Cerebral Ischemia and Mitral Valve Prolapse: Case-Control Study of Associated Factors

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We evaluated 36 patients with cerebral ischemia and mitral valve prolapse and compared them with 36 age-matched controls with cerebral ischemia who had similar attributes but who did not have mitral valve prolapse. Stepwise logistic regression analysis revealed an inverse relation between cerebral ischemia in the presence of mitral valve prolapse and hypertension, diabetes mellitus, occlusive cerebrovascular disease, and completed stroke at p<0.01. We also found, by correlation analysis, a negative correlation between both hypertension and diabetes mellitus versus mitral valve prolapse at p<0.05. Overall, 10 study patients compared with two control patients had no risk factors for cerebrovascular disease detected (χ² = 4.9, p<0.05). These data indicate that the association of mitral valve prolapse and cerebral ischemia is of special importance in patients who do not have other detected risk factors for cerebrovascular disease. (Stroke 1988;19:443–446)

There continues to be considerable controversy about the exact role of mitral valve prolapse (MVP) in cerebral ischemia (CI). The numerous reports suggesting an association have been influenced by patient selection and possible referral bias. One would expect, for example, that with a 2.5–7% prevalence of MVP in the general population a significantly higher percentage of patients in prospective stroke series would be detected with MVP. This has not been found to be the case. In one large stroke series, no patient with MVP was detected despite 55% of those with presumptive cerebral embolus having echocardiography performed. In a recent series of 144 young patients with ischemic stroke, eight patients (5.6%) had MVP, and only three of these eight were believed to have MVP as the primary etiologic factor after intensive investigation. This has led to speculation that, although MVP has the potential to promote cerebral embolus, its relative importance is quite small, and that published reports to the contrary are artifactual.

The purpose of our study was to assess the frequency of risk factors for stroke in a group of patients with CI plus MVP (study patients) and to compare the results with those from a group of patients with CI who had similar characteristics but who did not have MVP (control patients). The primary objective, therefore, was to assess possible differences in the stroke-prone profile between the two groups.

Subjects and Methods

From July 1983 through June 1987, 36 patients with acute CI who were found to have MVP were compared with 36 patients with CI seen over the same time period who did not have evidence of MVP by echocardiography; neither group had other possible anatomic sources of cerebral embolus by this study. Patients were pair-matched on the basis of age (± 5 years), sex, race, and type of ischemia (transient ischemic attack [TIA], large artery embolus/thrombus, or lacuna). The patients were assessed in a prospective, standardized fashion on coded forms. This format hopefully served to avoid selection bias in terms of associated factors when matching patients with and without MVP.

All patients were personally evaluated and a detailed medical history, physical examination, and review of pertinent diagnostic studies were obtained. Particular attention was paid to the presence of risk factors for cerebrovascular disease, history compatible with migraine, results of cardiac evaluation, and results of neurologic evaluation including computed tomographic (CT) brain scan, magnetic resonance imaging (MRI) brain scan, carotid noninvasive battery (consisting of B-mode ultrasonography, direct Doppler ultrasonography, peribortal Doppler ultrasonography, and oculouneumoplethysmography), and cerebral angiography. All but one study patient had a CT brain scan, and that patient had a MRI brain scan. All control patients had a CT brain scan. A total of 25 study patients had either carotid noninvasive battery (n = 18) or cerebral angiography (n = 7), while 20 control patients had either carotid noninvasive battery (n = 11) or cerebral angiography (n = 9). Twenty-nine study patients (81%) had 24-hour cardiac monitoring compared with 26 control patients (72%). All patients underwent routine blood laboratory screening including complete blood count, platelet count, prothrombin time, partial thromboplastin time, and syphilis serology as well as fasting serum glucose, cholesterol, and triglyceride.

Each patient underwent M-mode and two-dimensional (2-D) echocardiography. Standard views for the latter were obtained from the parasternal and apical windows. A diagnosis of MVP in each patient was made on the basis of published criteria for M-mode and 2-D images. The echocardiograms were all independently read by a board-certified car-
diologist. Two study patients had corroborated evidence of MVP by angiocardiology. All patients with MVP were believed to have a midsystolic click on cardiac auscultation. One control patient was believed to have a possible midsystolic click, but she did not have evidence of MVP by echocardiography performed twice.

Risk factors for stroke that were analyzed by correlation analysis and stepwise multiple logistic regression included age, sex, race, hypertension, diabetes mellitus, coronary artery disease, atrial fibrillation, congestive heart failure, ventricular ectopy (≥ 10 ventricular premature contractions/min or those occurring in couplets or runs), previous stroke, oral contraceptive use, hyperlipidemia, hypercoagulable state, occlusive cerebrovascular disease, and cigarette smoking. Occlusive cerebrovascular disease was judged to be significant on the basis of carotid noninvasive examination or cerebral angiography, and we included those patients with extracranial or intracranial stenoses of ≥ 30%. Cigarette smoking was defined as significant if the patient smoked an average of ≥ 1 pack/day over a 1-year consecutive time period. We also included in the analysis whether there was completed stroke or TIA and whether there was migraine. The presence of factors such as hypertension, ischemic heart disease, diabetes mellitus, and migraine was based on history and the need for specific ongoing therapy for these disorders.

