Platelets, Thromboembolism and Mitral Valve Prolapse

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SUMMARY  Cerebral and retinal ischemic events have been described in mitral valve prolapse. To determine whether platelets play a part in the pathogenesis of thromboembolism we studied 29 patients with mitral valve prolapse, including nine (group I) with thromboembolism (cerebral, retinal and deep venous), eight (group II) with transient visual obscurations 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 concerned with 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 mitral valve prolapse 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.

MITRAL VALVE PROLAPSE is a retrograde displacement of one or more of the mitral valve leaflets into the left atrium during systole. The auscultatory findings include one or more systolic clicks followed by a late systolic murmur, and the diagnosis can be confirmed by echocardiography or angiocardiography.1-3 At least 20% of patients with mitral valve prolapse are free of all symptoms, whereas others experience chest pain, fatigue, dyspnea, light-headedness and palpitations.4-5 Electrocardiographic abnormalities, arrhythmias and sudden death may also occur.6-9 Although various etiologies of the systolic click-murmur complex have been documented, including connective tissue disorders, rheumatic and congenital heart disease, cardiomyopathy and coronary artery disease, in the majority of patients the etiology is unknown.10 The major pathologic finding is myxomatous degeneration leading to redundancy of the mitral leaflets and prolapse during systole.6, 8, 10 The syndrome is especially common among young women, in whom its incidence may be as high as 10%.9

Cerebral and retinal ischemic events and other thromboembolic manifestations have been described in patients with mitral valve prolapse.11-18 Barnett et al.11 suggested that ischemic events in these patients are related to emboli emanating from the abnormal mitral valve with or without associated paroxysmal cardiac arrhythmia. Kostuk et al.12 suggested that changes on the surface of the leaflet might initiate platelet adherence and aggregation, resulting in formation of a platelet-fibrin thrombus that could later become detached.

Platelets function in hemostasis by adhering and forming aggregates at sites of vascular injury and secreting their granular contents. Recent evidence indicates that platelets can promote several reactions of intrinsic coagulation involving contact activation, factor-X activation and prothrombin activation leading to the formation of thrombin on the platelet surface, which can protect activated coagulation enzymes from inactivation by plasma proteinase inhibitors.17 Assessments of the contribution of platelets to coagulation by measurements of platelet coagulant activities in patients with venous thromboembolism,18 transient cerebral ischemic attacks19 and acute primary retinal venous20 and arterial21 occlusion suggest that platelets may contribute to the pathogenesis of these disorders by promoting the formation of venous and arterial thrombi.

In this study, we assessed platelets and coagulation in patients with mitral valve prolapse, with or without cerebrovascular occlusive disease or other thrombotic disorders. If the association between mitral valve prolapse and thromboembolism is more than fortuitous and is mediated by platelet activation, patients with mitral valve prolapse and thromboembolism might have platelet abnormalities, which might be detected even in patients without thromboembolism.

Patients and Methods

Twenty-seven females and two males, ages 22-62 years (mean 29 years), who had mitral valve prolapse were included in the study. Diagnostic criteria for inclusion included echocardiographic evidence of prolapse of either the anterior or posterior mitral leaflet during systole and either a mid-systolic apical click or a late systolic apical murmur or both. Patients were obtained from the Wills Eye Hospital Neuro-Ophthalmology Unit, where they presented with neurologic or visual symptoms and were found to have mitral prolapse and from the Cardiology Unit,
Thomas Jefferson University Hospital, where they were referred for nonvisual symptoms and were found to have mitral valve prolapse. All patients with documented mitral valve prolapse from these two sources who were available for study were included. Each patient had a detailed personal and family history and a complete general physical and neuro-ophthalmologic examination. All were evaluated by two of the authors. Cardiologic evaluation included ECG and echocardiogram in all patients. Phonocardiogram (12 patients), Holter monitor (eight patients) and cardiac catheterization (three patients) were performed when deemed necessary. Laboratory investigations included a complete blood count, urinalysis, SMA$_6$ and SMA$_{12}$. Serum cholesterol and triglycerides were determined after a 14-hour period of fasting and were normal in all patients.

