028$), LVEF ($r = -0.39$, $p = 0.006$), and LV global ESS ($r = 0.50$, $p = 0.0002$) (Fig. 3). The relationship to global ESS showed the highest correlation coefficient.

Δ*Ln* BNP was positively correlated with Δheart rate, ΔLVEDVI, ΔLVESVI, and Δglobal ESS, and negatively with ΔLVEF (Table 3). Results of multivariate regression analysis showed that Δglobal ESS had the most important contribution to Δ*Ln* BNP, which

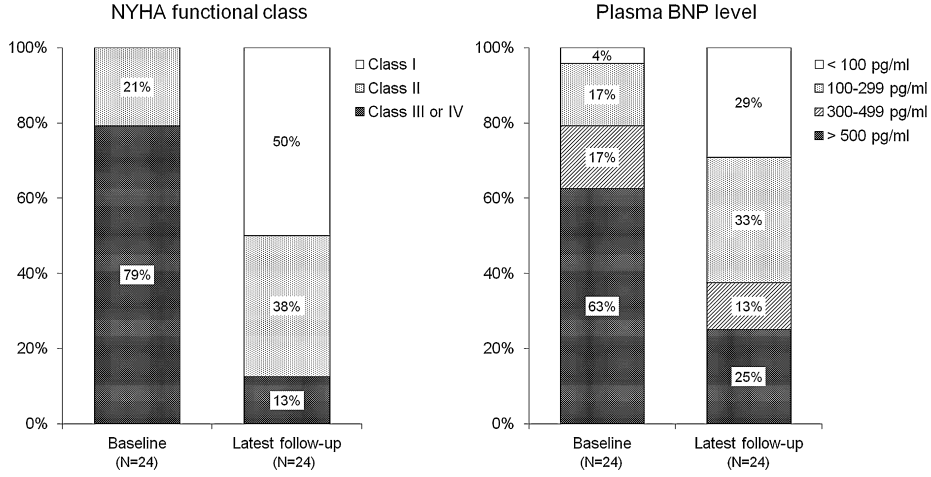

Fig. 1. NYHA functional class and plasma BNP levels at baseline and latest follow-up examination (median, 48 months). NYHA, New York Heart Association; BNP, B-type natriuretic peptide.

Table 2
Pre- and postoperative hemodynamics, LV function, and wall stress.

Variables	Pre-op ($n=24$)	Post-op ($n=24$)	Percent change (%)	p-value
Plasma BNP (pg/ml), median (IQR)	597 (360–935)	207 (124–271)	−48 ± 36	<0.0001
Hemodynamics				
Heart rate (beats/min)	77 ± 17	76 ± 13		0.778
Systolic blood pressure (mmHg)	118 ± 25	115 ± 21		0.399
Diastolic blood pressure (mmHg)	69 ± 16	66 ± 12		0.247
Mean arterial pressure (mmHg)	86 ± 18	82 ± 15		0.243
End-systolic pressure (mmHg)	96 ± 18	89 ± 15		0.063
LV volume and function				
LVEDVI (ml/m^2)	134 ± 26	117 ± 34	−13 ± 17	0.003
LVESVI (ml/m^2)	100 ± 27	78 ± 33	−22 ± 26	0.0003
LVEF (%)	26 ± 7	36 ± 13	9 ± 12[a]	0.001
Global ESS (kdyne/cm^2)	246 ± 34	194 ± 34	−20 ± 15	<0.0001
Basal average ESS (kdyne/cm^2)	265 ± 42	202 ± 28	−22 ± 15	<0.0001
Mid average ESS (kdyne/cm^2)	266 ± 42	223 ± 45	−15 ± 16	0.0002
Apex average ESS (kdyne/cm^2)	196 ± 59	157 ± 40	−21 ± 20	0.002

Pre-op, preoperative; Post-op, postoperative; BNP, B-type natriuretic peptide; LVEDVI, left ventricular end-diastolic volume index; LVESVI, left ventricular end-systolic volume index; LVEF, left ventricular ejection fraction; ESS, end-systolic wall stress.
[a] Absolute change from baseline to 1.4 months after surgery.

indicated a strong association between decrease in LV afterload and reduction in plasma BNP level after RMA.