**Results**

There were 36 patients, 17 men and 19 women, 23 white and 13 black, in each group. The mean ± SD age was 47.2 ± 17.4 years in the study group and 46.7 ± 15.3 years in the control group. The age distribution is shown in Table 1. There were 25 patients with completed infarction and 11 patients with TIA in each group. Of the patients with completed stroke, there were three matched pairs with capsular lacunae.

The most obvious difference in the frequency of risk factors between the two groups was hypertension (14% in study patients vs. 47% in controls) and diabetes mellitus (0% in study patients vs. 31% in controls). Although the numbers were small, we found previous results (8% vs. 19%) and occlusive cerebrovascular disease (6% vs. 28%) also to be more common in the control group. No patient with hyperlipidemia was detected. One study patient was believed to be hypercoagulable on the basis of protein S deficiency. This patient had deep venous thrombosis (DVT) and pulmonary embolus. A control patient had DVT and the lupus anticoagulant. Two study patients versus one control patient were using oral contraceptives at the time of their CI.

By stepwise logistic regression analysis, factors negatively associated with CI in the presence of MVP at p<0.01 were diabetes mellitus, hypertension, occlusive cerebrovascular disease, and completed stroke. Two other factors that were negatively correlated with each other at p<0.01 were hypertension and migraine.

Table 2 summarizes the results of the correlation analysis using Kendall τ correlation coefficients of all risk factors. The correlations at p<0.05, whether positive or negative, are recorded. Age was positively correlated with hypertension, diabetes mellitus, and coronary artery disease while it was negatively correlated with migraine. Migraine was also negatively correlated with hypertension but was found more frequently in women. Hypertension was positively correlated with completed stroke but, as in the logistic regression analysis, negatively correlated with MVP. Diabetes mellitus was also negatively correlated with MVP. The positive correlation of cigarette smoking and oral contraceptive use in patients with CI is not unexpected, and neither is the correlation between atrial fibrillation and congestive heart failure or the correlation between ventricular ectopy and occlusive cerebrovascular disease. Completed stroke was negatively correlated with migraine.

**Discussion**

Our data indicate that the association of MVP with CI is of primary importance in patients who do not have major risk factors for stroke. We found no difference in the frequency of risk factors between TIA patients (mean age 42 years) and those with completed stroke (mean age 48 years). Overall, there were 10 study patients, six with TIA and four with completed stroke, compared with two control patients (χ² = 4.9, p<0.05) who had no detectable risk factors. The mean age of the study patients without risk factors was 43 years, while that of the study patients with risk factors was 48 years.

Age was not found to be a significant factor in the relation between CI and MVP in the logistic model. A positive correlation between age and hypertension as well as between age and diabetes mellitus was noted (p<0.05), but no additional correlations were detected, and age was systematically eliminated with the use of a step-down procedure. Presumably, however, one would expect MVP-related CI to be of greatest significance in younger stroke patients in whom arteriosclerosis is less likely to play a role in cerebral thromboembolic disease.

<p>| Table 1. Age Distribution in Age-Matched Patients With and Without Mitral Valve Prolapse |
|-----------------------------------------------|-----------------------------------------------|
| Age group (yr) | Mitral valve prolapse | No mitral valve prolapse |</p>
<table>
<thead>
<tr>
<th></th>
<th>Completed stroke</th>
<th>Transient ischemic attack</th>
<th>Total</th>
<th>Completed stroke</th>
<th>Transient ischemic attack</th>
<th>Total</th>
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<td>10-19</td>
<td>1</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>20-29</td>
<td>3</td>
<td>3</td>
<td>6</td>
<td>3</td>
<td>2</td>
<td>5</td>
</tr>
<tr>
<td>30-39</td>
<td>4</td>
<td>4</td>
<td>8</td>
<td>4</td>
<td>3</td>
<td>7</td>
</tr>
<tr>
<td>40-49</td>
<td>4</td>
<td>1</td>
<td>5</td>
<td>3</td>
<td>3</td>
<td>8</td>
</tr>
<tr>
<td>50-59</td>
<td>6</td>
<td>0</td>
<td>6</td>
<td>6</td>
<td>0</td>
<td>6</td>
</tr>
<tr>
<td>60-69</td>
<td>4</td>
<td>2</td>
<td>6</td>
<td>4</td>
<td>3</td>
<td>7</td>
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<tr>
<td>70-79</td>
<td>3</td>
<td>1</td>
<td>4</td>
<td>2</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>Total</td>
<td>25</td>
<td>11</td>
<td>36</td>
<td>25</td>
<td>11</td>
<td>36</td>
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</table>
There are a number of theoretical reasons to expect a higher frequency of CI in patients with MVP. These include an increased risk of infective endocarditis,\textsuperscript{16,17} the relatively high frequency of MVP in severe coronary artery disease\textsuperscript{18} with the attendant risk of acute myocardial infarction for cerebral embolus,\textsuperscript{19} the association of atrial fibrillation with MVP,\textsuperscript{20} which may be of special importance in the promotion of cerebral embolus,\textsuperscript{21,22} and thrombus formation in the region of MVP.\textsuperscript{23} In addition, migraine is seen in association with MVP,\textsuperscript{24} and symptoms of migraine can mimic TIA or there can actually be migrainous infarction.\textsuperscript{25} Also, CI associated with MVP may be related to platelet hyperaggregability.\textsuperscript{26-28} Thus, it is not unexpected that Sandok and Giuliani\textsuperscript{29} reported that the prevalence rate of CI in patients with MVP was four times greater than that for the normal population.

