Natural History of Asymptomatic Mitral Valve Prolapse in the Community

Jean-François Avierinos, MD; Bernard J. Gersh, MB, ChB, DPhil; L. Joseph Melton III, MD; Kent R. Bailey, PhD; Clarence Shub, MD; Rick A. Nishimura, MD; A. Jamil Tajik, MD; Maurice Enriquez-Sarano, MD

Background—The outcome of mitral valve prolapse (MVP) is controversial, with marked discrepancies in reported complication rates.

Methods and Results—We conducted a community study of all Olmsted County, Minn, residents first diagnosed with asymptomatic MVP between 1989 and 1998 (N=833). Diagnosis, motivated by auscultatory findings (n=557) or incidental (n=276), was always confirmed by echocardiography with the use of current criteria. End points analyzed during 4581 person-years of follow-up were mortality (n=96, 19±2% at 10 years), cardiovascular morbidity (n=171), and MVP-related events (n=109, 20±2% at 10 years). The most frequent primary risk factors for cardiovascular mortality were mitral regurgitation from moderate to severe (P=0.002, n=131) and, less frequently, ejection fraction <50% (P=0.003, n=31). Secondary risk factors independently predictive of cardiovascular morbidity were slight mitral regurgitation, left atrium ≥40 mm, flail leaflet, atrial fibrillation, and age ≥50 years (all P<0.01). Patients with only 0 or 1 secondary risk factor (n=430) had excellent outcome, with 10-year mortality of 5±2% (P=0.17 versus expected), cardiovascular morbidity of 0.5%/y, and MVP-related events of 0.2%/y. Patients with ≥2 secondary risk factors (n=250) had mortality similar to expected (P=0.20) but high cardiovascular morbidity (6.2%/y, P<0.01) and notable MVP-related events (1.7%/y, P<0.01). Patients with primary risk factors (n=153) showed excess 10-year mortality (45±9%, P=0.01 versus expected), high morbidity (18.5%/y, P<0.01), and high MVP-related events (15%/y, P<0.01).

Conclusions—Natural history of asymptomatic MVP in the community is widely heterogeneous and may be severe. Clinical and echocardiographic characteristics allow separation of the majority of patients with excellent prognosis from subsets of patients displaying, during follow-up, high morbidity or even excess mortality as direct a consequence of MVP. (Circulation. 2002;106:1355-1361.)

Key Words: mitral valve ■ ventricles ■ atrium ■ mortality ■ regurgitation

Mitral valve prolapse (MVP) is common, with a prevalence between 0.6% and 2.4%,1,2 but the clinical outcome of MVP remains controversial. Series from referral centers have reported notable but widely discrepant risks of complications3–7 (from 10% to 44%) and of mortality.3,4,6,8 Accordingly, current guidelines underscore the risks of serious complications,9 but the Framingham study recently reported 84 persons with MVP with no mortality and minimal morbidity.2

Unfortunately, design issues compromise the generalizability of published reports. Series from tertiary care centers3–7 often used diagnostic criteria now considered inappropriate,10,11 limiting their current relevance,3,6 and were subject to referral bias.12,13 Alternatively, in the Framingham study, subjects were systematically screened but were alive, by definition, at diagnosis, and only past complications were reported.2 Hence, the reported uniformly benign outcome, subject to healthy-participant bias, contrasts with other results9 and has been sharply contested.14 Because applicability to community patients is questionable, it is essential to define the natural history of MVP in the community.

Olmsted County, Minn, is a community with major advantages, in that a high proportion of its population is regularly examined and is cared for locally by a few health care providers joined by a common medical record linkage system15 and a single echocardiographic laboratory. Thus, we conducted a community study of residents of Olmsted County, Minn, and hypothesized that prognosis of MVP is widely heterogeneous, with adverse outcomes concentrated in specific subsets of patients who can be identified at diagnosis by clinical and echocardiographic features.
Methods

Study Subjects
Because medical care to residents is offered by a few providers joined by a medical record linkage system, the Rochester Epidemiology project, it was possible to identify all Olmsted County, Minn, residents first diagnosed with MVP between January 1989 and December 1998. With a single laboratory providing echocardiographic services, it was possible to identify all diagnoses confirmed by echocardiography. Residency in Olmsted County ≥1 year before diagnosis was required. Patients with notable dyspnea or angina or with mitral surgery before diagnosis were excluded.