Patients with mitral valve prolapse were prospectively divided into three groups as defined in the Results section. To establish normal values, we studied 38 normal subjects (20 males and 18 females), ages 20–48 years. We also studied 18 patients with nonvascular, nonthrombotic eye diseases (nine males and nine females), ages 26–70 years (mean 57 years). None of the latter had detectable atherosclerotic or thrombotic vascular disease, hypertension, diabetes mellitus or serum lipid abnormalities. Their diagnoses included glaucoma (13 patients), idiopathic optic atrophy (three patients), and idiopathic retinal degeneration (two patients).

Platelet studies were performed during an asymptomatic interval in all patients and 10 days to 8 weeks after the onset of symptoms in patients with mitral valve prolapse and permanent neurologic defects. Studies were repeated at least once in all patients, and the results reported represent the means of two to eight determinations. Studies done on separate occasions gave generally similar results. All studies were performed after a 14-hour period of fasting and abstinence from medications known to affect platelets, coagulation or serum lipids for at least 2 weeks before study.

Preparative Procedures

Nine volumes of blood were collected by clean venipuncture directly into 1 vol of 3.8% trisodium citrate with plastic containers and equipment. Platelet-rich plasma (PRP) and high-spun platelet-poor plasma were prepared$^{26}$ and platelets were washed and suspensions stored as previously described.$^{26, 24}$ Platelets were counted by phase microscopy$^{26}$ and electronically with a Model ZBI Particle Counter (Coulter Electronics).

Coagulation Assays

Determination of one-stage prothrombin times and activated partial thromboplastin times and assays for fibrin degradation products, fibrinogen and factors V and VIII were done as previously described.$^{18}$

Platelet Aggregation and Serotonin Release

Platelet aggregation and [14C]-5-hydroxytryptamine (5HT) release studies were done as previously described with ADP, epinephrine and collagen.$^{19, 26}$ Threshold concentrations of each agent resulting in secondary aggregation and release of more than 20% of [14C]-5HT were determined. Quantitative detection of platelet aggregates was carried out by comparing platelet counts in PRP obtained from blood collected either in EDTA/formalin or EDTA alone.$^{27}$ The result was expressed as a platelet aggregate ratio obtained by dividing the platelet count in EDTA PRP into the platelet count in EDTA/formalin PRP. A decrease in the ratio denoted an increase in platelet aggregates.

Platelet Coagulant Activities

The platelet coagulant activities assayed included (1) contact product-forming activity, the capacity of normal platelets to respond to ADP and participate in the activation of factor XII$^{28, 29}$ (2) collagen-induced coagulant activity, the capacity of collagen-stimulated platelets to participate in the initiation of intrinsic coagulation by an alternative mechanism in the apparent absence of factor XII$^{28, 30}$ (3) intrinsic factor-Xa forming activity, by which platelet membrane components become available and promote the interactions of factors XI$_a$, VIII and IX to activate factor X in the presence of calcium$^{31, 32}$ and (4) platelet factor 3 activity, by which platelet membrane phospholipoproteins become available and promote the interactions of factors X$_a$ and V to activate prothrombin in the presence of calcium.$^{33, 34}$ These platelet coagulant activities were assayed by modifications$^{88}$ of previously described methods.$^{38}$ Briefly, these assays involve incubation of various dilutions of either patient or normal PRP or washed platelets with the activating agents ADP, collagen or kaolin, followed by determination of clotting times after addition of either calcium chloride (contact product-forming activity) or Russell's viper venom and calcium chloride (platelet factor 3 activity). For the assay of collagen-induced coagulant activity and intrinsic factor-Xa forming activity, washed platelet suspensions were incubated with partially purified factors XIa, IX, X and thrombin-activated factor VIII, and the factor Xa formed was measured by determination of clotting times in factor-X deficient plasma. The results were expressed as percentages of normal platelets by reference to a double logarithmic plot of clotting time and platelet concentration. Results obtained in normal donors were normally distributed when the logarithms of these percentages were examined.

Statistical Methods

Results are expressed as mean ± SD or SEM. Groups were compared by t test or chi-square analysis, using the logarithms of platelet coagulant activities for these analyses when appropriate.
Results

The clinical characteristics of the 29 patients with mitral valve prolapse are given in Table 1. None of them had evidence of hypertension, hyperlipidemia, diabetes mellitus, the Marfan syndrome or other connective tissue disease, rheumatic heart disease, ischemic heart disease, congenital heart disease or cardiomyopathy.

