Mild Expression of Mitral Valve Prolapse in the Framingham Offspring: Expanding the Phenotypic Spectrum

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Background: Mitral valve (MV) prolapse (MVP) is a common disorder associated with mitral regurgitation, endocarditis, heart failure, and sudden death. Nondiagnostic morphologies have been described in the familial context and may represent early expression of MVP in those genetically predisposed. The aim of this study was to explore the spectrum of MVP abnormalities in the community and compare their clinical and echocardiographic features.

Methods: We measured annular diameter MV leaflet displacement, thickness, anterior and posterior leaflet projections onto the annulus, MV leaflet coaptation height (posterior MV leaflet projection/annular diameter), and MR jet height in 296 individuals of the Framingham Offspring Study with MVP (n = 77), the "abnormal anterior coaptation" (AAC) phenotype (n = 11) or "minimal systolic displacement" (MSD) (n = 57), and 151 age-matched and sex-matched referents with no MVP or its nondiagnostic forms.

Results: AAC did not meet diagnostic displacement criteria but resembled MVP with regard to annular diameter and leaflet thickness ($P > .05$ for both). AAC was similar to posterior MVP with regard to posterior leaflet asymmetry and an anteriorly shifted coaptation ($P = .91$). Compared to patients with MSD and referents, patients with AAC had greater leaflet coaptation height, thickness, and annular diameter ($P < .05$ for all). MSD shared the posterior leaflet asymmetry with MVP, but the coaptation point was more posterior (coaptation height = 31% vs. 42%, $P < .0001$), as seen in referents. A higher proportion of patients with MVP had jet height $\geq$ 2 mm (mild or greater MR) compared with the other participants (44% vs. 16%, $P < .0001$).

Conclusions: Nondiagnostic morphologies are observed in the community and share the common feature of posterior leaflet asymmetry with MVP. AAC and MSD may thus represent early expressions of MVP. Longitudinal studies are warranted to elucidate the natural history of these phenotypes. (J Am Soc Echocardiogr 2014;27:17-23.)

Keywords: Mitral valve prolapse, Echocardiography

Mitral valve (MV) prolapse (MVP) is a common disorder (2%–5%)[1-3] characterized by fibromyxomatous changes in one or both of the mitral leaflets with leaflet displacement into the left atrium.[4,5] When associated with significant mitral regurgitation (MR), MVP can lead to endocarditis, heart failure, arrhythmia, and even sudden death.[6-13] Despite its being the most common cause of primary MR requiring surgery,[14] little is known about the genetic mechanisms underlying the genesis and progression of MVP. To date, three loci for autosomal-dominant, nonsyndromic MVP have been described on chromosomes 11, 16, and 13.[15-17] Whereas filamin A has been identified as causing an X-linked form of MVP,[18,19] the genes for the more common form of autosomal-dominant MVP are unknown.

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This work was supported by the Founders Affiliate American Heart Association Clinical Research Program (Dr Delling) and by the National Heart, Lung, and Blood Institute's Framingham Heart Study (Contract No. N01-HC-25195), R01HL080124, and RO1HL0107385 (Dr Vasan).

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0894-7317/$36.00

http://dx.doi.org/10.1016/j.echo.2013.09.015

Abbreviations

AAC = Abnormal anterior coaptation

FHS = Framingham Heart Study

JH = Mitral regurgitation jet height

LV = Left ventricular

MR = Mitral regurgitation

MSD = Minimal systolic displacement

MV = Mitral valve

MVP = Mitral valve prolapse

In the family linked to chromosome 13 and in other families,[17] we have shown that previously nondiagnostic morphologies of MVP may represent mild or early stages of phenotypic expression in gene carriers. These morphologies include the "abnormal anterior coaptation" (AAC) form and "minimal systolic displacement" (MSD). Both the AAC phenotype and MSD share features of excessive leaflet motion with fully affected patients, as demonstrated by superior motion toward the left atrium, bulging of the posterior leaflet relative to the anterior (albeit not diagnostic by quantitative assessment), and coaptation asymmetry. In addition, in the AAC form, leaflet excess can also manifest itself by anterior motion and a shift of the coaptation point toward the septum and the aortic root (Figure 1), as detailed below (see "Methods"). In our genetic studies, AAC members and individuals with MSD shared either the complete or a major portion of the haplotype with fully diagnostic MVP.[17] These nondiagnostic forms may therefore represent an early expression of MVP in those genetically predisposed.

