

Cerebral Ischemic Events After Diagnosis of Mitral Valve Prolapse

A Community-Based Study of Incidence and Predictive Factors

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Background and Purpose—Association of mitral valve prolapse (MVP) with ischemic neurological events (INEs) is uncertain.

Methods—In the community of Olmsted County (Minn), we identified all MVP diagnosed (1989 to 1998) in patients in sinus rhythm with no prior history of INE. We measured INE rates and compared them with expected rates in our community to define the excess risk of INE.

Results—Among 777 eligible subjects (age, 49 ± 20 years; 66% female; follow-up, 5.5 ± 3.0 years), 30 patients had at least 1 INE during follow-up (at 10 years, $7 \pm 1\%$). Compared with expected INEs in the same community, subjects with MVP showed excess risk of lifetime INE (relative risk [RR], 2.2; 95% CI, 1.5 to 3.2; $P < 0.001$) and during follow-up under purely medical management (RR, 1.8; 95% CI, 1.1 to 2.8; $P = 0.009$). Independent determinants of INE were older age (RR, 1.08 per year; 95% CI, 1.04 to 1.11; $P < 0.001$), mitral thickening (RR, 3.2; 95% CI, 1.4 to 7.4; $P = 0.008$), atrial fibrillation (AFib) during follow-up (RR, 4.3; 95% CI, 1.9 to 10.0; $P < 0.001$), and need for cardiac surgery (RR, 2.5; 95% CI, 1.1 to 5.8; $P = 0.03$). INE 10-year rates were low in patients < 50 years of age ($0.4 \pm 0.4\%$, $P = 0.60$ versus expected) but were excessive in patients > 50 years of age ($16 \pm 3\%$, $P < 0.001$ versus expected) or with thickened leaflets ($7 \pm 2\%$, $P < 0.001$ versus expected). Predictors of follow-up AFib were age, mitral regurgitation, and left atrium diameter (all $P < 0.01$).

Conclusions—In the community, subjects with MVP display a lifetime excess rate of INE compared with expected. Clinical (older age) and echocardiographic (leaflets thickening) characteristics define patients with MVP at high risk for INE, and subsequent AFib or need for cardiac surgery, both related to the degree of mitral regurgitation, increase the risk of INE. (*Stroke*. 2003;34:1339-1345.)

Key Words: atrial fibrillation ■ mitral valve ■ mitral valve prolapse ■ morbidity ■ residence characteristics

Mitral valve prolapse (MVP) has been considered a potential source of ischemic neurological events (INEs) since thrombi adherent to the prolapsing mitral leaflets were anatomically described.^{1,2} However, the relationship between MVP and INEs remains controversial. Reports of high INE risk among patients with MVP,³ mainly among young patients,⁴ contrast with other reports of intermediate⁵ and low rates.⁶⁻⁹ Recent publications cast doubt on MVP-associated INE risk,¹⁰ particularly in young patients.¹¹ The discordances between these data and current guidelines¹² confuse the management of patients with MVP. Estimating the risk of INEs in MVP is particularly challenging because it has been inferred primarily from case-control studies^{4,11,13,14} in which inhomogeneous cases and controls likely explain wide discordances.¹⁵ Changes in MVP echocardiographic diagnostic criteria¹⁶ confounded the risk analysis and

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question the relevance of older reports.^{3,4,6,7,17,18} Furthermore, analysis of past complications before MVP diagnosis,^{2,3,5,10} as opposed to postdiagnosis events, prevented determination of rates and predictors of INE. However, 3 major limitations have prohibited a more suitable approach to this problem. First, low INE rates¹⁹ require very large populations for appropriate statistical power. Second, studies of patients referred to tertiary-care centers^{2-9,11,13,14} may lead to selection bias.^{20,21} Conversely, despite relatively high MVP prevalence,¹⁰ population systematic echocardiographic studies will be underpowered because 500 MVP occurrences would require $\approx 25\,000$ echocardiographic screenings. Third, background population INE rates, necessary to determine excess risk attached to MVP,

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are usually unknown.¹⁸ Thus, rates and predictors of INEs associated with MVP remain uncertain.

