Survival in Patients with Degenerative Mitral Stenosis: Results from a Large Retrospective Cohort Study

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Background: Severe mitral annular calcification causing degenerative mitral stenosis (DMS) is increasingly encountered in patients undergoing mitral and aortic valve interventions. However, its clinical profile and natural history and the factors affecting survival remain poorly characterized. The goal of this study was to characterize the factors affecting survival in patients with DMS.

Methods: An institutional echocardiographic database was searched for patients with DMS, defined as severe mitral annular calcification without commissural fusion and a mean transmitral diastolic gradient of ≥2 mm Hg. This resulted in a cohort of 1,004 patients. Survival was analyzed as a function of clinical, pharmacologic, and echocardiographic variables.

Results: The patient characteristics were as follows: mean age, 73 ± 14 years; 73% women; coronary artery disease in 49%; and diabetes mellitus in 50%. The 1- and 5-year survival rates were 78% and 47%, respectively, and were slightly worse with higher DMS grades (P = .02). Risk factors for higher mortality included greater age (P < .0001), atrial fibrillation (P = .0009), renal insufficiency (P = .004), mitral regurgitation (P < .0001), tricuspid regurgitation (P < .0001), elevated right atrial pressure (P < .0001), concomitant aortic stenosis (P = .02), and low serum albumin level (P < .0001). Adjusted for propensity scores, use of renin-angiotensin system blockers (P = .02) or statins (P = .04) was associated with better survival, and use of digoxin was associated with higher mortality (P = .007).

Conclusions: Prognosis in patients with DMS is poor, being worse in the aged and those with renal insufficiency, atrial fibrillation, and other concomitant valvular lesions. Renin-angiotensin system blockers and statins may confer a survival benefit, and digoxin use may be associated with higher mortality in these patients. (J Am Soc Echocardiogr 2016;■:■-■.)

Keywords: Mitral stenosis, Degenerative, Mitral annular calcification, Survival

Mitral annular calcification (MAC) is a marker for atrial fibrillation, atherosclerosis, and higher stroke risk.[1-4] However, calcific or degenerative mitral stenosis (DMS) resulting from severe MAC continues to be an ill-defined disease process with frequent occurrence in the aging population.[5] It is being increasingly encountered in elderly patients undergoing mitral and aortic valve interventions. However, outcomes and factors affecting outcomes in patients with DMS are not well known. Observational studies have suggested multiple potential targets to modify the disease process in calcific aortic stenosis, which shares pathogenetic mechanisms with DMS.[6-11] We investigated the clinical associations and outcome determinants in a large cohort of well-characterized patients with DMS.

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METHODS

Patient Population

This retrospective cohort study was conducted at a large university medical center. The study was approved by the institutional review board, which waived the requirement to obtain patient consent. The echocardiographic database was electronically searched for the period from June 1995 to June 2011 for patients with DMS (this is a searchable field in our database) or mitral stenosis plus severe MAC and mean mitral valve gradient ≥2 mm Hg. Those classified as having rheumatic mitral stenosis and those noted to have commissural fusion were not included. Diagnosis of severe MAC in our laboratory was based on modified Framingham criteria of echodense structure with associated acoustic shadowing, at the junction of the atrioventricular groove and the anterior and posterior mitral leaflet with a thickness of ≥5 mm on M-mode or two-dimensional echocardiography.[12] The severity of MAC was qualitatively assessed in the parasternal long-axis view, the parasternal short-axis view at the mitral valve level, and the apical two- or four-chamber view, as marked echodensity with extension into the anterior or posterior leaflets. Commissural fusion was assessed in the parasternal short-axis view at the mitral valve level. Although our categorization of MAC was created before the Multi-Ethnic Study of Atherosclerosis, it was fairly similar.[13] Duplicate records were removed, yielding a cohort of 1,004

Abbreviations

ACE = Angiotensin-converting enzyme

ARB = Angiotensin II receptor blocker

CKD = Chronic kidney disease

DMS = Degenerative mitral stenosis

LV = Left ventricular

MAC = Mitral annular calcification

MG = Mean transmitral gradient

patients. Comprehensive chart reviews were performed, and clinical, echocardiographic, and pharmacologic data were compiled. Mortality data were compiled primarily through the use of the Social Security Death Index, supplemented by chart review.

Clinical Variables

Hypertension was defined as blood pressure > 140/90 mm Hg or a history of hypertension and the use of antihypertensive medications. Diabetes mellitus was defined as fasting blood glucose ≥ 126 mg/dL or being on a regimen of antidiabetic medications. Renal insufficiency was defined as serum creatinine ≥ 2 mg/dL. Also, the stage of renal dysfunction (chronic kidney disease [CKD] stages 1–5) was determined on the basis of glomerular filtration rate, calculated using the Cockcroft-Gault equation. Coronary artery disease was deemed to be present if any of the following were present: a history of angina pectoris, myocardial infarction, positive stress test results, angiographic evidence of coronary artery disease, coronary intervention, coronary artery bypass surgery, or presence of significant Q waves on the surface electrocardiogram.