Clinical Data and Follow-Up
Diagnosis, baseline clinical variables, and events after diagnosis were defined prospectively by attending physicians and collected from inpatient and outpatient medical records. Atrial fibrillation (AF) was diagnosed by ECG. Associated conditions were summed as the comorbidity index. Cause of death was ascertained by hospital notes, death reports, death certificates, and autopsy records or by contacting the patients’ physicians.

Echocardiographic Methods
All patients underwent comprehensive Doppler echocardiography during routine examination. Diagnoses of MVP (annular overshoot of leaflets >2 mm in long-axis views), of flail segment, and of thickened leaflets were based on recommended criteria. Left ventricular diameters and ejection fraction (EF) and left atrial diameter measurements were guided by 2D echocardiography. The degree of mitral regurgitation (MR) was assessed semiquantitatively and stratified into 3 categories: absent or trivial, slight (mild to less than moderate), and moderate to severe. Doppler echocardiographic data were obtained from the original record by direct electronic transfer. For methodological assessment, MR quantification (n=49) was compared by semiquantitative grading, and in randomly selected study (n=50) and nonstudy (n=20) community subjects, echocardiographic tapes were blindly reinterpreted by 2 investigators to assess the reproducibility of thickening and MVP diagnosis.

Statistical Analysis
Data are presented as mean±SD for continuous variables. For comparisons between groups, t tests, χ² tests, and ANOVAs were used as appropriate. Agreement among categorical variables was assessed by the κ statistic.

End points analyzed were total mortality, cardiovascular (CV) mortality, CV morbidity, and MVP-related events. MVP-related events included death and heart failure related to MVP, endocarditis, and mitral surgery. Event rates (Kaplan-Meier) and linearized rates were calculated. Observed total mortality was compared with expected mortality of age- and sex-matched white Minnesota residents with a 1-sample log-rank test. To assess the effect of baseline variables, including age, on excess mortality, time to death was transformed into cumulative hazard based on Minnesota white population tables and was analyzed by using proportional hazards. Baseline clinical and echocardiographic variables were candidate predictors of outcome with use of the univariate Cox proportional hazards method. Variables with univariate P<0.10 were incorporated in multivariate analysis, and P<0.05 was considered significant. Baseline primary risk factors (RFs) were then defined as variables independently predictive of CV mortality. Secondary RFs were defined as variables independently predictive of CV morbidity alone.

Results
Baseline Characteristics
Baseline characteristics of 833 eligible Olmsted County residents (Table 1) revealed a generally healthy population with a median age of 47 years, low comorbidity, and rare history of myocardial infarction or hypertension. AF was present in 67 (8%) of the patients, which was slightly more prevalent than in the population. EF, usually normal, was <50% in only 31 (3.7%) of the patients. MR from moderate to severe was more frequent with posterior than with anterior or bileaflet prolapse (21% versus 14%, respectively; P=0.012) but was similar with and without leaflet thickening (16% versus 15%, respectively; P=0.47).

Diagnostic echocardiography was suggested by auscultatory abnormalities in 557 patients (systolic murmur and click in 478 and 181 patients, respectively). MVP was silent, and diagnosis was incidental in 276 patients, for whom echocardiography was performed because of minor cardiopulmonary symptoms in 79 patients, because of family history of murmur in 7 patients, because of possible vascular symptoms in 45 patients, and because of non-CV concerns in 36 patients. In 109 patients, echocardiography was ordered for general medical examination and considered systematic. Compared with patients with incidental diagnoses, those with auscultatory-suggested diagnoses showed no differences for variables in Table 1 (all P>0.11), apart from more MR from moderate to severe (21% versus 5% for patients with incidental diagnoses, P<0.001), larger left atrium (38±8 mm versus 37±7 mm for patients with incidental diagnoses, P=0.06), and less AF (6% versus 11% for patients with incidental diagnoses, P=0.01).