The patients were prospectively divided into three groups before laboratory studies were done. Group I consisted of nine patients with evidence of thromboembolic disease, none of whom had a personal or family history of migraine and none of whom was receiving oral contraceptives when symptoms appeared, except for patient 1, who had a history of thrombophlebitis 6 years before her cerebral ischemic event. Four patients presented with homonymous hemianopsia (three left, one right), and each had a completed stroke in the occipital lobe. Computer-

<table>
<thead>
<tr>
<th>Patients</th>
<th>Age (years)</th>
<th>Sex</th>
<th>Clinical features</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group I</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>43</td>
<td>F</td>
<td>Right homonymous hemianopsia; history of thrombophlebitis while on oral contraceptives</td>
</tr>
<tr>
<td>2</td>
<td>24</td>
<td>F</td>
<td>Left homonymous hemianopsia, paresthesias, headache</td>
</tr>
<tr>
<td>3</td>
<td>57</td>
<td>F</td>
<td>Left homonymous hemianopsia</td>
</tr>
<tr>
<td>4</td>
<td>32</td>
<td>F</td>
<td>Left homonymous hemianopsia</td>
</tr>
<tr>
<td>5</td>
<td>36</td>
<td>F</td>
<td>Transient cerebral ischemic attacks; history of four episodes of thrombophlebitis</td>
</tr>
<tr>
<td>6</td>
<td>45</td>
<td>F</td>
<td>Recurrent deep vein thrombosis</td>
</tr>
<tr>
<td>7</td>
<td>22</td>
<td>F</td>
<td>Central retinal vein occlusion (right eye)</td>
</tr>
<tr>
<td>8</td>
<td>37</td>
<td>F</td>
<td>Bilateral amaurosis fugax and transient cerebral ischemic attacks</td>
</tr>
<tr>
<td>9</td>
<td>50</td>
<td>F</td>
<td>Amaurosis fugax (left eye)</td>
</tr>
<tr>
<td>Group II</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>10</td>
<td>29</td>
<td>F</td>
<td>Visual fortifications in right visual field without headache</td>
</tr>
<tr>
<td>11</td>
<td>52</td>
<td>F</td>
<td>Scotomas with fortifications in left visual field without headache; family history of migraine</td>
</tr>
<tr>
<td>12</td>
<td>56</td>
<td>F</td>
<td>Transient alternating, unilateral visual obscurations; history of common migraine</td>
</tr>
<tr>
<td>13</td>
<td>27</td>
<td>F</td>
<td>Transient bilateral visual obscurations</td>
</tr>
<tr>
<td>14</td>
<td>32</td>
<td>F</td>
<td>Transient bilateral visual obscurations (single episode), left-sided paresthesias, on oral contraceptives; history of common migraine</td>
</tr>
<tr>
<td>15</td>
<td>53</td>
<td>F</td>
<td>Scintillating scotomas in homonymous field; history and family history of migraine</td>
</tr>
<tr>
<td>16</td>
<td>40</td>
<td>F</td>
<td>Scotomas with waviness on hemifield; family history of migraine</td>
</tr>
<tr>
<td>17</td>
<td>62</td>
<td>F</td>
<td>Bilateral transient visual obscurations</td>
</tr>
<tr>
<td>Group III</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>18</td>
<td>42</td>
<td>F</td>
<td>Occipital headaches, fatigue</td>
</tr>
<tr>
<td>19</td>
<td>40</td>
<td>F</td>
<td>Palpitations, tachycardia, malaise, fatigue</td>
</tr>
<tr>
<td>20</td>
<td>33</td>
<td>F</td>
<td>Chest pain, palpitations, fatigue</td>
</tr>
<tr>
<td>21</td>
<td>47</td>
<td>M</td>
<td>Left arm paresthesias</td>
</tr>
<tr>
<td>22</td>
<td>34</td>
<td>F</td>
<td>Palpitations, light-headedness, fatigue, chest pain, dyspnea on exertion</td>
</tr>
<tr>
<td>23</td>
<td>43</td>
<td>F</td>
<td>Two transient episodes of left facial and hand paresthesias many years apart; osteoarthritis</td>
</tr>
<tr>
<td>24</td>
<td>48</td>
<td>F</td>
<td>Asymptomatic; arteriovenous malformation in right occipital lobe operated 7 years before study</td>
</tr>
<tr>
<td>25</td>
<td>40</td>
<td>F</td>
<td>Palpitations</td>
</tr>
<tr>
<td>26</td>
<td>50</td>
<td>M</td>
<td>Headache, dizziness</td>
</tr>
<tr>
<td>27</td>
<td>23</td>
<td>F</td>
<td>Chest pain, shortness of breath, palpitations</td>
</tr>
<tr>
<td>28</td>
<td>37</td>
<td>F</td>
<td>Recurrent visual blurring, anxiety, palpitations</td>
</tr>
<tr>
<td>29</td>
<td>23</td>
<td>F</td>
<td>Headaches, nervousness, irritability</td>
</tr>
</tbody>
</table>
assisted tomography of the brain (CT scan) was done in all four patients and was abnormal in three (patients 1, 2 and 3). Aortic arch studies performed in all four of these patients were normal. Cerebral angiography in patient 2 showed nonfilling of the posterior cerebral artery and patient 4 had occlusion of the branches of the calcaine artery on cerebral angiography. Of the remaining five patients, patient 5 presented with transient cerebral ischemic attacks and had three episodes of thrombophlebitis before these complaints. Patient 6 had a history of recurrent deep vein thrombosis documented by venography but had no visual or cerebral ischemic symptoms. Patient 7 presented with acute primary retinal vein occlusion confirmed by fluorescein angiography. Patients 8 and 9, who had typical amaurosis fugax, underwent complete investigations, including CT scan, aortic arch study and cerebral arteriography, but no other cause could be found.

