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Mitral Valve Enlargement in Chronic Aortic Regurgitation as a Compensatory Mechanism to Prevent Functional Mitral Regurgitation in the Dilated Left Ventricle

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Objectives The aim of this study was to test the hypothesis that mitral valve (MV) enlargement occurring in chronic aortic regurgitation (AR) prevents functional mitral regurgitation (FMR).

Background Chronic AR causes left ventricular (LV) dilation, creating the potential for FMR. However, FMR is typically absent during compensated AR despite substantial LV enlargement. Increased mitral leaflet area has been identified in AR, but it is unknown whether increased MV size can represent a compensatory mechanism capable of preventing FMR.

Methods Database review of 816 patients with at least moderate AR evaluated the prevalence of FMR. A total of 90 patients were enrolled prospectively for 3-dimensional echocardiography (30 AR, 30 FMR, and 30 controls) to assess MV geometry including total leaflet area.

Results FMR was present in 5.6% of AR patients by database review. Prospectively, only 1 AR patient had more than mild FMR despite increased LV end-diastolic volume (82 ± 22, 86 ± 23, and 51 ± 12 cm^3/m^2, respectively, for AR, FMR vs. control patients; $p < 0.01$) and similar sphericity index, annular area, and tethering distances compared with FMR. Total MV area was largest in AR (31.3% greater than normal), increasing significantly more than in FMR. The ratio of valve size to closure area was maintained in AR, whereas decreases in this ratio and LV ejection fraction independently predicted FMR.

Conclusions FMR prevalence is low in chronic AR. MV leaflet area is significantly increased compared with control and FMR patients, preserving a normal relationship to the area needed for closure in the dilated LV. Understanding the mechanisms underlying this adaptation could lead to new therapeutic interventions to prevent FMR. (J Am Coll Cardiol 2013;61:1809–16) © 2013 by the American College of Cardiology Foundation

Functional mitral regurgitation (MR) is a common complication of cardiomyopathies associated with higher mortality (1–4). Its mechanisms have been related to left ventricular (LV) enlargement and distorted shape, restricting mitral valve (MV) closure (5–8). However, LV remodeling alone fails to explain why MR severity varies among individuals with similar degrees of tethering (9). Recent evidence showed that MV leaflets can enlarge in response to LV morphological changes (9–12), with the potential to reduce MR (10). Experimentally, mechanical stretch can promote adaptive MV growth (11), but little is known about the clinical implications of this phenomenon. A naturally occurring setting in which MV adaptation can be studied is in patients with chronic aortic regurgitation (AR), in whom functional MR is infrequent (13,14) despite often severe LV dilation (6,8,13–21). This absence of MR challenges the concept linking functional MR (FMR) solely to LV remodeling. Interestingly, necropsy data previously demonstrated MV enlargement in chronic AR (22), but this finding has

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Abbreviations and Acronyms

3D = 3-dimensional
AR = aortic regurgitation
FMR = functional mitral regurgitation
LV = left ventricular
MR = mitral regurgitation
MV = mitral valve

not been related to FMR or its determinants in vivo. Whether this phenomenon can be seen as an adaptation counterbalancing LV dilation to prevent MR is unknown.

We tested the hypothesis that MV enlargement occurs in chronic AR and preserves normal mitral geometry relative to the dilated left ventricle to prevent MR. We first assessed FMR prevalence in chronic AR by database review. We then prospectively enrolled patients for 3-dimensional (3D) echocardiography to assess MV size and its relation with LV geometry and function in patients with either chronic AR or MR (ischemic or nonischemic) and in normal control patients using recently developed capabilities for measuring MV area noninvasively (10).

Methods

Retrospective analysis. To assess the prevalence of MR in patients with AR, we searched our institutional echocardiographic database for patients older than 18 years of age with moderate or severe AR who had a transthoracic echocardiogram within the past 5 years. Exclusion criteria were more than mild systolic dysfunction (left ventricular ejection fraction [LVEF] <40%), LV regional wall motion abnormality, severe aortic stenosis (valve area <1.0 cm^2), MV organic pathology (prolapse, rheumatic disease, mitral cleft, endocarditis, and extensive annular calcification), presence of an aortic or mitral prosthesis, and Marfan syndrome. In all patients having more than mild MR, the echocardiographic images were reviewed to confirm the presence of FMR.

