Brain Events Associated with Mitral Valve Prolapse

Maurice R. Hanson, M.D., John P. Conomy, M.D., and James R. Hodgman, M.D.

SUMMARY The clinical and laboratory features of 24 patients with proven mitral valve prolapse (MVP) and brain dysfunction are reported. The age range of affected patients was between 20 and 63 years (average of 43) and 70 percent were women. MVP was documented prior to the brain illness in only 4 patients. The majority of patients experienced bland cerebral infarction. Disorders also included transient ischemic attacks, cerebellar infarctions, parenchymatous and subarachnoid hemorrhage, seizures and retinal artery occlusion. Significant risk factors for stroke other than MVP were lacking in the patient group. Cerebral angiograms occasionally showed distal occlusions of small arteries suggesting embolic brain lesions. Our study suggests that MVP is a risk factor for stroke. We recommend echocardiography in patients with cerebral ischemia who lack clear, recognized risk factors for stroke. We believe the basis for this brain disorder to be emboli from damaged mitral valve leaflets.

In the 16 years since Barlow, Pocock, Marchand et al. demonstrated the valvular origin of mid-systolic clicks and late systolic murmurs occurring in patients with these unusual auscultatory findings, an abundant literature has emerged which has established the clinical correlates, cardiac pathophysiology and pathophysiology of the entity which has come to be known as mitral valve prolapse (MVP). The cardiac auscultatory features, consisting of clicks and murmurs, have been emphasized and their origin within the structure of abnormal mitral valves and chordae tendineae established. The application of newer diagnostic techniques including echocardiography, Holter monitoring, and angiography have added to the understanding of this disorder. MVP is a common condition estimated to involve approximately 6 percent of an unselected population. Within this subgroup, those factors selecting a small percentage of patients with MVP for serious health complications, including stroke, is not clearly known.

The cardiac pathologic features of MVP have been recognized to consist of thin and attenuated chordae tendineae and myxomatous degeneration of the mitral valves resulting in ballooning and furling of the valve structures. Pomerance has demonstrated that the surfaces of these valves are the source of thrombi and potentially embolic material. The precise pathophysiology of MVP as related to cardiac dysfunction is a matter of considerable dispute but there is no doubt that elongation and attenuation of the chordae tendineae and aneurysmal dilatation and redundancy of the mitral valve leaflets play a dominant role in the origin of the characteristic auscultatory findings and in the health consequences of individuals with idiopathic mucoid degeneration of the mitral valve. When initially described, the mid-systolic click seemed to represent no more than an auscultatory curiosity. In recent years important, albeit relatively uncommon, sequelae have emerged as important complications of MVP. Ten to 15 percent of individuals with MVP incur such complications as serious atrial and ventricular cardiac arrhythmias, infective endocarditis, progressive mitral valvular regurgitation, and rupture of the chordae tendineae. Sudden death, presumably of arrhythmic origin, has been shown to be a particular risk even in those individuals with "asymptomatic" MVP.

In 1976 Barnett and his colleagues described an unrecognized consequence of MVP, namely, neurologic complications in the form of cerebral ischemic episodes. Since that initial report a variety of cerebral and ophthalmic disturbances occurring in patients with MVP have been reported from centers in France, Canada, England, South Africa, and the United States. This report summarizes our experience over the past 3 years with brain disorders occurring in 24 patients with MVP.

Subjects and Methods

During the past 3 years, patients admitted to the neurologic service in our hospital with diagnoses of stroke or transient ischemic attack (TIA), in whom clear ischemic risk factors or anatomic lesions were not evident, were scrutinized for the auscultatory findings of MVP and studied by echocardiography. In addition, we reviewed the complete medical records of 225 patients obtained from the Echocardiography Section, Department of Cardiology, examined between 1976 and 1978. Certain comparative data between patients forming the neurologic series and the cardiology series could then be established. We excluded patients from the neurologic series who demonstrated significant clinical, laboratory, or radiologic evidence of recognized precursors of cerebrovascular disease such as cervico-cranial bruits, significant hypertension, rheumatic heart disease, arteriosclerotic heart disease, diabetes mellitus, vasculitis, or radiographic findings of extracranial or intracranial atherosclerotic arterial disease. Twenty-four patients were found to have a substantiated brain event, mitral valve prolapse, and no clear risk factor for cerebrovascular disease or other brain illness. These patients form the basis of the present report. All of these patients were examined by one or more of the authors at the time of their neurologic illness or subsequent to it.
Demographic Features

Our series was comprised of 18 women and 6 men, a ratio of 3 to 1. Of 225 patients diagnosed as having mitral valve prolapse by retrospective review of Cardiology records, 141 were women and 84 men, a ratio of 3 to 2. While women predominated in the series with brain events, the series itself is too small to draw firm conclusions. The average age in the entire group at the onset of neurologic illness was 42.6 years for women and 45.0 years for men, with a range from 20 to 63 years for the group as a whole. This age distribution is very similar to the 225 patients in the cardiology series who had an average age of 42.5 for females and 44.4 years for men at the time a prolapsed mitral valve was diagnosed.