Group II consisted of eight patients, all of whom presented with various forms of transient visual blurring (patients 12, 13, 14 and 17) or homonymous fortification scotomas similar to the migrainous variety (patients 10, 11, 15 and 16). Three patients had a single episode and the others had recurrent visual symptoms. Only patient 14 was taking oral contraceptives at the time of symptoms. Four patients (patients 11, 12, 14 and 15) had a history of migraine and three patients (patients 11, 15 and 16) had a family history of migraine.

Group III consisted of 12 patients with mitral valve prolapse. Their symptoms included chest pain, palpitations, light-headedness, dyspnea, malaise and fatigue. They had no visual or neurologic symptoms and neuro-ophthalmologic examination was normal.

Coagulation Results

The results of determinations of prothrombin times, partial thromboplastin times, factors V and VIII and fibrinogen concentrations for each group of patients with cerebrovascular insufficiency were compared with the control group. No significant differences were observed.

Platelet Aggregation, SHT Release and Platelet Counts (table 2)

The mean threshold concentrations of ADP, epinephrine and collagen resulting in secondary aggregation and release of ≥ 20% [¹⁴C]-5HT for each group of patients with mitral valve prolapse were compared with the results for both control patients and normal subjects. The mean threshold concentration of epinephrine (but not ADP or collagen) required was significantly higher (p < 0.025) in group I than in control patients or normal subjects. No significant differences were observed in group II and group III. Platelet counts were similar in all groups.

Platelet Coagulant Activities

Platelet coagulant activities concerned with the initiation by two alternative pathways (contact product-forming activity and collagen-induced coagulant activity) and early stages (intrinsic factor-Xa-forming activity) of intrinsic coagulation were increased in group I and group II patients compared with control patients and normal subjects (fig. 1). The differences between the means of group I and group II patients and either normal subjects or control patients were highly significant (p < 0.005). In contrast, the means of contact product-forming activity, collagen-induced coagulant activity and intrinsic factor-Xa forming activity for group III patients were not significantly different from those of control patients or normal subjects. The mean percentages of platelet factor 3 activity in response to collagen and kaolin for patients in groups I, II and III were not significantly different from results for normal subjects or control patients.