In blind echocardiographic reinterpretation, agreement was 97% for MVP diagnosis (κ statistic 0.93, displacement 3.1±1.0 mm) and 93% for leaflet thickening >5 mm (κ statistic 0.85) between reinterpretation and initial report.

Mortality
Follow-up was complete in 97% of the patients. During 4581 person-years of follow-up (median 5.4 years), 96 deaths occurred (41 were CV, 31 of which were exclusively or partly due to MVP). Ten-year mortality was 19±2% (Figure 1), and risk ratio to expected mortality was 1.08 but did not reach statistical significance (P=0.4). Ten-year CV mortality was 9±2% (Figure 1) and was not different between auscultatory and incidental diagnoses (8±2% versus 11±4%, respectively; P=0.83). The most frequent baseline predictors (independent of age, sex, and comorbidity) of CV mortality were MR from moderate to severe (P=0.002, n=131) and, less frequently, EF <50% (P=0.003, n=31). Adjusted hazard ratios (HRs) for these predictors were, respectively, 3.0 (95% CI 1.5 to 5.8) and 3.8 (95% CI 1.6 to 8.1). Patients with MR from moderate to severe compared to those with lesser degree of MR had similar comorbidity scores (0.74±1.4 versus 0.62±1.5, P=0.39) but more frequently EF <50% (6.9% versus 3.2%, P=0.056), showing that association of MR to outcome is not due to comorbidity, is in part related to the ventricular dysfunction it induces, but mostly is independent. Indeed, both variables were also independent predictors of total mortality (adjusted HR 1.8 with 95% CI 1.03 to 3.0 and 2.3 with 95% CI 1.05 to 4.4, respectively; both P=0.04). The mode of diagnosis (auscultatory or incidental) showed no influence on CV mortality (P=0.80) or interaction with effect of EF (P=0.54) or MR (P=0.72).
There was no association between leaflet involved (P=0.20), flail leaflet (P=0.43), or ventricular diameters (P>0.29) and CV mortality. Predictors of CV mortality, univariately but not independently, were male sex (P=0.60), valve thickening (P=0.43), AF (P=0.25), left atrial diameter ≥40 mm (P=0.90), and slight MR (P=0.82). Advancing age was predictive of survival but not of excess mortality versus the expected rate (P=0.18).

**CV Morbidity**

CV morbidity occurred in 171 patients; heart failure, in 60; new (not present at baseline) AF, in 51; ischemic neurological event, in 38; peripheral arterial thromboembolism, in 11; and endocarditis, in 4. Seventy-seven patients required cardiac surgery, including mitral repair or replacement in 65 patients. Mitral surgery was performed for severe symptomatic MR in 62 of 65 patients. Ten-year CV morbidity (Figure 1) was 30±2% (22%/y), which was not different whether the diagnosis was auscultatory or incidental (32±3% versus 25±4%, respectively; P=0.10) but was higher for patients ≥50 years versus patients <50 years at diagnosis (45±4% versus 10±2%, respectively; P<0.001).

Independent predictors of CV morbidity (adjusted HR) were as follows: age ≥50 years (HR 3.1, 95% CI 2.0 to 5.0; P<0.001), left atrium ≥40 mm (HR 2.7, 95% CI 1.9 to 3.8; P<0.001), slight MR (HR 3.6, 95% CI 2.0 to 7.0; P<0.001), MR from moderate to severe (HR 9.1, 95% CI 4.9 to 18.3; P<0.001), flail leaflet (HR 2.6, 95% CI 1.5 to 4.6; P=0.002), and baseline AF (HR 2.0, 95% CI 1.2 to 3.0; P=0.004). The diagnosis mode, auscultatory or incidental, did not influence CV morbidity (P=0.75) and showed no interaction with predictors (all P>0.33).
Mortality and Morbidity

Figure 1. Outcome among 833 Olmsted County, Minn, residents first diagnosed with MVP between 1989 and 1998. Cumulative incidence of total mortality (solid bold line), CV mortality (solid nonbold line), and CV morbidity (dotted line) is shown.