Impact of RMA with or without CABG on postoperative LV reverse remodeling and function

Preoperative clinical profile of patients who received RMA alone and those who received RMA plus CABG is summarized in the supplemental data 1. There were no significant differences in the demographics between the groups, except for a higher prevalence of ischemic etiology of heart failure in patients who received RMA plus CABG, as compared with those who received RMA alone.

From baseline to 1 month after surgery, RMA alone group decreased LVEDVI by 12% and LVESVI by 21%, yielding improved LVEF (absolute change 9.8 ± 14.5%). Similarly, RMA plus CABG decreased LVEDVI by 13% and LVESVI by 23%, yielding improved LVEF (absolute change 8.7 ± 10.3%). Importantly, there were no differences between the groups with regard to the magnitude of change in LV volumes and improvement in LVEF, as well as decrease in LV global ESS (interaction effect $p > 0.05$ for all) (supplemental data 2).

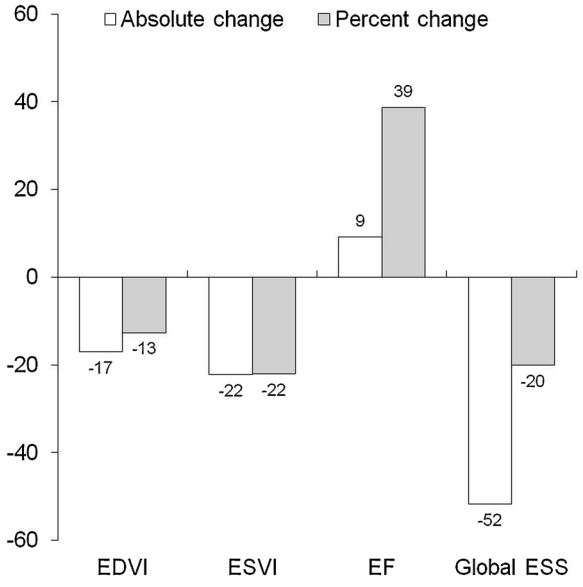

Fig. 2. Absolute and percent changes in the LVEDVI, LVESVI, and EF from baseline (before surgery) to 1.4 months after surgery. LVEDVI, left ventricular end-diastolic volume index; LVESVI, left ventricular end-systolic volume index; EF, ejection fraction.

Discussion

This is the first study to examine the association among LV reverse remodeling, myocardial wall stress, and changes in plasma BNP concentration after surgical correction of functional MR in patients with cardiomyopathy. We used cine-MDCT images, an emerging technique that enables more accurate and reproducible contour definition than echocardiography, along with our in-house software to measure LV volumes, function, and regional and global myocardial wall stress. The following results were obtained: (1) RMA effectively eliminated functional MR and improved symptoms, (2) RMA abolished LV volume overload and partially reversed LV remodeling, and reduced LV end-systolic wall stress and plasma BNP concentration, (3) the reduction in myocardial wall stress was significantly associated with improvement in LVEF, and, most importantly, (4) among the LV function parameters measured with cine-MDCT images, change in systolic wall stress was significantly correlated with decrease in plasma BNP at 1.4 months after RMA. Together, these findings indicate that decreased systolic wall stress (LV afterload reduction), derived from LV volume unloading conferred by RMA with optimal medical treatment, is the major factor contributing to both improved LV ejection performance and reduced plasma BNP concentration.