The frequency of abnormal results for platelet coagulant activities was examined by tabulating the number of patients in groups I, II and III with all normal values and the number of patients with at least one abnormal result compared with similar data for control patients (table 3). The incidence of abnormal results in patients was 76% (100% in group I, 75% in group II, 58% in group III), compared with 6% in control patients (p < 0.005 by chi-square analysis).

Platelet Aggregate Ratios (fig. 2)

The platelet aggregate ratios in group I patients were significantly decreased (p < 0.005) compared with control patients or normal controls, signifying a higher-than-normal proportion of platelets present as aggregates in blood samples drawn from these patients. Values not significantly different from control patients or normal controls were found in groups II and III.

Table 2. Platelet Aggregation, Serotonin Release and Platelet Counts

<table>
<thead>
<tr>
<th>Aggregating agent</th>
<th>Group I</th>
<th>Group II</th>
<th>Group III</th>
<th>Control</th>
<th>Normal value</th>
</tr>
</thead>
<tbody>
<tr>
<td>ADP (μM)</td>
<td>3.1 ± 0.9*</td>
<td>1.1 ± 0.3</td>
<td>3.2 ± 0.8</td>
<td>2.7 ± 0.3</td>
<td>3.0 ± 0.2</td>
</tr>
<tr>
<td>Epinephrine (μM)</td>
<td>4.1 ± 1.6†</td>
<td>1.5 ± 0.6</td>
<td>1.2 ± 0.2</td>
<td>2.2 ± 0.5</td>
<td>2.7 ± 0.3</td>
</tr>
<tr>
<td>Collagen (mg/l)</td>
<td>1.4 ± 0.6</td>
<td>1.3 ± 0.8</td>
<td>0.8 ± 0.2</td>
<td>1.2 ± 0.3</td>
<td>1.2 ± 0.1</td>
</tr>
<tr>
<td>Platelet count (× 10⁶/l)</td>
<td>263 ± 28</td>
<td>224 ± 24</td>
<td>229 ± 20</td>
<td>226 ± 12</td>
<td>150–300</td>
</tr>
</tbody>
</table>

*Mean ± SEM threshold concentration resulting in secondary aggregation and release of ≥ 20 [¹⁴C]5-HT.
†p < 0.025 vs control.
**FIGURE 1.** Platelet coagulant activities in patients with mitral valve prolapse and thromboembolic events (dots), transient visual obscurations (circles) and neither thromboembolic nor visual complications (squares) and in control patients (triangles). The bars and brackets represent the mean ± SEM. The broken lines represent the range of normal values based on the study of 38 normal subjects. Results of all three assays were significantly (p < 0.005) higher for patients with mitral valve prolapse and either thromboembolic events or transient visual obscurations than in control patients.

**Discussion**

The frequent occurrence of the systolic click-murmur syndrome, especially in young, asymptomatic women (6–10%), raises questions about the clinical significance of mitral valve prolapse. Recent reports have emphasized the possible association of neurologic disturbances, including transient cerebral ischemia, stroke, amaurosis fugax, migraine and retinal vascular disease, with mitral prolapse. However caution is required in interpreting these reports because proof of such an association would require a demonstration that cerebrovascular occlusive disease is significantly more common in patients with mitral valve prolapse than in age- and sex-matched control subjects with normal mitral valves. Suggestive evidence of an association comes from the recent demonstration that 40% of 60 young patients with nonarteriosclerotic cerebral ischemic events had documented mitral valve prolapse, compared with a 5.7% incidence in older patients with cerebral ischemia presumed due to arteriosclerotic

**TABLE 3. Frequency of Abnormal Platelet Coagulant Activities**

<table>
<thead>
<tr>
<th>Results of platelet coagulant activities</th>
<th>Group I</th>
<th>Group II</th>
<th>Group III</th>
<th>Total</th>
<th>Control patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal*</td>
<td>0</td>
<td>2</td>
<td>5</td>
<td>7</td>
<td>17</td>
</tr>
<tr>
<td>Abnormal†</td>
<td>9</td>
<td>6</td>
<td>7</td>
<td>22</td>
<td>1</td>
</tr>
<tr>
<td>Total</td>
<td>9</td>
<td>8</td>
<td>12</td>
<td>29</td>
<td>18</td>
</tr>
</tbody>
</table>

The incidence of abnormal results in patients in groups I, II and III combined (76%) was significantly (p < 0.005) higher than that in control patients (6%) when examined by chi-square analysis.

