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Comprehensive Imaging in Women With Organic Mitral Regurgitation

Implications for Clinical Outcome

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ABSTRACT

OBJECTIVES The purpose of this study was to compare women and men with organic mitral regurgitation (MR) using pre- and post-operative comprehensive imaging and to analyze the effect on outcome.

BACKGROUND Management of organic MR has no sex-specific guideline recommendation, and sex differences on the basis of comprehensive imaging and links to outcome remain largely unknown.

METHODS Comprehensive imaging (MR cause, quantitation, ventricular and atrial measures, and post-operative reverse cardiac remodeling) was analyzed in 217 women and 447 men who underwent operations for organic MR from 1990 to 2000 with long-term follow-up analysis.

RESULTS Pre-operatively, women and men had similar age and ejection fraction. In women, a smaller left ventricle (LV) more often labeled as normal size (23% vs. 13%), left atrium size, and regurgitant volume (all $p < 0.01$) contrasted with higher pulmonary pressure and more heart failure symptoms (41% vs. 19%), which more often triggered surgery (all $p < 0.01$). However, normalizing for body size, LV and left atrial diameters and regurgitant volume were at least as large in women versus men. Similar normalized MR severity was confirmed by similar post-operative reverse cardiac remodeling in women and men (all $p > 0.06$). During follow-up (10.4 ± 3.7 years) women had similar survival as men ($p = 0.5$) but experienced more heart failure (at 15 years: $36 \pm 7\%$ vs. $19 \pm 3\%$; $p = 0.03$; adjusted hazard ratio 1.63 [95% confidence interval: 1.08 to 2.43]; $p = 0.02$) linked to more frequent pre-operative heart failure symptoms ($p < 0.001$).

CONCLUSIONS Women who undergo mitral surgery for organic MR receive similar repair for similar degenerative lesions defined by echocardiography and enjoy similar survival and reverse cardiac remodeling, but they incur excess post-operative heart failure linked to worse pre-operative presentation. Imaging that does not account for body size shows smaller absolute cardiac dimensions and regurgitant volumes, which tends to underestimate MR severity in women. (J Am Coll Cardiol Img 2016;9:388–96) © 2016 by the American College of Cardiology Foundation.

Mitral regurgitation (MR) is the most frequent valvular heart disease (1). Despite similar MR prevalence in men and women (1), few studies have analyzed sex differences (2), and potential sex differences (3,4) are hindered by lack of comprehensive pre- and post-operative imaging. Furthermore, the links between sex differences vis-a-vis imaging, surgical-referral triggers, cardiac reverse remodeling, and post-operative outcomes remain undefined. Because of these uncertainties, U.S. and European guidelines mention no sex-specific differences in management or outcome, do not account for body size of men and women for MR surgical triggers, and refer only to absolute left ventricular (LV) dimensions (5,6). To address these uncertainties, comprehensive imaging data are warranted regarding specific MR cause, quantitative MR assessment, LV and left atrial (LA)

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remodeling before surgery, and reverse-remodeling after surgery. Thus, we analyzed a consecutive cohort of men and women who underwent operations for organic MR with comprehensive imaging and long-term post-operative outcome. We aimed at verifying the null hypothesis that women who underwent mitral surgery for organic MR: 1) had similar clinical presentation, particularly similar MR severity and cardiac remodeling; and 2) had similar clinical and LV outcomes as men. Rejection of these null hypotheses would have major clinical implications for organic MR assessment and management in women, for whom no specific recommendation has yet been made.

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METHODS

We analyzed consecutive patients who underwent mitral surgery for pure, acquired, isolated organic MR (repair or replacement) at Mayo Clinic, Rochester, Minnesota, from 1990 through 2000. Our main cohort of interest required comprehensive imaging defining MR cause, MR quantitation, LV/LA remodeling, and post-operative reverse remodeling, thus including patients with: 1) complete clinical and echocardiographic assessment within 6 months prior to and after surgery; 2) quantitative pre-operative assessment of MR severity; and 3) detailed post-operative outcome (**Figure 1**). A verification cohort (organic MR operated during the same period, irrespective of comprehensive imaging availability) was also analyzed to verify bias-absence. We excluded patients age <18 years, with previous valve surgery, functional MR, cardiomyopathy, or congenital or pericardial disease. MR that was considered "moderate" with surgery indicated for symptoms, LV dysfunction (ejection fraction <60%, end-systolic dimension ≥40 mm), pulmonary hypertension, or atrial fibrillation considered linked to MR was not excluded (7). The study was approved by the Mayo Clinic Institutional Review Board.

DOPPLER ECHOCARDIOGRAPHIC ASSESSMENT. Comprehensive Doppler and 2-dimensional echocardiography provided data prospectively recorded and obtained by direct electronic transfer. Echocardiography was performed pre-operatively at 27 ± 35 days (median 14 days) and post-operatively at 6 ± 10 months. This time frame allows for LV reverse remodeling in MR (8).

MR cause was defined by echocardiography and confirmed by surgical direct valve inspection.

LV and LA dimensions were obtained by 2-dimensional echocardiography. Normal range for left ventricular end-diastolic diameter (LVEDD) used Gardin regression (9). We considered LVEDD enlargement mild-moderate if it was <20% and severe if it was >20% above the upper normal limit. Left ventricular ejection fraction (LVEF), when used unaltered by electronic download, is strongly predictive of outcome in patients with organic MR after surgery (10) and who are under medical management (11,12). LV mass was obtained using a recommended formula (13).

MR severity, quantified by the PISA (proximal isovelocity surface area) method, quantitative Doppler (14), or both, was expressed as effective regurgitant orifice (ERO) and regurgitant volume (RVol). The PISA method was used more frequently (81%) than quantitative Doppler (62%), but use of the 2 methods was attempted as often as possible and correlations between methods remained >0.90 ($p < 0.0001$), with slopes of regressions not different from 1.0, as previously validated (15). Severe MR was considered for RVol ≥60 ml/beat (14) obtained in all patients, whereas incomplete continuous-wave Doppler limited ERO calculation in some patients. However, RVol and ERO are highly correlated ($r = 0.92$) and provide similar categorization power.

All measurements were also indexed by body surface area (BSA) at echocardiography.

CLINICAL ASSESSMENT AND FOLLOW-UP. Pre-operative clinical data were collected during systematic consultation and echocardiography. Cardiac rhythm was assessed by electrocardiogram. Comorbid conditions were summarized by the Charlson score (16). Cardiovascular history, medications, and follow-up events involved reviewing all medical records, regular follow-up questionnaires, contacts with personal physicians and next of kin, and death certificates. Clinical endpoints were all-cause post-operative mortality and heart failure (HF). HF diagnosis relied on combination of symptoms and signs in Framingham criteria (17), on the basis of a comprehensive review of patients' records, notes, and documents as well as direct consultations/contacts with patients/physicians/next of kin.

STATISTICAL ANALYSIS. Data are presented as percentages for categorical variables and as mean ± SD or median (25th, 75th percentiles) for continuous variables. Distribution of continuous variables was tested by Shapiro-Wilk test. Direct comparison between men and women used Student *t* tests or Wilcoxon rank sum tests for continuous variables and chi-square or Fisher exact tests for categorical variables as appropriate. Survival and HF rates, estimated using the

ABBREVIATIONS AND ACRONYMS

BSA = body surface area
ERO = effective regurgitant orifice
HF = heart failure
LA = left atrial
LV = left ventricular
LVEDD = left ventricular end-diastolic diameter
MR = mitral regurgitation
RVol = regurgitant volume