Analysis of MVP in Olmsted County (Minn) takes advantage of numerous subjects with long-term follow-up after diagnosis in a community in which background INE rates²² and subsequent occurrence of atrial fibrillation (AFib) are defined. We hypothesized that patients diagnosed with MVP in the community incur an excess lifetime INE risk but that INEs are confined to high-risk subsets predictable by clinical and echocardiographic variables and that complex interactions exist between mitral regurgitation (MR) caused by MVP and subsequent occurrence of AFib and INEs.

Materials and Methods

Eligibility

Medical care in Olmsted County is largely community contained; only 1 laboratory provides echocardiography, and all care providers are linked through the Rochester Epidemiology Project.²² It was therefore possible to identify all Olmsted County residents with diagnosis of MVP between 1989 and 1998 confirmed by echocardiography.²³ Of those, patients with no past history of INE, no documented AFib, and no mitral surgery before diagnosis were included. Residency in Olmsted County before diagnosis was required to avoid temporary residency motivated by medical care.

Clinical Definitions

Cardiovascular history (including history of hypertension, myocardial infarction, congestive heart failure, and endocarditis), baseline clinical status, and comorbidity were noted. Follow-up care was similarly provided to the general and MVP populations, and events were determined by review of medical records, by questionnaires, or through telephone interviews. AFib, paroxysmal or permanent, was considered present if recorded on ECG. INEs included both cerebral infarction and transient ischemic attack (TIA). Cerebral infarction was defined as the persistence for >24 hours of a focal neurological deficit caused by altered circulation of the cerebral hemispheres, brain stem, or cerebellum with or without CT or MRI documentation.²⁴ TIA was defined as focal neurological symptoms of sudden occurrence and rapid resolution (<24 hours) related to altered circulation of the brain.²⁵ Neurological diagnoses were confirmed by a neurologist from our group for all INEs among the general and MVP populations.

Echocardiographic Methods

All patients underwent comprehensive Doppler echocardiography during routine examination. MVP diagnosis used current criteria^{10,23,26} based on systolic leaflet displacement beyond the mitral annulus >2 mm in long-axis views. Diagnoses of flail or thickened leaflets¹⁰ were based on previously recommended criteria. Left ventricular diameters, left ventricular ejection fraction, and left atrial (LA) diameter measurements were guided by 2-dimensional echocardiography. MR severity was assessed semiquantitatively in 3 categories: absent or trivial, slight, and moderate or worse. All Doppler echocardiographic data were used as originally recorded without alteration.

Statistical Analysis

Baseline characteristics are presented as mean \pm SD for continuous variables. Comparison between groups used the 2-sample *t* test, χ^2 , or analysis of variance. Event rate estimations used the Kaplan-Meier method overall and stratified by age, for lifetime risk (censoring at death or last follow-up), and under conservative management (censoring at cardiac surgery). INE rates were also determined during follow-up in patients in sinus rhythm only by censoring at occurrence of AFib and during follow-up in patients sinus rhythm and without surgery. Observed INE rates were compared with expected rates by use of the 1-sample log-rank test. Expected INE hazards were calculated from incidence rates of both cerebral infarctions²⁴ and TIAs²⁵ from the Olmsted County population with

sex, age, rhythm, and surgical history similar to those of MVP subjects. Comparison was performed overall to define excess lifetime risk of INE and censored at specific follow-up AFib or cardiac surgery to define excess risk in sinus rhythm, under conservative management, and both. Baseline clinical and echocardiographic variables were tested as potential predictors of INEs with Cox proportional-hazards modeling. Follow-up AFib and cardiac surgery were used as time-dependent variables. Variables with $P<0.10$ by univariate analysis were incorporated into multivariate models, and $P<0.05$ was considered significant.