*Figures listed are numbers of patients in each group with normal values for all platelet coagulant activities.

†Figures listed are numbers of patients in each group with at least one result more than 2 standard deviations greater than the mean of normal.
thromboembolism and a 6.8% incidence in sex- and age-matched control subjects. The studies reported here do not address the question of a possible association between mitral valve prolapse and thromboembolic disease. Our purpose was to determine whether the purported association can be explained on the basis of platelet activation possibly by exposure to an abnormal valve or to hemodynamic irregularities. The data presented here indicated the presence of platelet coagulant hyperactivity, circulating platelet aggregates and platelets relatively insensitive to epinephrine in the group of patients with thromboembolism (group I) and platelet coagulant hyperactivity in patients with transient visual obscurations (group II). Further, the frequency of abnormal results of assays for platelet coagulant activities was significantly higher in all patients with mitral valve prolapse than in control patients with nonthrombotic eye diseases. All patients with definite thromboembolic complications (group I) had platelet coagulant hyperactivity, compared with 75% of those with transient visual obscurations (group II) and 58% of those without thromboembolic or visual manifestations (group III). The demonstration of these abnormalities is consistent with the view that exposure of flowing blood to the abnormal hemodynamics or valve surfaces in mitral prolapse gives rise to in vivo platelet stimulation resulting in intravascular thromboembolism.

Dougherty and co-workers showed that the percentage of circulating platelet aggregates was increased and platelet sensitivity to aggregating agents was enhanced within 10 days of ictus in acute cerebral ischemia. These abnormalities returned to normal 10 days to 6 weeks after the acute event. In the present study measurements were made 10 days to 8 weeks after the initial manifestation in patients with permanent neurologic defects and were confirmed subsequently on two to eight occasions in all patients. Therefore, the results reported were obtained during an asymptomatic interval temporarily remote from an acute episode and are unlikely to reflect secondary effects of ischemia or extensive intravascular thrombosis.

A previous study from our laboratory demonstrated that platelet coagulant activities concerned with the initiation and early stages of intrinsic coagulation were increased two- to threefold in young patients with transient cerebral ischemic attacks not associated with recognized risk factors such as diabetes mellitus, hypertension, generalized atherosclerosis and hyperlipoproteinemia. In contrast, normal results for platelet coagulant activities were found in patients with transient cerebral ischemia associated with these risk factors. There is a considerable body of clinical, experimental and pathologic evidence to support the theory that cerebral ischemic events often arise from emboli composed either of platelet-fibrin thrombi or atheromatous material. These and other studies suggest that platelets may have a role in pathogenesis in some patients with cerebrovascular occlusive disease. Additional evidence from our laboratory indicates that abnormal platelet coagulant activity is present in patients with acute primary retinal vein occlusion and in retinal artery occlusion in relatively young patients without traditional risk factors for these disorders. These observations raise important questions. The first of these is whether platelet coagulant hyperactivity plays a part in pathogenesis of the thromboembolic diseases in question or whether the platelet activation arises as a result of intravascular thrombosis. There is no definitive answer to this question, but the absence of platelet abnormalities in patients with disease secondary to other known risk factors is consistent with a pathogenetic role for platelets. Experimental evidence supports the hypothesis that platelets can participate in the contact-phase reactions that trigger intrinsic coagulation, and the evidence summarized above suggests that platelets may also promote these reactions in vivo, with resultant platelet-fibrin thrombi and emboli.

A second important question is whether the platelet coagulant hyperactivity observed in group I patients with thromboembolic diseases bears any relationship to mitral valve prolapse. There is no definitive answer to this question; however, none of the patients reported here had any of the risk factors traditionally associated with cerebral or other thromboembolic disease. Further, less extensive platelet abnormalities were observed even in patients without thromboembolic complications, suggesting an association between mitral valve prolapse and hyperactive platelets. If such an association does in fact exist, by what mechanism does platelet coagulant hyperactivity arise? The results presented here are consistent with the view that platelet abnormalities arise from exposure of flowing blood to an abnormal mitral valve and contribute to thromboembolic complications and possibly even transient visual obscurations. A similar mechanism has been suggested in patients with chronic rheumatic valvular disease, in whom a 33% incidence of transient visual obscurations has been reported.

