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Original article

Mechanisms of changes in functional mitral regurgitation by preload alterations

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ABSTRACT

Background: This study aimed to investigate the mechanisms of acute changes in functional mitral regurgitation (FMR) by preload alterations.
Methods: Twenty-two consecutive patients with left ventricular ejection fraction <40% and at least mild FMR underwent transthoracic echocardiography. Passive leg lifting and sublingual administration of nitroglycerin were performed to alter preload. Mitral regurgitant volume (MRV) was assessed using the Doppler method.
Results: MRV changed in parallel with preload alterations. MRV correlated better with tenting height (TH) than with mitral annular area (MAA) at baseline, whereas the difference in the correlate coefficients was not statistically significant ($R = 0.69$ and $R = 0.40$, respectively; $p = 0.19$). On the other hand, changes in MRV between each sequential stage correlated better with those in MAA than with those in TH ($R = 0.68$ and $R = 0.44$, respectively; $p = 0.043$). Multiple regression analysis revealed that baseline TH was the independent determinant of baseline MRV ($R = 0.69$, $p = 0.0004$), whereas changes in MAA with preload alteration were the independent determinant of the changes in MRV ($R = 0.68$, $p < 0.0001$). Changes in left atrial (LA) volume were the independent determinant of the changes in MAA ($R = 0.30$, $p = 0.0063$).
Conclusions: Acute changes in FMR with preload alterations resulted from the transverse changes in MAA rather than the longitudinal changes in tethering–tenting of mitral geometry, and mitral annular deformation was determined by changes in LA volume. Preload reduction might help heart failure treatment through the reduction in FMR resulting from the decrease in LA and mitral annular size.

Introduction

An increase in preload induces worsening of congestive heart failure and is an important cause of hospitalization due to acute decompensated heart failure [1]. It also deteriorates functional mitral regurgitation (FMR) observed in patients with heart failure with reduced left ventricular (LV) ejection fraction [2,3]. However, little evidence is available regarding the mechanisms of the changes in FMR induced by preload alterations. Passive leg lifting (PLL) is a simple maneuver that rapidly returns 150–200 ml of blood from the veins of the lower extremities to the central circulation [4]. Nitroglycerin (NTG) is a short-lived veno- and arterial vasodilatory agent presumed to influence mainly the preload reduction and, to a lesser extent, the afterload reduction [5,6]. By using these methods to change the preload condition, we investigated the mechanisms of acute changes in FMR by preload alterations in this study.

Methods

Patients

Twenty-two consecutive patients with LV systolic dysfunction and at least mild FMR referred to the echocardiography laboratory of Osaka City General Hospital were enrolled in this study. LV

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systolic dysfunction was diagnosed with LV ejection fraction <40%. Patients with New York Heart Association functional class IV heart failure, acute decompensated heart failure, non-sinus rhythm, structurally abnormal valvular disease, and more than mild aortic regurgitation were excluded. Patients treated with hemodialysis were also excluded. The study protocol was approved by the institutional review board of the Osaka City General Hospital, and written informed consent was obtained from all patients.

Echocardiography

All patients underwent two-dimensional transthoracic echocardiography. Echocardiography was performed with Philips IE33 instrument with second-harmonic mode (Philips Medical Systems, Bothell, WA, USA). Examinations were performed after the following conditions were stabilized: (1) baseline rest in supine position after maintaining it for 10 min, (2) PLL at 45° angle after maintaining it for 3 min to increase preload as previously described [7], (3) another rest in supine position after maintaining it for 3 min to restore preload (re-rest), and (4) 3 min after sublingual spray administration of 0.3 mg NTG to further decrease preload.

LV end-diastolic volume, LV end-systolic volume, LV ejection fraction, and maximal left atrial (LA) volume were obtained using the method of discs according to the guidelines from the American Society of Echocardiography [8]. Transmitral flow velocity curves in diastole and annular tissue Doppler imaging signals were obtained as previously described [9]. Peak pulse Doppler velocities were analyzed to determine early (E) and late (A) diastolic flow across the mitral valve, and the E/A ratio was calculated. The deceleration time of the E-wave was also measured. Tissue Doppler imaging of the mitral annulus was obtained from the apical 4-chamber view. Peak early diastolic tissue Doppler velocities of the medial mitral annulus (e') were measured, and the E/e' ratio was calculated as an index of the mean LA pressure. The inferior vena cava (IVC) diameter and its respiratory change were evaluated as indices of the right atrial pressure to reveal the degree of preload. The diameter of IVC was measured at expiration. Respiratory change in IVC was calculated as the ratio of the dimensional difference between inspiration and expiration to the diameter at expiration [10]. For the assessment of systolic mitral valve structure, mitral annular area (MAA) and mitral tenting height (TH) were measured. MAA was calculated as the ellipse with two annular diameters obtained from the apical long-axis and the apical commissure views in mid-systole [11] (Fig. 1A and B). Mitral TH was measured as the shortest distance between the mitral coaptation and the mitral annular plane at 4-chamber view in mid-systole [12] (Fig. 1C).