Results

Study Population

Among 19 370 screened, 777 Olmsted County residents diagnosed with MVP during the study period presented in sinus rhythm with no documented AFib or INE history before diagnosis. The diagnostic echocardiography was suggested by auscultatory abnormalities (systolic murmur or click) in 542 patients. MVP was silent and diagnosis was incidental in 235 patients in whom echocardiography was motivated by minor cardiorespiratory symptoms ($n=62$), family history of murmur ($n=7$), possible vascular symptoms ($n=30$), or noncardiovascular concerns ($n=34$). In 102 patients, echocardiography was ordered for general medical examination and considered systematic. Table 1 details baseline clinical and echocardiographic characteristics. The population was young (median age, 45 years) with normal blood pressure and with rare history of hypertension or myocardial infarction. Left ventricular ejection fraction was $62\pm 7\%$; in only 31 patients (4%), it was $<50\%$. The MR was moderate or worse in 124 patients (16%), and the LA was ≥ 40 mm in 192 (25%). In 70 randomly selected echocardiograms, agreement of 93% for leaflets thickening >5 mm ($\kappa=0.85$; thickness, 5.6 ± 1.1 versus 3.5 ± 1.0 mm; $P<0.001$) and $\kappa=0.89$ for degree of MR were found between reinterpretation and initial report.

Lifetime Risk of INEs

During a mean follow-up of 5.5 ± 3.0 years (complete in 96%), 30 patients (14 men, 16 women) experienced a first INE (12 TIAs, 18 cerebral infarctions). In 7 patients, 8 recurrent INEs during follow-up resulted in a total of 38 INEs (17 TIAs, 21 cerebral infarctions). Diagnosis was confirmed by a neurologist in all cases and by either CT or MRI in 28 patients. Only 2 of 28 INE patients tested had concomitant cerebrovascular stenosis by Doppler ultrasound (both with cerebral infarction). One INE (TIA) only occurred in a patient <50 years of age at diagnosis. Regarding temporal relationship between cardiac surgery and INE, INEs occurred after cardiac surgery (9 mitral surgery for severe MR, 2 events occurring within the first postoperative month) in 10 patients (6 TIAs, 4 infarctions) and in 20 patients (7 TIAs, 13 infarctions) under medical management. Regarding temporal relationship between AFib and INE, in 16 patients, the first INE occurred after follow-up AFib (8 TIAs, 8 infarctions), and among these, 10 were postsurgery and 6 were under medical management. Finally, in 14 patients, the first INE occurred without detected AFib and under conservative management (5 TIAs, 9 infarctions).

Hence, 5- and 10-year first INE rates (Table 2) were $3\pm 0.7\%$ and $7\pm 1\%$, respectively (linearized rate, 0.7% per year). Comparison of observed to community expected INE rates showed excess INE risk among MVP subjects (relative risk [RR], 2.2; 95% CI, 1.5 to 3.2; $P<0.001$). When analysis

TABLE 1. Baseline Characteristics of 777 Residents Olmsted County (Minn) With MVP in Sinus Rhythm at Diagnosis and Association With Lifetime Risk of INEs

	Baseline Characteristics				Association With Time to INE*		
	Total Population (n=777)	No INE During Follow-Up (n=747)	INE During Follow-Up (n=30)	P	RR	95% CI	P
Clinical variables							
Age, y	49±20	48±20	72±9	<0.001	1.08	1.06–1.11	<0.001
Systolic blood pressure, mm Hg	127±21	127±20	151±21	<0.001	0.99	0.97–1.02	0.9
Diastolic blood pressure, mm Hg	75±11	75±10	80±8	0.02	1.01	0.97–1.04	0.6
Comorbidity index	0.6±1.3	0.5±1.3	1.1±1.9	0.003	1.1	0.8–1.3	0.6
Female sex, n (%)	514 (66)	498 (67)	16 (53)	0.13	1.7	0.8–3.4	0.2
History of myocardial infarction, n (%)	24 (3)	24 (3)	0	0.17	NA		
History of hypertension, n (%)	87 (11)	77 (10)	10 (33)	<0.001	1.7	0.8–3.7	0.2
History of endocarditis, n (%)	5 (0.6)	5 (0.7)	0	0.50	NA		
Recent congestive heart failure, n (%)	33 (4)	29 (4)	4 (13)	0.04	1.8	0.5–5.0	0.3
Echocardiographic variables							
Ejection fraction, %	62±7	62±7	62±8	0.90	1.0	0.96–1.05	0.9
LVS, mm	30±5	30±5	31±9	0.26	1.1	1.0–1.2	0.05
LVD, mm	49±6	49±6	50±8	0.32	1.0	0.9–1.1	0.2
LA diameter, mm	37±7	37±7	43±8	<0.001	1.1	1.0–1.2	0.05
MR moderate or worse, n (%)	124 (16)	113 (15)	11 (37)	0.005	1.9	0.9–4.1	0.09
Posterior leaflet prolapse, n (%)	499 (64)	278 (64)	21 (70)	0.50	0.9	0.5–2.2	0.9
Mitral leaflet thickening, n (%)	437 (56)	415 (56)	22 (73)	0.049	3.6	1.6–8.7	0.001