### Table 1  Brain Events

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age/sex</th>
<th>Location and type</th>
<th>Risk factors for stroke other than MVP</th>
<th>Laboratory investigation</th>
<th>Course and treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. J.B.</td>
<td>55/F</td>
<td>Bilateral hemorrhagic cerebral infarction</td>
<td>Migraine</td>
<td>HI N N N N</td>
<td>APT/stable</td>
</tr>
<tr>
<td>2. M.A.</td>
<td>42/F</td>
<td>Brainstem infarct</td>
<td>None</td>
<td>N N N N</td>
<td>APT/stable</td>
</tr>
<tr>
<td>3. F.R.</td>
<td>60/M</td>
<td>Bilateral carotid TIA</td>
<td>Mild hypertension</td>
<td>N N N</td>
<td>Chol 318 Antiocoag/stable</td>
</tr>
<tr>
<td>4. M.K.</td>
<td>38/M</td>
<td>Brainstem infarct</td>
<td>None</td>
<td>N N N ND</td>
<td>APT/stable</td>
</tr>
<tr>
<td>5. G.E.</td>
<td>52/F</td>
<td>R. cerebral infarct</td>
<td>None</td>
<td>BI N ND RFS</td>
<td>APT/stable</td>
</tr>
<tr>
<td>6. M.H.</td>
<td>45/F</td>
<td>Seizures</td>
<td>None</td>
<td>ND ND ND N</td>
<td>None/stable</td>
</tr>
<tr>
<td>7. J.M.</td>
<td>51/M</td>
<td>R. cerebral infarct</td>
<td>None</td>
<td>BI ND N N</td>
<td>None/stable</td>
</tr>
<tr>
<td>8. M.J.</td>
<td>44/F</td>
<td>Seizures</td>
<td>None</td>
<td>BI ND N N</td>
<td>None/stable</td>
</tr>
<tr>
<td>9. B.G.</td>
<td>24/M</td>
<td>L. cerebral infarct</td>
<td>Migraine</td>
<td>N ND N</td>
<td>APT/stable</td>
</tr>
<tr>
<td>10. K.D.</td>
<td>59/F</td>
<td>Brainstem TIA</td>
<td>Hyperlipidemia</td>
<td>N ND N</td>
<td>Chol 300 APT/stable</td>
</tr>
<tr>
<td>11. J.B.</td>
<td>34/M</td>
<td>R. cerebral infarct</td>
<td>Migraine</td>
<td>BI ND Embolic Br. occlusion</td>
<td>APT/stable</td>
</tr>
<tr>
<td>12. M.S.</td>
<td>56/F</td>
<td>L. carotid TIA</td>
<td>Mild hypertension</td>
<td>N ND N</td>
<td>APT/stable</td>
</tr>
<tr>
<td>13. H.B.</td>
<td>54/F</td>
<td>Hemorrhagic brainstem infarct</td>
<td>None</td>
<td>N Hem. N</td>
<td>Chol 320 Antiocoag/recurrent</td>
</tr>
<tr>
<td>14. S.A.</td>
<td>25/F</td>
<td>L. cerebral infarct</td>
<td>None</td>
<td>N N Embolic Br. occlusion</td>
<td>None/stable</td>
</tr>
<tr>
<td>15. D.K.</td>
<td>55/F</td>
<td>Hemorrhagic brainstem infarct</td>
<td>None</td>
<td>N Hem. N</td>
<td>None/stable</td>
</tr>
<tr>
<td>16. R.S.</td>
<td>44/F</td>
<td>L. carotid TIA</td>
<td>None</td>
<td>N N N LTS</td>
<td>Antiocoag/stable</td>
</tr>
<tr>
<td>17. J.L.</td>
<td>44/F</td>
<td>Brainstem infarct</td>
<td>Hyperlipidemia</td>
<td>N N</td>
<td>Chol 326 None/stable</td>
</tr>
<tr>
<td>18. J.T.</td>
<td>48/F</td>
<td>L. cerebral infarct</td>
<td>None</td>
<td>BI N N</td>
<td>APT/stable</td>
</tr>
<tr>
<td>19. M.L.</td>
<td>44/F</td>
<td>R. cerebral and brainstem infarcts</td>
<td>Hyperlipidemia</td>
<td>BI ND ND</td>
<td>Antiocoag/stable</td>
</tr>
<tr>
<td>20. B.H.</td>
<td>29/M</td>
<td>Retinal artery branch occlusion</td>
<td>None</td>
<td>ND ND ND N</td>
<td>APT/stable</td>
</tr>
<tr>
<td>21. E.M.</td>
<td>56/F</td>
<td>L. cerebral infarct</td>
<td>None</td>
<td>N ND ND N</td>
<td>APT/stable</td>
</tr>
<tr>
<td>22. M.B.</td>
<td>46/F</td>
<td>Brainstem infarct</td>
<td>None</td>
<td>N N ND</td>
<td>None/stable</td>
</tr>
<tr>
<td>23. T.P.</td>
<td>63/M</td>
<td>R. carotid TIA</td>
<td>None</td>
<td>ND N Embolic Br. occlusion</td>
<td>APT/stable</td>
</tr>
<tr>
<td>24. A.T.</td>
<td>20/F</td>
<td>L. carotid TIA</td>
<td>None</td>
<td>N N ND LTS</td>
<td>None/stable</td>
</tr>
</tbody>
</table>