It was once believed that the presence of chronic MR creates a systolic unloading effect by providing a low resistance ejection into the left atrium [14]. This traditional hypothesis held that the mitral valve functions as a "pop-off valve" for the failing ventricle and surgical correction might have prohibitive risks in patients with severely remodeled LV because of postoperative afterload (systolic myocardial wall stress) excess and subsequent decline in LV ejection performance [3,11]. However, several recent studies showed that RMA procedure could induce reverse LV remodeling (decrease in LV volumes and increase in ejection fraction) after correction of MR in failing ventricle [15–18]. This controversial fact was partially settled by the previous publication from Takeda and colleagues which confirmed a strong association between the improvement in LV ejection fraction and the reduction in LV end-systolic wall stress in patients with advanced cardiomyopathy who received RMA procedure. This indicates that the mechanism of reverse LV remodeling process is related to the afterload reduction derived from ventricular volume unloading by eliminating MR [3]. Those findings lead us to hypothesize that reduction in systolic

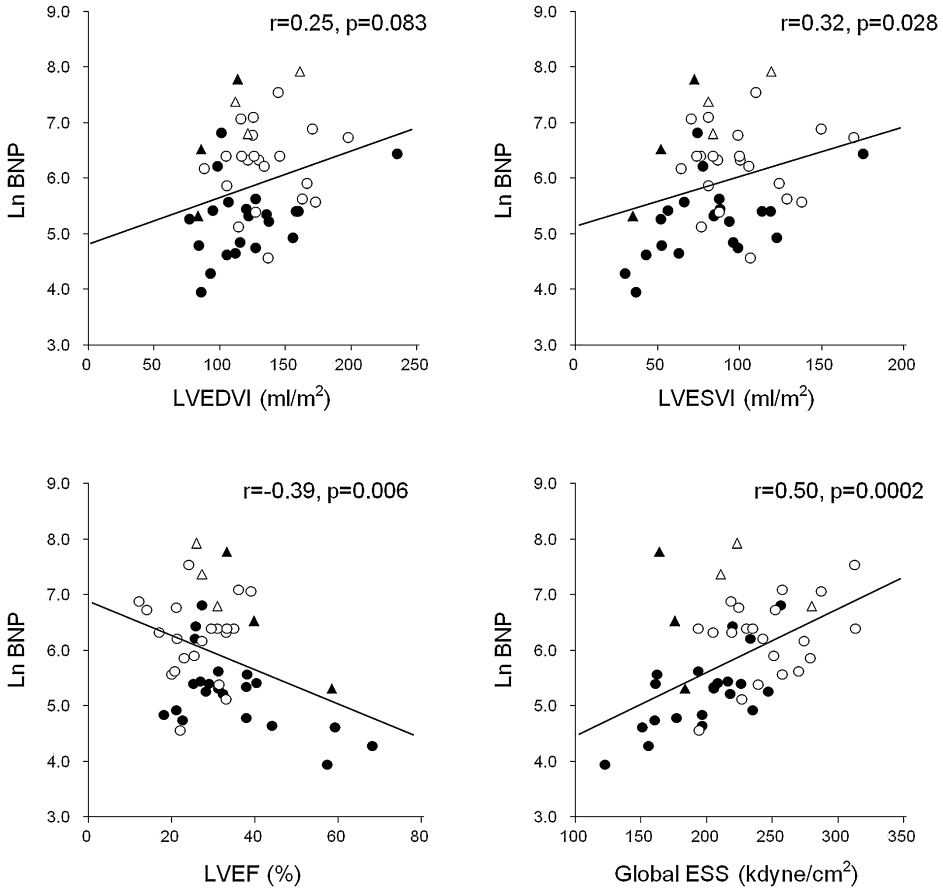

Fig. 3. Associations between *Ln* BNP and LVEDVI, LVESVI, LVEF, and global ESS. The open and filled circles indicate values without hemodialysis at baseline and 1.4 months after surgery, respectively. Open and filled triangles indicate values in the cases with hemodialysis. *Ln*, natural log-transformed; BNP, B-type natriuretic peptide; LVEDVI, left ventricular end-diastolic volume index; LVESVI, left ventricular end-systolic volume index; LVEF, left ventricular ejection fraction; ESS, end-systolic wall stress.

myocardial stress is a key factor that mainly contributes to LV reverse remodeling and plasma BNP changes after surgical correction of MR, although the relationship between LV afterload reduction and relief of neurohormonal activation was not fully investigated in their studies.