LVS, LVD indicates left ventricular systolic and diastolic diameter.

*Adjusted for age at diagnosis.

was restricted to cerebral infarctions, comparison with expected rates also showed excess risk in MVP (RR, 1.72; 95% CI, 1.02 to 2.73; $P=0.02$) (Figure 1).

Predictors of First INE

Differences in baseline characteristics between patients with and without INEs and Cox proportional-hazards analysis for time to first INE adjusted for age are presented in Table 1.

In multivariate analysis, independent baseline predictors of INEs were older age (RR, 1.08 per year; 95% CI, 1.05 to 1.12; $P<0.001$), mitral valve thickening (RR, 3.4; 95% CI, 1.3 to 10.5; $P=0.01$) with borderline association of LA diameter (RR, 1.05 per 1 mm; 95% CI, 0.99 to 1.10; $P=0.083$). These variables were also independent predictors of INEs, when analysis was restricted to medical management (older age, $P<0.001$; mitral valve thickening, $P=0.01$). When models included follow-up events as time-dependent variables, independent predictors of INEs were older age (RR, 1.08; 95% CI, 1.04 to 1.11; $P<0.001$), mitral valve thickening (RR, 3.2; 95% CI, 1.4 to 7.4; $P=0.008$), occurrence of follow-up AFib (RR, 4.3; 95% CI, 1.9 to 10.0; $P<0.001$), and need for cardiac surgery during follow-up (RR, 2.5; 95% CI, 1.1 to 5.8; $P=0.03$). When analysis was restricted to cerebral infarctions, independent predictors were older age (RR, 1.10; 95% CI, 1.05 to 1.15; $P<0.001$), mitral valve thickening (RR, 3.2; 95% CI, 1.1 to 9.3; $P=0.03$), and follow-up AFib (RR, 5.9; 95% CI, 2.1 to 16.1; $P<0.001$).

MR severity of moderate or worse was associated with higher INE risk (RR, 7.6), but adjusted for age, the trend

toward higher risk did not reach significance (RR, 1.45; $P=0.35$). Heart failure, although overrepresented among INE patients because it more frequently required mitral surgery ($P=0.006$), did not independently predict INEs ($P=0.47$).

Subgroup Analysis

Table 2 presents INE rates (lifetime and under medical management) of patients subsets formed according to predictors defined, with comparison in each subset to expected rates.

Excess INE lifetime risk observed globally was marked in patients developing follow-up AFib but was also observed in patients remaining in sinus rhythm. Patients <50 years of age at diagnosis had very low INE risk (Figure 2), and most excess risk was observed in patients >50 years of age. Patients with thickened and nonthickened leaflets appeared to have very close INE rates, but patients with thickened leaflets were much younger (46 ± 19 versus 52 ± 21 years, $P<0.001$) and therefore had lower expected INE rates than patients with nonthickened leaflets and a much higher and significant risk ratio of INEs compared with expected. The pattern was similar with INEs occurring under conservative management (Table 2, middle), although statistical significance was lower because of lower event numbers. Remarkably, for patients remaining in sinus rhythm and never undergoing mitral surgery, excess INE risk was detectable with thickened leaflets (at 10 years, $4\pm 1\%$; RR, 2.2; 95% CI, 1.1 to 4.1; $P=0.009$) (Figure 3).