Univariate but not independent predictors of CV morbidity were male sex ($P = 0.2$), posterior leaflet prolapse ($P = 0.89$), and ventricular diameters ($P = 0.23$). Leaflet thickening did not predict CV morbidity ($P = 0.8$).

Clinical Outcome in Specific Patient Subsets

Table 2 lists baseline RFs predictive of outcome. Primary RFs were noted in 153 patients, EF $<50\%$ was noted in 31, and MR from moderate to severe was noted in 131. Patients with versus patients without primary RF (even adjusting for age, sex, and comorbidity) had higher total ($P = 0.005$) and CV ($P < 0.001$) mortality and higher CV morbidity ($P < 0.001$). Patients without primary RF but with $\geq 2$ secondary RFs had (adjusting for age, sex, and comorbidity) no increase in total ($P = 0.53$) or CV ($P = 0.10$) mortality but higher CV morbidity ($P = 0.005$).

Accordingly, 3 groups were formed: (1) a low-risk group with no primary RF and 0 or 1 secondary RF, (2) a medium-risk group with no primary RF but $\geq 2$ secondary RFs, and (3) a high-risk group with primary RFs (outcomes in Table 3). Adjusting for age, comorbidity was similar between groups ($P = 0.32$). Importantly, patients with primary RFs demonstrated excess mortality versus expected ($P = 0.01$). Outcomes were statistically different (all $P < 0.001$) but were also widely divergent between groups (Figure 2 and 3).

Widely divergent outcomes between groups were observed in all subsets, whether analysis was restricted to males (all $P < 0.001$) or females (all $P < 0.001$), to patients in sinus rhythm (all $P < 0.001$), or to patients with AF (all $P < 0.006$). Five-year combined CV mortality or morbidity rates in the low-, medium-, and high-risk groups were as follows: $1 \pm 1\%$, $22 \pm 10\%$, and $49 \pm 10\%$, respectively, in patients aged $<50$ years at diagnosis; $12 \pm 6\%$, $29 \pm 3\%$, and $68 \pm 5\%$, respectively, in patients aged $\geq 50$ years; $3 \pm 1\%$, $26 \pm 4\%$, and $66 \pm 5\%$, respectively, when diagnosis was auscultatory; and $1 \pm 1\%$, $33 \pm 5\%$, and $51 \pm 12\%$, respectively, when diagnosis was incidental (all $P < 0.001$). Adjusted HRs of combined CV mortality or morbidity for medium- and high-risk groups versus the low-risk group were 4.3 and 15.9, respectively, with auscultatory abnormalities and 4.0 and 9.1, respectively, with incidental diagnosis ($P = 0.50$ for interaction).

MVP-Related Events

Of 219 patients who died or who experienced CV complications, 109 (50\%) had a conservatively defined MVP-related event (heart failure due to MR, 48; mitral surgery, 65; endocarditis, 4; and death related to MVP, 31) with rates of $14 \pm 1.4\%$ and $20 \pm 2\%$ at 5 and 10 years, respectively. Baseline characteristics of patients who subsequently developed MVP-related events compared with those who did not are presented in Table 1. Primary and secondary RFs were also predictive of MVP-related events (all $P < 0.0001$). MVP-related events at 10 years were 22\% with 0 or 1 secondary RF, 15\% (HR 6.9, 95\% CI 3.0 to 18.8) with $\geq 2$ secondary RFs, and 78\% (HR 60, 95\% CI 28 to 155) with primary RFs ($P < 0.0001$) (Table 3, Figure 4), confirming widely heterogeneous MVP outcomes.