A study reported by Steele et al. after the present study was completed demonstrated decreased platelet survival in five patients with mitral valve prolapse and stroke and in seven of 17 patients with mitral valve prolapse without stroke. Platelet survival was also shortened in 98% of patients with rheumatic heart disease and associated thromboembolic complications and in 78% of patients with rheumatic heart disease and no history of thromboembolism. Increased platelet turnover has also been demonstrated in patients with arterial and venous thromboembolism, and it has been suggested that younger, more metabolically and functionally active platelets can thereby appear in the circulation. Finally, if an association between mitral valve prolapse and thromboembolic complications can be established and platelet abnormalities confirmed, platelet-inhibiting drugs should be evaluated in this group of patients.
Acknowledgment

We thank Cheryl Beckett, Sarah Casper and Beverly White for excellent technical assistance and Anne Arker and Constance Moody for invaluable assistance in data retrieval and for typing the manuscript.

References

52. Davidge NJ, Kintworth GK, Friedberg SJ, Dillon M: Fatal atheromatous cerebral embolism associated with bright plaques
Diastolic Sounds and Murmurs
Associated with Mitral Valve Prolapse

JEANNE Y. WEI, M.D., PH.D., AND NICHOLAS J. FORTUIN, M.D.

SUMMARY Although mitral valve prolapse is often associated with a systolic click or murmur, it is not widely appreciated that a sound or murmur may also occur in diastole. Nine patients with a systolic click or murmur and echocardiographic evidence of mitral prolapse had, in addition, a diastolic sound or an early diastolic murmur best heard at the apex or left sternal border. The sound, which was of high frequency and easily audible, followed Av by 70–110 msec (mean 94 ± 5 msec), and coincided with the point where the prolapsed posterior leaflet returned from the left atrium and recoapted with the anterior mitral leaflet. The diastolic sound occurred 40–60 msec (mean 53 ± 4 msec) before the E point of the echocardiogram and O point of the apicalcardiogram, and even longer before the rapid-filling wave. The diastolic murmur, also of high frequency, was brief and decrescendo, and simulated aortic regurgitation in two patients. Thus, mitral prolapse may be associated with a sound or murmur in diastole. When a diastolic sound or murmur is best heard apically, even if accompanied by a systolic murmur, mitral valve prolapse should be considered.

MITRAL VALVE PROLAPSE, a common and generally benign condition in which serious problems occur occasionally,1–11 is often diagnosed on the basis of characteristic auscultatory findings. The auscultatory features associated with this syndrome include a mid-systolic click that may be followed by a late systolic murmur, a late systolic or holosystolic murmur without a click, or the absence of both click and murmur.8–11 However, a diastolic sound or murmur may also be a part of the auscultatory features of mitral valve prolapse.12 We studied nine patients with mitral valve prolapse who also had a prominent diastolic sound or murmur that appeared to be related to motion of the prolapsing leaflet. These results show that mitral valve prolapse may be associated with sounds and murmurs in diastole as well as systole. The presence of diastolic findings, therefore, should not exclude the possibility of mitral prolapse. The diastolic sound bore a consistent relationship to the time of valvar recoaptation in all nine patients.

Methods This study included all patients evaluated at the Johns Hopkins Hospital over the past 3 years who had a click or murmur in systole, echocardiographic evidence of mitral valve prolapse, and an early diastolic sound or murmur. Of approximately 150 patients with auscultatory and echocardiographic evidence of mitral prolapse, nine patients met all three criteria. In each patient we obtained a phonocardiogram, an apexcardiogram, carotid pulse tracing and the simultaneous recording of these techniques combined with echocardiography. These tracings were analyzed in detail and correlated with the physical findings.

The echocardiographic examination was performed with the patient in the supine position, rotated slightly leftward, using a Smith-Ekoline 20A Ultrasonoscope with a 2.25-MHz, 1.25-cm-diameter transducer. The echocardiograms, phonocardiograms and pulse
Platelets, thromboembolism and mitral valve prolapse.
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