The Doppler-derived volumetric method was applied for measurements of total LV stroke volume (LVSV), forward LVSV, and mitral regurgitant volume (MRV) [13]. Total LVSV was determined as the time velocity integral of transmitral flow velocity in the pulsed-wave Doppler mode at the mitral annular multiplied by the MAA measured at early to mid-diastole. Forward LVSV was determined as the time velocity integral of trans-LV outflow tract flow velocity in the pulsed-wave Doppler mode multiplied by LV outflow tract area. The LV outflow tract area was calculated as the circle with the diameter of the length measured in the parasternal long-axis view at the position of the pulsed-wave Doppler data at systole. MRV was obtained as the difference between the total LVSV and the forward LVSV: MRV (ml) = total LVSV (ml) – forward LVSV (ml). The degree of MR was determined as follows, as previously described: mild, MRV 10–29 ml; and moderate or severe, ≥30 ml [14]. We compared echocardiographic parameters during 4 stages. Changes between sequential stages in each parameter were calculated, and Δ implied the changes derived from preload alterations. Consequently, each parameter in 22 patients between 3 sequential preload alterations had 66 values of Δ.

Statistical analysis

Categorical variables were expressed as absolute values and percentages and were compared using the chi-square test. Continuous variables were expressed as mean ± standard deviation. The differences in the continuous variables between the sequential stages, baseline, PLL, re-rest, and NTG were assessed using the A-priori repeated measures single-factor analysis of variance followed by the post hoc pairwise comparisons. Linear regression analysis was conducted to assess the correlation and correlation coefficients, which were expressed as R values. Using the Fisher r-to-z transformation, the significance of the difference between two correlation coefficients was assessed as the difference between two z values. To analyze independent determinants of MRV and ΔMRV by preload alterations, we performed multivariate analyses based on stepwise multiple linear regression, with the p-values for entry into and removal from the model set at 0.05 and 0.10, respectively. Intraobserver and interobserver variabilities of the baseline values of TH and MAA and the changes in TH and MAA among four adjacent stages were assessed as correlation coefficients (R) with linear regression analysis and

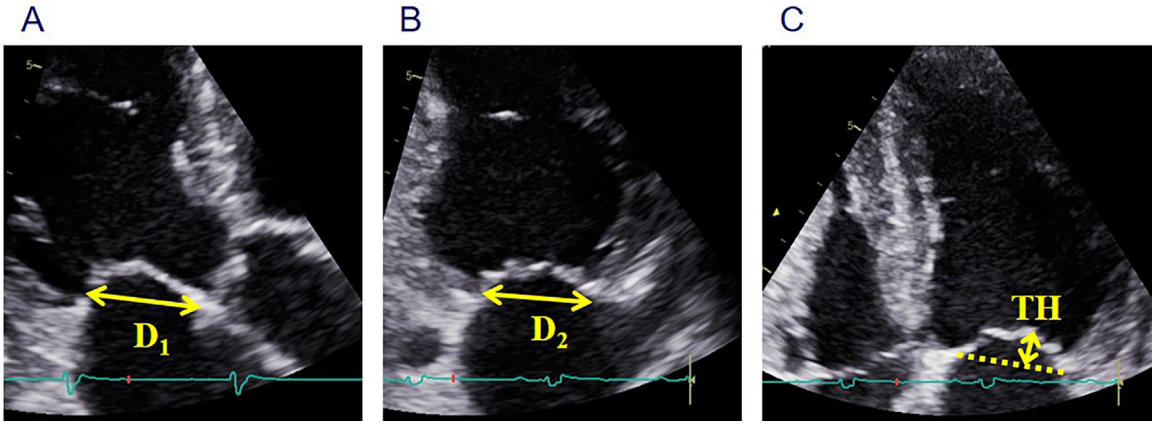

Fig. 1. The measurement of MAA and TH. Two annular diameters were measured calculated from the apical long-axis view; D_1 (A) and the apical commissure view; D_2 (B). MAA was calculated as follows: MAA = $(D_1 \times D_2 \times \pi)/4$ (cm^2). TH was measured as the shortest distance between the mitral coaptation and the mitral annular plane at 4-chamber view (C). Each measurement was performed in mid-systole.
MAA, mitral annular area; TH, tenting height.

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