Prospective recruitment. From January 2011 to June 2012, we prospectively enrolled 90 subjects for 3D echocardiography: 30 consecutive patients who had at least moderate AR without any previously stated exclusion criteria, 30 patients with moderate or severe FMR (ischemic or nonischemic) and LV end-diastolic dimension comparable to the AR group, and 30 normal control patients (age and sex comparable to AR group) with normal echocardiograms and without known cardiac disease (patients with treated hypertension and no evident LV hypertrophy were not excluded). AR severity was assessed with an integrative approach using color Doppler (vena contracta), regurgitant volume and fraction, and assessment of flow reversal in the descending aorta (23). MR was graded as trace, mild, moderate, or severe integrating color Doppler jet area and vena contracta width (23–25). Medical records were consulted to assess the cause and known duration of AR. All patients gave informed consent before enrollment. The study was approved by the hospital's institutional review board.

Echocardiography. All prospectively enrolled patients underwent standard transthoracic echocardiography using a Philips iE33 scanner with a 5-MHz transducer (Philips Healthcare, Andover, Massachusetts). Full-volume 3D datasets were obtained from the apical window using an X3 matrix-array transducer. The analysis was performed by a single observer using QLAB 5.1 (Philips Healthcare) and custom software for MV area and tethering geometry (Omni 4D, M.D.H.). The 3D datasets were analyzed separately and blinded to the presence and severity of AR and MR. The 3D LV end-diastolic and end-systolic volumes were measured. LV sphericity was evaluated by the ratio of short-axis diameter/long-axis length at end-diastole and end-systole (8,26). Midsystolic (identified by frame count) tethering distances from papillary muscle tips to contralateral annulus (26) were measured from the 3D dataset. Midsystolic mitral annular area was calculated as the projection of the annular trace onto its average or least-squares plane. Total mitral leaflet area was measured in diastole (Fig. 1) using a previously described and validated method that integrates valve area traced from the 3D dataset (10). Closure area was defined as the closed leaflet surface between the LV and left atrium in mid-systole, and thus represents the minimal area that needs to be covered by the leaflets to occlude the mitral orifice. The ratios of total leaflet to annular area and of total leaflet area to closure area were calculated to assess the adequacy of leaflet adaptation relative to LV and annular changes. Dimensions, areas, and volumes were indexed for body surface area. MV thickness was measured in the 2-dimensional echocardiography datasets in the parasternal long-axis view in a diastolic frame without rapid motion with the leaflets as perpendicular as possible to the echocardiographic beam to take advantage of its axial resolution (27–29). As FMR can be related to decreased closing forces in a failing ventricle (30,31), we also measured key parameters of LV contractility including 3D calculated LVEF, end-systolic wall stress reflecting afterload (32,33), and end-systolic volume index, which is relatively preload independent. In the absence of continuous-wave Doppler in the patients without MR to provide true transmitral pressure, mitral closing forces were estimated as: force (N) = 0.0133 · systolic arterial pressure (mm Hg) · leaflet area (cm^2).

Statistics. Continuous variables are expressed as mean ± SD and categorical variables as number (percentage). Differences in proportions were assessed by the chi-square test. Logistic univariate and multivariate regressions were used to assess the predictors of significant MR in the database population. Age, sex, LVEF, and LV end-diastolic and end-systolic dimensions were included in the model. In the prospectively recruited population, echocardiographic variables of the AR group were compared with those of the FMR and control groups. Differences in means among the 3 groups were assessed by 1-way analysis of variance with Bonferroni multiple-comparison tests. We assessed the differential relationship of mitral leaflet area and LV end-diastolic volume by linear regression including group (AR or FMR) as an interaction term. Known AR duration and