Journal of Cardiology 66 (2015) 279–285

Contents lists available at ScienceDirect

Journal of Cardiology

journal homepage: www.elsevier.com/locate/jjcc

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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ARTICLE INFO

Article history:
Received 23 October 2014
Received in revised form 21 January 2015
Accepted 16 February 2015
Available online 4 April 2015

Keywords:
Advanced cardiomyopathy
Functional mitral regurgitation
Restrictive mitral annuloplasty
Plasma B-type natriuretic peptide
Wall stress

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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http://dx.doi.org/10.1016/j.jjcc.2015.02.015
0914-5087/

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