The spectrum of mild MVP abnormalities noted above has been described to date only in families. Our aim was to demonstrate the existence of nondiagnostic forms of MVP in the community. The Framingham Heart Study (FHS) represents an ideal setting to explore the phenotypic heterogeneity of MVP in the general population with a focus on AAC morphologies and MSD. We also aimed to compare nondiagnostic forms with full-blown MVP with regard to anatomic features (MV and left chamber characteristics) and functional parameters (degree of MR).

Recognizing "early forms" of MVP is important because MVP has been shown to manifest clinically in the fifth or sixth decade of life as a severe cardiac event in tertiary care–based studies.[6,7,9-11,13,20,21] Early recognition of nondiagnostic morphologies, if they indeed progress, may facilitate newer therapeutic approaches, analogous to those currently being investigated in both the Marfan syndrome and nonsyndromic MVP, in which angiotensin II receptor blockade leads to down regulation of transforming growth factor–β and limitation of clinical disease progression.[22-25]

METHODS

Participants

Individuals who participated in the fifth examination cycle of the FHS Offspring Cohort (1991–1995) constituted the sampling frame for our investigation. The examination protocol was approved by the institutional review board of Boston University Medical Center, and all subjects provided written informed consent.

At the fifth examination cycle, all attendees underwent routine transthoracic echocardiography (see below). Because quantification of echocardiographic parameters on all 3,845 individuals of the Offspring generation was deemed challenging, the fifth Offspring Cohort was reviewed qualitatively by one investigator (E.J.B.), with special emphasis placed on subjects identified in previous examinations by Framingham sonographers as having possible superior leaflet displacement. The 151 individuals identified in this way were paired with controls (1:1) matched for age and sex who were also drawn from the fifth examination cycle but who were initially coded as having no evidence of prolapse. Leaflet coaptation point (anterior vs. posterior) was not among the selection criteria of cases or controls when our sample was originally generated on the basis of qualitative parameters only. Of this initial sample of 302 individuals, echocardiographic images of six individuals were deemed of inadequate quality for detailed analysis. Therefore, the final sample for our quantitative investigation consisted of 296 individuals (151 controls). Also, for the purpose of this investigation, the total number of Offspring individuals in the fifth generation was 3,485 (3,491 − 6). The Offspring Cohort prevalence of MVP was calculated on the basis of this denominator.

Clinical Characteristics

At the fifth examination cycle, all attendees underwent routine medical histories, targeted physical examinations for cardiovascular disease, anthropometry, and laboratory assessments of cardiovascular disease risk factors. Clinical variables used in the present investigation included age, sex, body mass index (weight in kilograms divided by the square of height in meters), and, to evaluate the potential for clinical detection of nondiagnostic morphologies compared with MVP, the presence of a precordial systolic murmur on auscultation. Additional clinical variables, such as history of smoking, systolic and diastolic blood pressure, and treatment for hypertension, were included in the analysis, because tobacco use and hypertension may be considered potential "stressors" to the MV.

Echocardiographic Characteristics

All subjects underwent standard two-dimensional echocardiography using a commercially available system (Sonos 1000; Hewlett-Packard Medical Products, Andover, MA) that used a 2.5-MHz transducer. Images included complete parasternal, apical, and subcostal views and color Doppler assessment of valvular regurgitation; they were stored on VHS tapes for subsequent review. All measurements were performed using an offline cardiac analysis system (DigiView, Houston, TX).

Echocardiograms were examined blinded to previous MVP diagnosis[3] and clinical history. Using current two-dimensional echocardiographic criteria,[26,27] the diagnosis of MVP was made by measurement of maximal MV leaflet superior systolic displacement relative to the line connecting the annular hinge points (annular diameter). The anterior MV leaflet projection and posterior MV leaflet projection onto the mitral annulus also were assessed at end-systole (Figure 1D).[17] The meeting point of the MV leaflets relative to the annulus was quantified by the leaflet coaptation height (posterior MV leaflet projection/annular diameter; see Figure 1). Normally, the MV leaflets meet within the posterior 25% to 30% of the left ventricular (LV) cavity[17] because the posterior leaflet is shorter than the anterior leaflet (Figure 1A). In patients with MVP, coaptation is typically displaced anteriorly,[17] consistent with elongation of the posterior MV leaflet, which can produce excessive leaflet motion not only into the left atrium but also toward the aortic root. Left atrial size was calculated as the anteroposterior maximal left atrial diameter. Finally, MR severity was quantified using color Doppler as the maximum systolic proximal MR jet height (JH). Previous studies