AFib and Predictors

During follow-up, 63 patients experienced AFib (paroxysmal or permanent). In 18, AFib occurred after cardiac surgery (7

TABLE 2. Incidence of INEs in Residents Olmsted County (Minn) With MVP in Sinus Rhythm at Diagnosis

	Observed Rates in MVP		Comparison With Community INE Rates*	
	5-Year Rate	10-Year Rate	RR (95% CI)	P
Life time risk				
Overall	3±0.7	7±1	2.2 (1.5–3.2)	<0.001
<50 y of age	0	0.4±0.4	1.7 (0.4, 9.5)	0.6
≥50 y of age	7±2	16±3	2.3 (1.5, 3.3)	<0.001
No AFib in follow-up	2±1	4±1	1.7 (1.04, 2.6)	0.02
AFib in follow-up	16±5	41±9	5.9 (3.4, 9.5)	<0.001
Thickened leaflets	4±1	7±2	3.5 (2.2, 5.3)	<0.001
Nonthickened leaflets	2±1	6±2	1.1 (0.5, 2.2)	0.7
Risk under medical management				
Overall	2±1	5±1	1.8 (1.1–2.8)	0.009
<50 y of age	0	0.4±0.4	2.0 (0.5, 11.1)	0.5
≥50 y of age	5±1	13±3	1.8 (1.1, 2.8)	0.01
No AFib in follow-up	2±1	3±1	1.4 (0.8, 2.3)	0.2
AFib in follow-up	11±5	49±13	5.1 (2.0, 9.2)	<0.001
Thickened leaflets	3±1	6±2	2.8 (1.6, 4.8)	<0.001
Nonthickened leaflets	1±1	4±2	1.0 (0.3, 2.1)	0.9

*Comparison of observed INE rates in patients with MVP vs similar strata of sex, age, and rhythm in the Olmsted County community.

within the first postoperative month); in 45, AFib occurred under medical management. Five- and 10-year AFib rates were 7±1% and 13±2% and were 5±1% and 10±2% under medical management.

Independent predictors of AFib were older age (RR, 1.05; 95% CI, 1.04 to 1.08; $P<0.001$), LA ≥40 mm (RR, 1.9; 95% CI, 1.1 to 3.2; $P=0.01$), and higher MR severity complicating the MVP ($P<0.001$). The RR of AFib during follow-up compared with patients without MR was high for moderate or worse MR (RR, 8.1; 95% CI, 2.4 to 28.0; $P<0.001$) and slight MR (RR, 3.7; 95% CI, 1.1 to 12.6; $P=0.03$). Baseline LA ≥40 mm (adjusted RR, 1.8; 95% CI, 0.9 to 3.2; $P=0.07$) and moderate or worse MR (RR, 2.8; 95% CI, 1.5 to 5.3; $P=0.002$) remained predictive of AFib occurring under medical management.

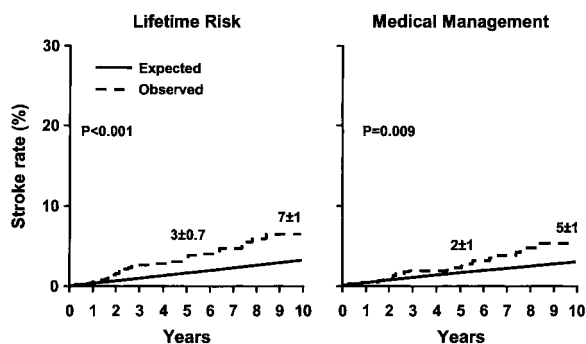


Figure 1. Rates of INE among 777 residents of Olmsted County (Minn) with MVP in sinus rhythm at baseline. Left, Lifetime risk of INEs; right, risk under medical management. Dashed lines represent observed INE rates; solid lines, expected INE rates. Probability value is for comparison of observed to expected rates.

Discussion

The present study shows that patients routinely diagnosed in the community with MVP in sinus rhythm incur an excess lifetime INE risk. This excess risk of INEs is observed even under conservative management and is independently predicted by age and mitral valve thickening and in a more borderline manner by LA enlargement. The risk of INEs is increased during follow-up by the need for mitral surgery. AFib during follow-up is frequent, increases the INE risk, and is determined by direct MVP consequences, ie, a large degree of MR and LA enlargement.

