

Mitral Valve Prolapse and Thromboembolic Events

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The mitral valve prolapse syndrome is known by several names, including the systolic click-murmur syndrome, Barlow syndrome, billowing mitral cusp syndrome, myxomatous mitral valve, floppy valve syndrome, and redundant cusp syndrome [1–6]. It is a common but variable clinical syndrome that results from diverse pathogenic mechanisms of one or more portions of the mitral valve apparatus, the valve leaflets, chordae tendineae, papillary muscle, and valve annulus. The MVP syndrome has become recognized as one of the most prevalent cardiac valvular abnormalities, affecting as much as 3 to 5% of the population [7,8]. It is twice as frequent in females than in males and has been noted in a wide age range but most commonly between the ages of 14 and 30 years.

In most patients with MVP, myxomatous degeneration is confined to the mitral valve leaflets, with the posterior leaflet usually more affected than the anterior leaflet. There are usually no other clinical or pathologic manifestations of connective tissue disease. MVP may lead to excessive stress on the papillary muscles, which in turn leads to dysfunction and ischemia of the papillary muscles and subjacent ventricular myocardium. Rupture of chordae tendineae and progressive annular dilatation and calcification also contribute to valvular regurgitation, which then places more stress on the diseased mitral valve apparatus, thereby creating a vicious cycle.

Our review will focus on the pathogenic mechanisms relating MVP with cerebral thromboembolism. We will also discuss the current literature on the subject, with an emphasis on the major clinical issue – namely, which, if any, patients with MVP have an increased risk for thromboembolic events.

Natural history

Some patients have an increased familial incidence, suggesting an autosomal dominant form of inheritance. MVP encompasses a broad spectrum of severities, ranging from only a systolic click and murmur and mild prolapse of the posterior leaflet of the mitral valve to severe MR due to chordal rupture and massive prolapse of both leaflets. Most patients are asymptomatic and remain so for their entire lives. While MVP is now the most common cause of isolated severe MR in the United States, severe MR is a relatively uncommon complication of MVP.

Palpitations, light-headedness and syncope may be caused by arrhythmias, most commonly ventricular premature contractions and paroxysmal supraventricular and ventricular tachycardia. Many patients have atypical chest pain that is difficult to evaluate. Transient cerebral ischemic attacks and non-reversible neurological damage secondary to emboli from the mitral valve due to endothelial disruption have been reported.

Pathogenetic mechanisms

Acute hemiplegia, transient ischemic attacks, cerebellar infarcts, amaurosis fugax, and retinal arteriolar occlusions occur more frequently in patients with the MVP syndrome, suggesting that cerebral emboli are unusually common in this condition [9,10]. Several mechanisms have been suggested, including shortened platelet survival, and loss of endothelial continuity and tearing of the endocardium overlying the myxomatous valve, both of which could initiate platelet aggregation and the formation of mural platelet-fibrin complexes [9]. Paroxysmal arrhythmias that occur in the MVP syndrome may contribute to the likelihood of embolization.

A study to determine whether platelets play a part in the pathogenesis of thromboembolism investigated 29 patients with MVP [11]. The patients included 9 (group I) with thromboembolism (cerebral, retinal and deep venous), 8 (group II) with transient visual obstructions, and 12 (group III) with neither thromboembolism nor visual complaints, compared with 18 control patients and 38 normal subjects. Patients in groups I and II had increased platelet coagulant activities related to the initiation and early stages of intrinsic coagulation, and group I patients had an increased proportion of circulating platelet aggregates and platelets relatively insensitive to epinephrine in aggregation and secretion. The incidence of platelet coagulant hyperactivity in patients with MVP was 76% (100% in group I, 75% in group II, 58% in group III), compared with 6% in control patients. These results suggest that platelets play a role in the purported association of thromboembolism and mitral valve prolapse [11]. In another study [12], platelet factor 4 (a marker protein of platelet activation) was elevated in 12 of 33 patients with MVP (36%) without a history of stroke. These findings indicate that platelets are frequently activated in asymptomatic MVP patients and may allow identification of a subgroup of MVP patients with activated platelets who are at increased risk for emboli.

MVP = mitral valve prolapse
MR = mitral regurgitation

Epidemiological studies

A historical cohort study that was conducted on 1,079 patients in whom MVP was diagnosed echocardiographically (with a follow-up of 9 years until the first stroke) found a twofold increase in the incidence of stroke among individuals with MVP relative to the reference population [13]. However, the increased risk of stroke in this cohort was attributed to mitral valve replacement and co-morbidity of ischemic heart disease, congestive heart failure and diabetes mellitus. In the absence of these conditions, there was no increase in the risk of stroke compared with the general population, but the 95% confidence interval indicates that a small increase in risk may not have been detected [13].

Nishimura et al. [14] followed 237 minimally symptomatic or asymptomatic patients by echocardiography for a mean of 6.2 years (range 1–10.4). The actuarial 8 year probability of survival was 88%, which is not significantly different from that for a matched control population. An initial left ventricular diastolic dimension exceeding 60 mm was the best echocardiographic predictor of the subsequent need for mitral valve replacement (17 patients). Of the 97 patients with redundant mitral valve leaflets identified echocardiographically, 10 (10.3%) had sudden death, infective endocarditis, or a cerebral embolic event. In contrast, of the 140 patients with non-redundant valves, only 1 (0.7%) had such complications ($P < 0.001$). During the follow-up period, 10 patients (mean age 50 years) sustained a cerebral embolic event (defined as an acute neurological deficit with symptoms compatible with either vertebral basilar artery or internal carotid artery insufficiency, or as amaurosis fugax in the absence of clinically recognized carotid occlusive disease). None of these patients was taking anticoagulants at the time of the event. Two of the 10 patients had other factors predisposing to cerebral ischemic events: 1 had a documented left ventricular aneurysm with an apical thrombus, and the other had active infective endocarditis. Of the eight remaining patients with cerebral embolic events, six were in atrial fibrillation with left atrial enlargement at the time of the event. Two were not in atrial fibrillation and had no predisposing causes; both were women (29 and 34 years old) who had carotid angiographic findings consistent with multiple embolic occlusions [14].

Recently, Gilon et al. [15] found that MVP is considerably less common than previously reported among young patients with stroke or transient ischemic attack, including unexplained stroke, and no more common than among controls. Using more specific and currently accepted echocardiographic criteria, an association between the presence of MVP and acute ischemic neurological events in young could not be demonstrated. Another study [16] evaluated platelet function and coagulation in 28 consecutive patients with MVP, 7 of whom had previous cerebrovascular disorders. While platelet function tests were found to be normal with the exception of platelet aggregation

rate, there was a significant rise of von Willebrand factor and fibrinopeptide A. Six patients had high levels of both these factors, suggesting the existence of a particular subset of MVP patients with a higher risk of thromboembolic episodes.

Conclusion

Overall, mitral valve prolapse is considerably less common than previously reported among young people with stroke, and no more common than among controls [15].

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