Pharmacologic Data

Pharmacotherapy at the time of echocardiography was recorded. This was broadly categorized as using or not using aspirin, β-blockers, calcium channel blockers, diuretics, angiotensin-converting enzyme (ACE) inhibitors or angiotensin II receptor blockers (ARBs), digoxin, and statins.

Echocardiographic Data

All patients had previously interpreted two-dimensional echocardiographic examinations by a level III–trained echocardiographer according to standard guidelines.[14-16] Left ventricular (LV) ejection fraction was assessed either by planimetry or visually and entered into a database at the time of the examination.

There are no standard criteria for grading DMS, because the pressure half-time method–derived valve area is not validated for DMS. Hence, it was graded on the basis of mean transmitral gradient (MG) as mild or grade 1 for MG 2 to 5 mm Hg, moderate or grade 2 for MG 6 to 8 mm Hg, and severe or grade 3 for MG ≥ 9 mm Hg, somewhat arbitrarily. Also, because of significant acoustic shadowing, mitral valve area assessment by planimetry was not performed in these patients. Figure 1 shows representative images of different grades of DMS.

Aortic stenosis in our laboratory was defined by a mean transaortic Doppler gradient > 15 mm Hg or a peak transaortic velocity > 2 m/sec, and severity was graded as mild (MG 15–25 mm Hg or V2 2–2.9 m/sec), moderate (MG 25–40 mm Hg or V2 3–3.9 m/sec), or severe (MG > 40 mm Hg or V2 > 4 m/sec).[15]

Mitral regurgitation was graded qualitatively by color Doppler flow mapping. Mitral regurgitation severity was assessed by vena contracta width and jet area in multiple views and by related hemodynamic consequences, by the interpreting echocardiographer in accordance with American Society of Echocardiography guidelines.[16] Similarly, tricuspid regurgitation was also graded qualitatively by Doppler color flow imaging.[16]

Right atrial pressure was estimated from the diameter of inferior vena cava from the subcostal view. High right atrial pressure was defined as inferior vena cava diameter > 2.1 cm and <50% variation during inspiration.

Mortality Data

The end point of the study was death due to any cause. Mortality data were obtained from the National Death Index, supplemented by chart review.

Statistical Analysis

The data were imported into StatView version 5.01 (SAS Institute, Cary, NC) for statistical analysis. Group comparisons were made using Student's t test for continuous variables and the χ^2 test for categorical variables. Survival analysis was performed using various statistical tools, such as Kaplan-Meier analysis and Cox regression models, as discussed later in the "Results" section. In view of nonrandomized assignment of various pharmacologic agents, we performed propensity score analysis to reduce the effect of treatment bias. The effect of a particular therapy on survival was analyzed by adjusting for the propensity score for a particular therapy developed by logistic regression analysis of the variables predicting that treatment. Then the survival analysis by Cox regression analysis was adjusted for the propensity score to reduce the effect of treatment bias. Separate propensity scores were developed for different pharmacologic agents. Propensity score analysis has been shown to reduce bias by about 85%.[17,18] P value < .05 were considered to indicate statistical significance.

RESULTS

Baseline Patient Characteristics

Baseline patient characteristics are shown in Table 1. The mean age was 73 ± 14 years, 73% were women, 59% were Caucasian, and 21% were Hispanic. Coronary artery disease was present in 49%, diabetes mellitus in 50%, and chronic renal insufficiency in 37%. The prevalence rates of stages 1, 2, 3, 4, and 5 CKD were 12%, 19%, 36%, 20%, and 13%, respectively. The mean mitral diastolic gradient was 4.1 ± 1.7 mm Hg, and the mean grade of mitral stenosis severity was 1.2 ± 0.5 on a scale of 0 to 3. DMS was mild in 78%, moderate in 14%, and severe in 8% of the patients. The mean heart rate for the entire group was 75 ± 13 beats/min, with no difference among those with mild, moderate, or severe DMS. None of the subjects had a resting heart rate > 100 beats/min.

Survival Patterns and Effect of DMS Severity

Over a mean follow-up period of 3.5 ± 2.8 years, there were 549 deaths, with 1-, 5-, and 10-year survival rates of 78%, 47%, and 25%, respectively. Higher DMS grades were associated with lower 1- and 5-year survival (P = .02). Survival as a function stenosis severity is shown in Figure 2.

Clinical Variables Associated with Survival

Univariate clinical associations of poor survival included greater age (P < .0001), atrial fibrillation (P = .0009), and renal insufficiency