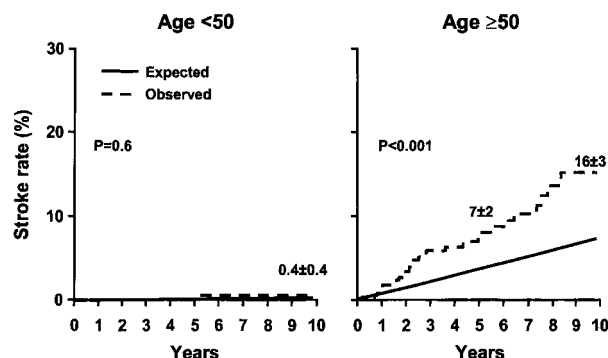


Figure 2. Lifetime risk of INEs among 777 residents of Olmsted County (Minn) with MVP in sinus rhythm at diagnosis. Left, INEs in patients <50 years of age; right, INEs in patients ≥50 years of age. Dashed lines represent observed INE rates; solid lines, expected INE rates. Probability value is for comparison of observed to expected rates.

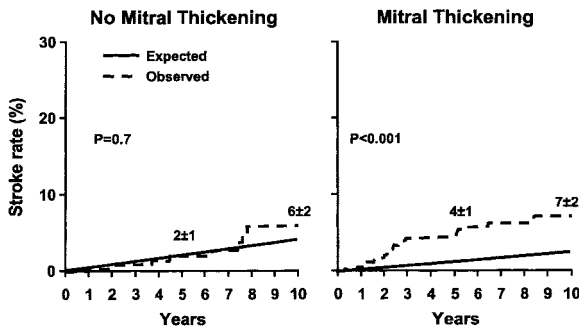


Figure 3. Lifetime risk of INE among 777 residents of Olmsted County (Minn) with MVP in sinus rhythm at diagnosis. Left, INE rates in patients without thickened leaflets; right, rates in patients with thickened leaflets. Dashed lines represents observed INE rates; solid lines, expected INE rates. Probability value is for comparison of observed to expected rates.

INEs in Patients With MVP

Initial suspicion of an MVP-INE association^{27,28} was supported by case reports²⁹ and case-control studies^{4,14} and by pathological description of thrombi adherent to MVP leaflets.^{1,2} This led to researchers considering a larger role of MVP in INE occurrence, particularly in patients <45 years of age⁴ and without other stroke causes.^{3,4} The MVP-stroke association encountered skepticism,¹⁷ particularly because of MVP overdiagnosis by criteria, which had to be revised in late 1980s.^{16,23,26} This raised legitimate questions about the relevance of studies based on these obsolete criteria.^{2–4,6,7,14,18,19,28–30} The MVP-INE association was recently denied in a high-profile case-control study,¹¹ which could not confirm MVP overrepresentation⁴ among young stroke patients.

These discordant data underscore major methodological issues in assessing MVP-INE association. Case-control studies are biased in the choice of cases and particularly of supposedly representative controls, which is questionable in hospital-based studies.¹⁵ Most data emanate from tertiary-care centers,^{3–9,11,14} where the referred populations do not reflect the community.^{20,21} Only 2 population-based studies reported an MVP-INE association.^{10,18} One in our community before 1989 used older echocardiographic criteria.¹⁸ The other reported no more past neurological complications among 84 individuals with MVP than among those without MVP.¹⁰ This small sample underscores power issues of echocardiographic screening, which would require 30 000 to 130 000 examinations to detect an MVP sample similar to ours. The present study takes advantage of the Rochester Epidemiology Project to include all community members (a large sample) routinely diagnosed with MVP with appropriate criteria and followed up long term after diagnosis. In this community, hazards of INEs by age, sex, occurrence of AFib, and cardiac surgery have been defined,^{24,25} allowing comparison of MVP-INE rates to rates expected with identical clinical characteristics in the same community. These unique advantages allow us to define INE hazard and most importantly excess lifetime INE risk.