Discussion

Our data provide unique clinical perspectives on MVP in the community, helping reconcile discordant information available from prior studies. Indeed, our data show that MVP cannot be described as uniformly severe or uniformly benign, and patients with MVP have widely heterogeneous outcomes. Patients with low-risk MVPs (half the population) have normal life expectancy and CV morbidity of only 0.5%/y. In contrast to these reassuring data, the high-risk group (18\% of MVPs) had excess mortality and considerable CV morbidity (18.5%/y) and MVP-related events (15%/y). In the medium-risk group (30\% of MVPs), survival was similar to expected, but 40\% had a morbid cardiac event, and 15\% had an MVP-related event over a 10-year period.

This separation into groups of widely different natural history is based on a combination of clinical and echocardiographic RFs, is similarly effective whether the diagnosis is suggested by auscultatory abnormalities or is incidental, and is essential for clinical management and therapeutic decision-making in the community.

MVP: Importance of Community Studies

MVP is clinically diagnosed by typical click and murmur.23,24 Echocardiography introduced noninvasive diagnosis but created ambiguity. With the use of initial diagnostic criteria,25 MVP prevalence has been reported as 5\% or even 17%.26,27 Pioneering 3D work10 resulted in new diagnostic criteria11 and in lower prevalence of MVP (0.6\% to 2.4%).1,2 Nonetheless, MVP is common enough, so that defining the natural history is of great importance.

TABLE 2. Baseline Risk Stratification Used in 833 Olmsted County, Minn, Residents First Diagnosed With MVP Between 1989 and 1998

<table>
<thead>
<tr>
<th>Primary RFs (Excess Mortality)</th>
<th>Secondary RFs (Cardiovascular Morbidity)</th>
</tr>
</thead>
<tbody>
<tr>
<td>EF $&lt;50%$</td>
<td>Slight MR</td>
</tr>
<tr>
<td>MR $\geq$ moderate</td>
<td>Flail leaflet</td>
</tr>
<tr>
<td></td>
<td>Left atrial diameter $&gt;40$ mm</td>
</tr>
<tr>
<td></td>
<td>AF</td>
</tr>
<tr>
<td></td>
<td>Age $\geq 50$ y</td>
</tr>
</tbody>
</table>

Outcomes were statistically different (all $P < 0.0001$) but were also widely divergent between groups (Figure 2 and 3).
Wide discrepancies exist among studies regarding the risk of serious complications,\textsuperscript{2–6} ranging from 5%\textsuperscript{2} to 44%.\textsuperscript{7} These divergent results reflect, in part, design issues, non-current diagnostic criteria,\textsuperscript{3,4} selection bias,\textsuperscript{3–6} very small samples,\textsuperscript{2} healthy-participant bias,\textsuperscript{28} or the recording of past rather than prospective events.\textsuperscript{2} These discrepant data raise the question of whether they are solely due to limitations of previous studies or whether a unique outcome pattern applied to MVP is a misconception in a heterogeneous disease. To resolve these uncertainties, new data in the community are necessary. For that purpose, Olmsted County, Minn, has unique advantages in that medical care is local, widely available, frequent, given by a few linked providers,\textsuperscript{15} and uses a single state-of-the-art echocardiographic laboratory. This community-based approach provides a large population (statistical power) and prospectively noted outcome events after MVP diagnosis.

**Heterogeneous Outcome of MVP**

Our results show that the outcome of MVP is widely heterogeneous. The natural history of MVP goes from extremely benign, with minimal mortality or morbidity, to severe, with excess mortality (with an intermediate group showing no excess mortality but high morbidity). These very widely different outcomes are noteworthy in a population asymptomatic at baseline and with little comorbidity or past CV history. Thus, MVP cannot be described as uniformly severe\textsuperscript{4,7} or uniformly benign,\textsuperscript{2,6} and the widely different results previously reported correspond to various facets of MVP and can now be reconciled. Remarkably, the natural history of MVP was similarly divergent whether the diagnosis was auscultatory or incidental, showing that RFs are predictive of outcome in all subgroups and circumstances of diagnosis.

The dominant RF was the baseline degree of MR,\textsuperscript{8} a direct consequence of MVP. The direct involvement of MVP in poor outcomes is further demonstrated by the higher frequency of other RFs (decreased EF, AF, flail leaflet, and left atrial diameter ≥40 mm) with increasing MR degree, by very low comorbidity that cannot explain high complication rates in high-risk patients, and by the large proportion of events purely MVP-related.

