Mitral Valve Prolapse and Cerebral Ischaemia — Is the Relationship Causal or Coincidental?

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Stroke is a very common and serious problem all over the world with a high morbidity and mortality. Lack of effective therapy in this condition reinforces the need to understand its aetiology so that rational, preventive and therapeutic strategies may be developed. Heart disease as a cause of cerebral embolism has been known for over a century. Initially rheumatic valvular heart disease and infective endocarditis were recognized as the main causes of cardioembolic strokes. In the past decade the application of new technology has linked a number of previously unrecognized cardiac conditions with increased risk of stroke — the prominent ones being mitral valve prolapse (MVP), atrial fibrillation and patent foramen ovale. The evidence is convincing that MVP is an important cause of cardioembolism especially in the young stroke patients. It should be carefully looked for in all unexplained cerebral ischaemic events and if found, appropriate therapeutic and prophylactic measures should be taken.

In Europe and North America mitral valve prolapse (MVP) is the commonest valvular heart disease affecting 2.5 to 5% of the general population. The prevalence of MVP in developing countries has not been well studied; however, a recent report indicates that it is as common in Saudi Arabia as in developed countries. In the vast majority of people MVP is a benign condition; nevertheless in some cases it may cause serious complications including arrhythmias, progressive mitral regurgitation, infective endocarditis, thromboembolism and sudden death.

In spite of great research interest and a very large number of publications on MVP, most aspects of this condition remain controversial and many questions remain unanswered. The main reason for conflicting reports is the variable criteria used for diagnosis of MVP, since a uniformly accepted definition still eludes us. One of the most controversial issues is the linking of cerebral and retinal
ischaemic episodes to MVP — is the relationship causal or coincidental? Several investigators from different countries have reported thromboembolic cerebral and retinal ischaemic episodes in patients with MVP and they believe there is a causal relationship. However, scepticism persists and many feel that these reports can be explained by mere coincidental occurrences of two common disorders. This report reviews the association of MVP and cerebral ischaemia with particular emphasis on possible mechanisms and prophylaxis.

Historical Perspective
Heart disease as a cause of stroke was recognized as long ago as the last century, but it was considered to be an uncommon cause. A retrospective autopsy review showed that cardioembolic stroke was much more common than clinically suspected, being responsible for half of 105 patients with cerebral infarction. The commonest cardiac lesions found were infective endocarditis and rheumatic valvular disease. Recent data indicate that 20 to 30% of ischaemic strokes are of cardiogenic origin of which only a minority are due to infective endocarditis and rheumatic valvular heart disease. The past decade has witnessed a great development in diagnostic technology and epidemiologic strategy. This has brought into focus the relationship between heart disease and stroke; generating great enthusiasm because of the potential for prophylaxis and therapy of a condition which results in serious disability. The relative importance of cardiac diseases as a source of emboli varies with the prevalence of these disorders in different geographic areas. In some developing countries rheumatic heart disease remains the most frequent cause; Chagas' disease is a common cause in South America, whereas in developed countries atrial fibrillation is the commonest cause. Recently, there have been many reports of MVP causing cerebral and retinal ischaemic episodes resulting in transient ischaemic attacks, amaurosis fugax and strokes.

In 1966 Barlow and Bosman described a 23-year-old woman with MVP who experienced transient left arm weakness, but they did not relate the neurological disorder to her cardiac lesion. In 1974 Barnett et al. reported four cases of cerebral ischaemia events in which no cause could be found ischaemia events in which no cause could be found but the patients were noted to have MVP.

The next year Woldoff reported two cases of retinal artery occlusion presumably caused by MVP. Subsequently, numerous reports came from Canada, England, South Africa, France and the USA. The author recently reported the first cases from the Middle East.

Epidemiology
From 1974 to 1982 more than 40 papers were published describing cerebral and retinal ischaemic events in more than 250 patients with no recognizable cause except MVP. In 1980, Barnett et al. published a study comparing 60 patients below the age of 45 years with cerebral ischaemia (transient ischaemic attacks and stroke) with an equal number of age- and sex-matched controls. He found that 40% of the cerebral ischaemic group had MVP (by M-mode echocardiography) compared with 6.8% in the control group. This was suggestive evidence of a causal relationship between stroke and MVP. Kouvaros and Bacoulas also reported that 34.8% of a group of 66 young stroke patients had MVP. However, several studies showed a substantially lower (2 to 11%) prevalence of MVP even in young stroke patients. Rice et al. reported two families with autosomal dominant patterns of inheritance of MVP with several young members of the family developing cerebral or retinal ischaemic episodes.

Despite several reports of cerebral and retinal ischaemic episodes attributed to MVP from North America, Europe, South Africa and the Middle East, there remains scepticism about MVP as a cause of embolism. This is because of a rather low incidence of unexplained strokes in MVP cases followed by cardiologists (Table 1). However, this can be explained by the extremely low incidence of embolism in MVP. The stroke incidence under the age of 40 years in the USA is 3 per 100 000 population per year. Assuming one-third of strokes in young adults is due to MVP (probably an overestimate) and a 6% prevalence of MVP in all young adults, the calculated risk of stroke in all young adults with MVP is only 1/6000/year. Therefore in order to determine the incidence and natural history of thromboembolism associated with MVP, prospective long-term follow-up studies of large groups of patients are needed. No such

<table>
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<th>Ref.</th>
<th>No. of MVP cases</th>
<th>No. of cases of unexplained strokes</th>
<th>Mean age (years)</th>
<th>Duration of follow-up (years)</th>
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<td>119</td>
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<td>(10)</td>
<td>1138</td>
<td>26 (2.3%)</td>
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<td>32 (7%)</td>
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<td>4 (2.8%)</td>
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<td>(25)</td>
<td>300</td>
<td>11 (3.7%)</td>
<td>42</td>
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</table>

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study has been done so far and may be impossible to do because of cost restraints and the relatively benign nature of MVP. All the reports linking MVP and thromboembolism are either anecdotal or are studies from University hospitals which consist of preselected referred patients and are, therefore, biased.