Hence, we observed that MVP patients have more than twice the lifetime INE risk as similar community members, in part because of cardiac surgery required by MVP but also

observed under conservative management. Excess INE risk is noticeable in view of minimal INE risk factors in this population and of the link between specific MVP characteristics with higher INE risk. Indeed, more MR resulting from MVP leads to LA enlargement and follow-up AFib, which is directly associated with INE occurrence. Hence, the excess INE risk is not incidental but is MVP related.

Risk of INEs in Specific Subsets of MVP

High- and low-risk subsets were predictable by clinical and echocardiographic parameters. Age is a major determinant of INEs in all populations.³¹ In MVP, age determines excess INE risk. In patients <50 years of age, INE rates were extremely low and not significantly different from the community. Whether the 1.7 RR truly represents excess INE risk in young MVP patients is beyond realistic analysis. With moderate MVP prevalence, the population-attributable INE risk resulting from MVP in patients <50 years of age appears low, giving little probability of positive results to low-power case-control series.¹¹ After 50 years of age, the excess INE risk with MVP appears unrelated to vascular obstructive lesions and may be related to aging-related thromboembolic risk factors³² and to higher rates of AFib and valvular surgery.

Echocardiographic mitral valve thickening independently predicts higher INE rates. Its outcome predictive value has been variably reported, from a strong risk factor for complications⁶ to lack of association with stroke.^{5,18} Our study demonstrates that leaflet thickening independently predicts subsequent INEs and even cerebral infarctions. Mitral thickening, possibly through higher risk of thrombus formation,^{1,2} may account for excess INE risk among patients conservatively managed and in sinus rhythm.

AFib occurrence predicts subsequent INEs in patients with but also without MVP.³³ AFib risk has been variably estimated in MVP,^{9,10} but recent data showed that it is high with severe MR.³⁴ AFib incidence for any given degree of MR and LA enlargement increases with aging,³⁴ explaining in part the marked excess INE risk in older patients with MVP compared with community members of similar age and sex. Ten years after diagnosis of MVP, at least 13% of patients initially in sinus rhythm will have presented a diagnosed episode of AFib and will be at high risk for INEs. This incidence is much higher than that reported in the general population of similar age,³¹ even though a formal comparison is not possible.

The degree of MR determines the need for cardiac surgery, which is a known cause of INEs, perioperatively and through prosthetic thromboembolic complications. Hence, MR emerges as an indirect risk factor for INEs in patients with MVP through LA enlargement, occurrence of AFib, and need for cardiac surgery. This complex interaction between MR and subsequent occurrence of INEs in patients with MVP is at variance with previous reports of INE-protective effects in nonvalvular AFib.³⁵ Hence, MVP puts patients at high risk for INEs through multiple ways.

Study Limitations

Our study analyzed INEs in community members clinically diagnosed with MVP as opposed to persons systematically screened. Systematic screening would require massive numbers of prospective echocardiograms that no existent epi-

miological program would qualify for, leaving community studies as the only possible source of cohorts of sufficient size. Our study was not designed to define the risk of INEs in silent MVP, but this goal is less relevant clinically. Indeed, no difference in INE risk was noted according to the indication for echocardiography ($P=0.26$) or in patients with and without auscultatory abnormality after adjustment for age ($P=0.11$). Furthermore, comparing observed INE rates in all community patients diagnosed with MVP to expected rates in the same community is the essential step in defining the excess risk of INEs associated with this condition.

Interventions to minimize INE risk in high-risk patients are important, but tracking all antithrombotic treatment and their timing was not possible. Careful analysis of their potentially harmful complications or preventive effect on INEs requires future clinical trials or risk-modeling studies.

Conclusions

Patients diagnosed with MVP in the community incur an overall excess lifetime risk of INEs compared with a similar community population. This excess risk is also observed under medical management during which it is confined to high-risk subsets of patients. Advancing age and thickened mitral leaflets at diagnosis are major baseline predictors of excess risk of INEs during follow-up. Subsequently, the need for cardiac surgery and occurrence of AFib in the course of the disease are independently associated with the risk of ischemic neurological complications. These time-dependent risk factors for excess rates of INEs are all related to the degree of MR resulting from MVP, which therefore plays an indirect role in the occurrence of INEs. High-risk subgroups that will require careful monitoring for the risk of INEs can be defined.