BNP is a hormone of cardiac origin that is released from the ventricular myocardium in response to cardiac overload [19]. In experimental studies, cardiac myocyte stretch is the key stimulus for BNP production and release [20], whereas that for BNP release in the clinical setting of systolic heart failure remains controversial. Some human studies have found that LV end-diastolic pressure or stress is the most important hemodynamic parameter regulating the level of circulating BNP [21], while others have noted that LVESVI or LV end-systolic wall stress is the key parameter for cardiac BNP release, indicating that LV geometry and systolic stress, rather than diastolic filling pressure or diastolic stress, are the most important mechanical determinants of cardiac BNP release [22,23]. Our finding that a reduction in BNP was most

Table 3
Determinants of change in natural log-transformed B-type natriuretic peptide level before and after restrictive mitral annuloplasty.

Variables	Univariate		Multivariate	
	r	*p*-value	SPRC	*p*-value
Hemodynamics				
ΔHeart rate (beats/min)	0.421	0.041	0.206	0.225
ΔSystolic blood pressure (mmHg)	0.130	0.549		
ΔDiastolic blood pressure (mmHg)	−0.046	0.832		
ΔMean arterial pressure (mmHg)	0.026	0.905		
ΔEnd-systolic pressure (mmHg)	0.002	0.993		
LV volume and function				
ΔLVEDVI (ml/m^2)[a]	0.471	0.019		
ΔLVESVI (ml/m^2)	0.560	0.004	0.075	0.738
ΔLVEF (%)	−0.599	0.002	−0.092	0.696
ΔGlobal ESS (kdyne/cm^2)	0.737	<0.0001	0.594	0.004

Δ indicates postoperative value minus preoperative value. SPRC, standardized partial regression coefficient; LVEDVI, left ventricular end-diastolic volume index; LVESVI, left ventricular end-systolic volume index; LVEF, left ventricular ejection fraction; ESS, end-systolic wall stress.
[a] ΔLVEDVI was not entered into the multivariate analysis because of a strong correlation between ΔLVEDVI and ΔLVESVI ($r = 0.901$).

significantly associated with decreased systolic wall stress after RMA may support the conclusions of the latter studies. Furthermore, this is a novel finding indicating a possible hemodynamic factor that contributes to changes in BNP after RMA in patients with severe systolic LV dysfunction. However, the hemodynamic determinants of BNP production and release, especially the relative contributions of systolic and diastolic wall stress, remain to be elucidated.

The impact of RMA on late survival in patients with significant functional MR remains controversial. In a previous study, there was no clearly demonstrable mortality benefit conferred by RMA as compared with medical therapy [7]. Some studies reported a lack of long-term functional improvements and survival benefit over and above that of medical therapy, including β-blockers or cardiac resynchronization therapy [24,25]. In addition, many other studies have failed to demonstrate long-term survival benefits for patients with ischemic functional MR who underwent RMA plus CABG as compared with patients treated with CABG alone [2,5,8]. On the other hand, Deja et al. analyzed the impact of RMA on survival in the recently reported Surgical Treatment for Ischemic Heart Failure (STICH) trial and suggested that adding MV annuloplasty to CABG may improve survival as compared with CABG or medical therapy alone [9]. It is well established that systolic wall stress is a strong prognostic indicator in patients with systolic LV failure. Plasma BNP concentration is also an important prognostic indicator in heart failure [26], while changes in BNP have been shown to be associated with corresponding improvement in survival [27]. Prior to surgical referral, most of our patients had been treated with optimal medical therapy. Therefore, the present results indicate that performance of RMA in patients with advanced cardiomyopathy and moderate to severe MR may consistently reverse LV remodeling, reduce systolic wall stress and plasma BNP and, consequently, yield a corresponding improvement in long-term survival.

The effects of RMA without CABG on postoperative LV reverse remodeling and function are uncertain. Many surgeons and cardiologists are not confident regarding beneficial effects on LV function gained from the RMA procedure alone. In a prior study, Takeda et al. [3] used cine-MDCT to investigate the effects of RMA on LV volumes and function in 24 patients with dilated cardiomyopathy (13 non-ischemic, 11 ischemic) and functional MR, and found a 13% reduction in LVEDVI, 21% reduction in LVESVI, and improvement in LVEF from 27% at baseline to 33% at 2.3 months after surgery. Their overall results are consistent with those of the present study. Additionally, we found that the changes in LV volume, function, systolic wall stress, and plasma BNP level from baseline to 1.4 months after surgery were similar between patients with and without concomitant CABG. Together, these results indicate that the beneficial changes during the acute phase of surgical intervention are at least partly related to LV volume unloading and afterload reduction conferred by RMA.