Mechanisms
It is well recognized that MVP may cause arrhythmias and infective endocarditis. Although both of these can cause cardioembolic strokes, they do not explain the great majority of cerebral ischaemic episodes in MVP. This raises a very important question—what then is the mechanism?

Our ability to study the relationship of MVP and cerebral ischaemia is limited by the following factors: first, definite diagnoses of both MVP and cerebral embolism are difficult due to lack of precise, unequivocal clinical and laboratory diagnostic criteria; second, cerebrovascular disease and cardiac disease often coexist especially in older patients; third, because of the relatively young age of the patients under consideration and the non-lethal nature of ischaemic cerebral or eye insults there is no autopsy series available.

Despite these obvious difficulties the increasing reports of the association of MVP and cerebral ischaemia cannot be lightly dismissed as just due to misdiagnosis or chance. Most investigators believe that the most likely cause of cerebral ischaemia is the formation of a non-infective platelet-fibrin thrombus initiated by platelet adherence to the fissured myxomatous leaflet of the mitral valve (Fig. 1).26 A larger thrombus forming in the cul-de-sac created between the ballooning posterior leaflet and the atrial wall has also been described (Fig. 2).27 Moreover, transient ischaemic attacks, recurrent amaurosis fugax, permanent monocular defects and small strokes have been reported which can be best explained by small platelet-fibrin emboli. This is further substantiated by several reported observations of embolic material resembling platelets and fibrin in the retinal arterioles.13,27 Interestingly, an abnormality of platelet activity has been observed by several authors.27,28 The observation of platelet hyperactivity is consistent with the hypothesis that the intravascular thromboembolism is due to the interaction of platelets and the surface tears on a mitral valve with myxomatous degeneration. The same abnormal platelet activity is also found in other cardiac conditions that are associated with an increased incidence of thromboembolism.

Although echocardiography is the best technique for the diagnosis of MVP, it has not been useful in identifying intra-atrial or mitral leaflet thrombus because the echocardiographic resolution does not permit the visualization of such small platelet-fibrin thrombi that occur in association with MVP. Echocardiography has also failed to define the characteristics of a subgroup of patients who are at a higher risk of developing cerebral or retinal ischaemic attacks.

Management
The formulation of a rational therapeutic approach for any condition requires proper understanding of the pathogenesis and natural history and well-designed prospective randomized clinical trials of therapeutic modalities which may be deemed potentially beneficial. Unfortunately, for thromboembolism in MVP, such data are not yet available. Further research to study the natural history and to develop beneficial therapeutic strategies is needed. Because of the greater awareness of the risk factors of atherosclerosis there has been nearly a 50% decline in deaths due to stroke in little over a decade in
the USA. There is reason to be optimistic that with the increased awareness of cardioembolic strokes coupled with the judicious use of prophylactic therapy, further reduction in strokes will be achieved.

Since the risk of embolism in MVP is clearly small (1 per 6000 patients per year) routine anticoagulation or antiplatelet therapy is not warranted in all MVP patients. So far, no clinical or laboratory characteristics have been observed that can reliably identify the subset of MVP patients who are at high risk for thromboembolism. However, MVP should be considered and looked for by careful auscultation and echocardiography in all unexplained strokes particularly in patients below the age of 45 years. Nevertheless, it is very important to exclude other causes such as a collagen disorder, polycythemia, sickle cell disease, oral contraceptives, patent foramen ovale and migraine. Once it is determined that the most likely cause of a cerebral ischaemic event is MVP then prophylaxis against future events must be considered. Jackson et al. reported 32 young patients with cerebral ischaemia due to MVP with a mean follow-up period of 8 years. They found that 44% had recurrent ischaemic events. Generally, anti-platelet therapy has been recommended. However, if recurrence occurs on antiplatelet therapy then oral anticoagulation with warfarin should be considered. The optimal duration of therapy is unknown but probably it should be given initially for 3 to 6 months and then it may be stopped if there is no further recurrence. Since most episodes in MVP are either transient or are small strokes, lifelong therapy is probably not justified. There is an indication that oral contraceptives increase the risk of thromboembolism in MVP; therefore, their use should be considered relatively contraindicated in MVP patients.

Conclusion

An extensive review of literature shows that there is overwhelming evidence that the relationship of MVP and cerebral ischaemia is causal rather than coincidental. The risk of serious morbidity and mortality is small. However, in a small number of patients permanent serious visual disturbances or neurological deficit may occur. In view of the high prevalence of MVP, it is exceedingly important for physicians to be aware of its complications and to institute appropriate prophylactic measures when indicated. It is equally important not to alarm patients unnecessarily about the complications, since in the vast majority of cases, MVP runs a benign course. All patients must be reassured in order to avoid unnecessary cardiac neurosis. Further prospective long-term studies are needed to determine the characteristics, if any, of patients with MVP who are at increased risk of thromboembolism; to learn about the natural history and to develop an effective prophylactic approach.

References