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Editorial Comment

Is MVP an MVP in Ischemic Cerebral Events?

Support for mitral valve prolapse (MVP) as a source of cardiac embolism has undergone undulating cycles of enthusiasm over the past 25 years. When the association between stroke and MVP was mooted by the pioneering work of Barnett and colleagues,¹ a new referral source opened for cardiologists. Then came the backlash. Many cases appeared to be incidental; studies did not identify an increased risk of cerebral embolism²; the condition was deemed to be a harmless variant, and common in the general population. Revised diagnostic criteria followed, and MVP was all but removed as a “most valuable player” in the team of cardiac abnormalities associated with cerebral embolism. The confounding associations did not help: MVP may be idiopathic and solitary with either familial or sporadic forms. Alternatively it may be secondary to connective tissue disorders or ischemic heart disease (a common cause in those over 50 years of age). In addition, both ventricular and atrial arrhythmias can accompany MVP; there are anatomic variants as well, with different degrees of myxomatous degeneration of the posterior or anterior leaflet, and of papillary muscle involvement and mitral regurgitation. Thus embedded in the condition are many subvariants with a range of embolic potential from benign to extremely severe.

Avierinos and colleagues³ have to some extent pulled a rabbit out of the magician’s hat. Using the Olmsted County database, they were able to overcome some methodological flaws confounding earlier studies. A community reference base was used rather than that derived from hospital or ambulatory care settings, reducing a common source of bias.

MVP is often asymptomatic, but, with an estimated prevalence of about 2%,⁴ an extraordinarily large number of patients would have to be screened in a community to recruit both symptomatic and asymptomatic cases in sufficient numbers to satisfy power considerations—clearly an impractical task. This study, therefore, follows a fairly specific group, selected for echocardiography on the basis of auscultation findings (70%), the remainder having vague cardiorespiratory symptoms or other nonspecific reasons for testing. Inclusion criteria were: no evidence of atrial fibrillation on ECG (although paroxysmal AF may thus be underdetected at entry, a point which should be considered when evaluating AF development during follow up), and no previous cardiac surgery or stroke/TIA. These patients thus represent the tip of the MVP iceberg.

The incidence of confounding risk factors for cerebrovascular events (Doppler vascular ultrasound investigation and history of hypertension, myocardial infarction, heart failure) was low in this group, which was young and followed for a mean of 5.5 ± 3 years. Prognostic indicators for stroke or TIA were: older age (>50 years), atrial fibrillation, cardiac surgery, and mitral valve

thickening. Older age is unlikely to be an independent factor: in this group, the etiology of MVP may be ischemic. The incidence of AF associated with MVP increases with age and left atrial dimension, all of which factors are themselves implicated in cardiogenic stroke.⁵ In dachshunds, MVP progressively worsens with age.⁶ Whether the same occurs in humans is unclear.

Cardiac surgery (whether valve repair or replacement is not stated) was performed in one third of patients. For these it could be argued that the prognosis is now related to the cardiac intervention and less to the pure natural history of MVP.

This study helps us identify which of the patients presenting in a clinical setting might be at risk of cerebral vascular events. In this it is valuable. However, recommendations as to treatment are complex. Any modifying effect of concomitant medications on outcome (for example, aspirin or anticoagulation) was not discussed. It would seem prudent that anticoagulation be considered in the higher risk group, notably those over 50 with atrial fibrillation and/or mitral valve thickening, and in those with a previous stroke or TIA. Indeed there is an appreciable recurrence rate once an event occurs (27% over the follow-up period). In patients under 50 without any of these accompanying factors, there may be no need for stroke prophylactic therapy given that the incidence of cerebral embolization is extremely low. In this regard, these results are similar to those from an earlier retrospective case-control report.² Clearly, further studies would be helpful to investigate the effect of intervention on prognosis.

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