What remains unexplained is the relatively low detection rate for MVP in large prospective series of stroke patients. Such series of stroke and TIA patients studied by echocardiography give a rather consistent prevalence of MVP of between 0\% and 5\%.\textsuperscript{30-33} On the other hand, Barnett et al\textsuperscript{1} reported that 24 of 60 patients younger than 45 (40\%) with TIA or partial stroke had MVP compared with 8 of 141 patients older than 45 years of age (5.7\%). Myxomatous degeneration of the chorda tendinea may be the more common mechanism of prolapse of the mitral valve in older patients,\textsuperscript{38} whereas primary degeneration of the valve leaflets is the primary factor in younger individuals.\textsuperscript{39} This might have implications for stroke risk in the two age groups. Two additional studies of stroke in younger individuals found MVP in 34.8\%\textsuperscript{40} and 32\%.\textsuperscript{41} These studies are not in agreement, however, with a study of 30 consecutive young stroke patients that found no significant difference in the prevalence of MVP compared with matched control patients.\textsuperscript{42}

Hart and Easton\textsuperscript{43} emphasize the importance of differentiating studies of CI in groups of unselected patients versus those in whom the ischemia is unexplained. They feel that the discrepancy in the prevalence of MVP between the two types of studies reflects a low absolute risk for MVP-associated stroke overall but a relatively high prevalence in young adults with unexplained CI. A recent survey of the literature\textsuperscript{44} cogently points out that even if MVP accounts for one third of stroke in persons younger than 40, the incidence of stroke in this age group (approximately 3/100,000/yr) results in an overall stroke risk for MVP of approximately 1/100,000/yr. This is approximately the same risk for MVP-associated stroke in older patients. Furthermore, assuming a prevalence of 6\% for MVP in younger individuals, the incidence of stroke in young individuals with MVP is relatively low, approximately 1/6,000/yr (0.2\%).

The complexity of the association of MVP and CI was underscored by one study patient who had a hypercoagulable state that was not discovered until 4 weeks after his stroke. This 23-year-old man presented with a moderate-sized, right middle cerebral artery distribution stroke and was found to have a midystolic click on cardiac auscultation, with MVP documented by echocardiography. Despite progressive recovery with increasingly independent walking, he developed DVT with secondary pulmonary embolus. Extensive hematologic investigation revealed protein S deficiency, which has recently been observed in association with ischemic stroke.\textsuperscript{45} This patient illustrates that, despite the potential of MVP to be associated with CI, other possible mechanisms require evaluation.

### Table 2. Kendall's $\tau$ Correlation Coefficients for Factors Possibly Related to Cerebral Ischemia in Patients With and Without Mitral Valve Prolapse

<table>
<thead>
<tr>
<th></th>
<th>Hypertension</th>
<th>Diabetes mellitus</th>
<th>Cigarette smoking</th>
<th>Coronal artery disease</th>
<th>Congestive heart failure</th>
<th>Completed stroke</th>
<th>Occlusive cerebrovascular disease</th>
<th>Migraine</th>
<th>Mitral valve prolapse</th>
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</thead>
<tbody>
<tr>
<td>Age</td>
<td>0.32</td>
<td>0.24</td>
<td>-0.25</td>
<td>-0.31</td>
<td>-0.02</td>
<td>0.32*</td>
<td>-0.27</td>
<td>-0.36</td>
<td>-0.42</td>
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<tr>
<td>Sex</td>
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<tr>
<td>Hypertension</td>
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<tr>
<td>Diabetes mellitus</td>
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<tr>
<td>Oral contraceptives</td>
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<tr>
<td>Completed stroke</td>
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<td></td>
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<tr>
<td>Atrial fibrillation</td>
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<td></td>
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<td>-0.25</td>
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<tr>
<td>Ventricular ectopy</td>
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<td></td>
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<td>0.39</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

$p<0.05$ for reported values.
*Women only.

References

44. Wolf PA, Sila CA: Cerebral ischemia with mitral valve prolapse. Arch Neurol 1987;113:1308–1315

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