Relation to previous studies

The reduction in LVESVI of 22% observed in our MDCT study is consistent with that reported in a recent study [2], in which LVESVI was measured using cardiac magnetic resonance (CMR), the gold standard for LV volume measurement. In that study, LVESVI in patients with ischemic cardiomyopathy who underwent mitral valve repair during CABG was reduced by 28% after 1 year. In contrast, Westenberg et al. conducted a CMR study [28] and reported that LVESV was not significantly changed at 2 months or 1 year after RMA in patients with early-stage non-ischemic cardiomyopathy. On the other hand, in their initial echocardiographic study, Bolling et al. [4] observed a reduction in LVESV of 15% after 4–6 months in patients with end-stage dilated cardiomyopathy. These contrasting results may be attributable to differences regarding disease etiologies, degrees of LV remodeling progression, MR quantification, time of follow-up examinations, suboptimal annuloplasty techniques, and incomplete coronary artery revascularization. Interestingly, the cases presented by Westenberg et al. showed a significantly smaller LVESV value at baseline, indicating early stage cardiomyopathy with less LV remodeling, as compared with other studies.

The results of plasma BNP levels after RMA in this study are consistent with an observational study [6] and randomized trial [2]. Paparella et al. [6] observed that mean BNP decreased from 471 pmol/L to 56 pmol/L at 6 months after surgery in patients who underwent CABG combined with RMA. They speculated that a greater postoperative decrease in BNP was associated with more extensive LV reverse remodeling. Chan et al. also found that BNP decreased from 748 pg/ml to 191 pg/ml (75% reduction) in their CABG plus RMA group as compared with a lower amount of decrease from 681 pg/ml to 287 pg/ml (58% reduction) in patients who underwent CABG alone ($p = 0.003$). They speculated that a persistent elevation in BNP level suggested persistent LV dysfunction and patients with BNP >100 pg/ml remain at high risk for cardiovascular mortality and morbidity, which was consistent with our results. Additional randomized studies with higher numbers of patients and longer follow-up periods are necessary to better confirm whether these favorable BNP responses and reverse remodeling can predict improved survival.

Limitations

This study was retrospective in nature and investigated a small number of subjects; thus, our results should be interpreted cautiously until verified in an independent, prospective study. Inclusion of patients with different etiologies for heart failure and those who had undergone concomitant surgical intervention might have influenced the results. In addition, the perioperative multimodal treatments might have affected the change in the plasma BNP. However, the preoperative medical therapies were continued without any modification after surgical intervention. In particular, the use and dosage of angiotensin-converting enzyme inhibitors and angiotensin-II receptor blockers were not changed; thus, their influence on the change in the plasma BNP might be considered to be negligible.

Lack of data regarding end-diastolic wall stress prevented us from determining relative contributions of systolic and diastolic wall stress on change in plasma BNP after RMA. Finally, we measured changes in the LV volumes, wall stress, and plasma BNP during the short-term period after surgery. The data with additional follow-up computed tomography scans would help us to discuss the long-term efficacy of RMA for functional MR, which remains to be determined. Despite these limitations, our findings may help elucidate therapeutic response mechanism and provide an impetus for the treatment strategy aimed at afterload reduction in patients with advanced cardiomyopathy.

Conclusion

There may be a significant association between LV reverse remodeling and plasma BNP change after RMA. Furthermore, LV end-systolic myocardial stress may be the key mechanical stimulus influencing plasma BNP after surgical correction for functional MR. Whether these favorable BNP responses and reverse remodeling can predict improved survival requires further study.

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Disclosures

The authors have no conflicts of interest to report.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.jjcc.2015.02.015.

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