However, the other baseline RFs add independent risk of poor outcome. For example, flail leaflets, an extreme form of prolapse, tend to progress fast and display high morbidity rates.\textsuperscript{8} Also, for any given MR degree, development of left ventricular\textsuperscript{29,30} and atrial\textsuperscript{29} remodeling and dysfunction are individually variable and contribute to poor prognosis.

**Clinical Implications**

The widely heterogeneous MVP outcomes underscore important clinical implications of our data. Baseline RFs are...
valuable tools for clinical management. The prognosis of patients with primary RFs at diagnosis is mediocre, with excess mortality and morbidity, and aggressive management should promptly be considered. Respectively therapeutic roles of early surgery or vasodilators for MR are disputed. While one awaits the results of appropriate clinical trials, decisions regarding the proper treatment of high-risk patients should be based on careful clinical assessment. Patients with ≥2 secondary RFs but no primary RF are at intermediate risk, with no excess mortality but with high morbidity and MVP-related events, and should be closely monitored. Patients with no RF or 1 secondary RF are at very low risk of mortality, morbidity, and MVP-related complications; thus, they can be reassured and do not require close follow-up.

**Study Limitations**

An entire community cannot be screened, and community-based versus systematically sampled population studies should be carefully weighed. The latter are suited to define prevalence, but are less suited to analyze natural history based versus systematically sampled population studies. An entire community cannot be screened, and community-based versus systematically sampled population studies should be carefully weighed. The latter are suited to define prevalence, but are less suited to analyze natural history based versus systematically sampled population studies.

**Figure 4.** MVP-related events according to 3 categories of baseline RFs (Table 2): (1) no primary RFs and 0 or 1 secondary RF, (2) no primary RFs but ≥2 secondary RFs, and (3) primary RFs.

During the study period, 63 other community residents diagnosed with MVP were in class III or IV. The outcome was poor, with 5-year mortality and CV morbidity of 52% and 88%, respectively, but their high risk is not surprising.

Age obviously determines survival but is not associated with excess mortality. Age also determines morbidity, but age-specific “excess” morbidity cannot be formally tested without validated expected morbidity. Despite this statistical limitation, age <50 years, obviously associated with very low CV morbidity, was considered a favorable factor. After 50 years of age, excess morbidity cannot be defined, and no further stratification is used. Future studies measuring expected morbidity with aging will be necessary.

The reliability of routine echocardiography can be questioned. High agreement between the initial report and blinded reinterpretation and between MR grading and regurgitant volumes with simultaneous MR quantification (slight MR [20±9 mL] versus MR from moderate to severe [61±42 mL], P=0.016) is reassuring. Finally, the routine echocardiography used in the present study is also used clinically and is highly predictive of outcome.

**Conclusion**

The present study, involving 833 patients with long-term follow-up after MVP diagnosis, shows that outcome of MVP in the community is widely heterogeneous. Prognosis ranges from a condition with normal life expectancy and little morbidity in half the patients to subsets with high morbidity or even excess mortality directly related to MVP and its major complication, MR. Baseline characteristics, clinical and echocardiographic, are strong predictors of outcome and are essential for clinical management.

**Acknowledgments**

The present study was funded in part by the National Institutes of Health grants AR 30582 and HL 64928.

**References**


Natural History of Asymptomatic Mitral Valve Prolapse in the Community
Jean-François Avierinos, Bernard J. Gersh, L. Joseph Melton III, Kent R. Bailey, Clarence Shub, Rick A. Nishimura, A. Jamil Tajik and Maurice Enriquez-Sarano

Circulation. 2002;106:1355-1361; originally published online August 19, 2002; doi: 10.1161/01.CIR.0000028933.34260.09
Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2002 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circ.ahajournals.org/content/106/11/1355

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Circulation can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at: http://www.lww.com/reprints

Subscriptions: Information about subscribing to Circulation is online at: http://circ.ahajournals.org/subscriptions/