N = Normal/negative; HI = Hemorrhagic infarct; BI = Bland infarct; ND = Not done; RFS = Right frontal slowing; LTS = Left temporal slowing; APT = Antiplatelet therapy; Misc. = GTT, lipids, clotting studies, vasculitis screen, serology blood cultures.
Miscellaneous events were present in 3 patients. Two sustained repeated generalized seizures unassociated with cardiac dysrhythmias. These patients, both women in their mid-40's, have required long-term anticonvulsant treatment. One additional patient suffered a retinal arterial branch occlusion which resulted in a permanent monocular visual field sector defect.

Fourteen of the 24 patients with ischemic brain lesions had no antecedent risk factors for stroke or transient ischemic episodes other than MVP. None of the 14 had cervico-cranial bruits, hypertension, diabetes, hyperlipidemia, lues, angina, myocardial infarction, cardiomegaly, or rheumatic heart disease. Two patients had mild, recently discovered, and easily controlled vascular hypertension. Neither had greatly elevated blood pressure at the time of their neurologic illness. Five patients had evidence of hyperlipidemia and 4 of these had cerebral angiography. None of the patients with hyperlipidemia had evidence of significant atherosclerotic cerebrovascular disease in either the intracranial or extracranial circulation. Two patients had a history of common migraine and one had classic migraine with a formed visual prodroma. In these 3 patients headache attacks were infrequent and none experienced migraine attacks at or about the time of the onset of their neurologic disorder. No female patient in the series was taking oral contraceptives at the time of the onset of their symptomatic brain event.

Neurodiagnostic Studies (Table 1)

Twenty-one of our 24 patients had computed tomographic (CT) brain scans. In 14 of 21 the scan was normal. Seven patients had abnormal CT brain scans, and of these 5 had a single hypodense lesion consistent with an ischemic, bland infarction. In 1 patient with multiple infarcts the CT pictures suggested infarctions of both the bland and hemorrhagic type.

The cerebrospinal fluid (CSF) was analyzed at the time of neurologic insult in 13 of 24 patients. In 11 instances the CSF was normal. In the remaining 2 patients, both with acute brain stem and cerebellar infarction, the cerebrospinal fluid findings were consistent with central nervous system hemorrhage.

Seventeen patients of the group of 24 had cerebral angiography. In 13 the angiograms, usually obtained several days after the onset of neurologic illness, were unremarkable. Four angiographic studies were abnormal. One patient who had a right cerebral infarction had evidence of a branch occlusion of the right posterior cerebral artery. A 25-year-old woman with a left cerebral infarct had a left middle cerebral artery branch occlusion. Our oldest patient, a 63-year-old man with right-sided carotid transient ischemic attacks, had occlusion of several of the smaller branches of the right middle cerebral artery without significant lesions at the carotid bifurcation or other sites along the extracranial arteries supplying the right cerebral hemisphere. The angiograms in this patient disclosed an abrupt, sharp cut off of Sylvian arteries with partial, late collateral filling in the ischemic area. We interpret these findings as being entirely consistent with emboli lodged in small surface brain arteries. One would expect, in a large number of patients, that emboli to small arteries might become fragmented or dispersed within several days after the production of distal occlusions and resulting cerebral infarction. Those patients in whom branch occlusions were identified, either in the retinal artery or in the intracranial circulation, had angiographic pictures entirely typical of embolic rather than in situ thrombotic arterial disease. In no patient could extracranial carotid or vertebral occlusive disease be held accountable for production of the nervous system disorder.

Ten of the 24 patients had an electroencephalogram at the time of their neurologic event. In 7 the electroencephalogram was normal and the remaining 3 showed focal slowing or transient cerebral dysrhythmia on the side appropriate to their neurologic defect. In both patients with seizures the interictal electroencephalogram was normal.

Clinical laboratory investigations in all patients included blood serology, glucose tolerance test, lipid profile, LE cell preparations, antinuclear factor titers, multiple blood cultures, and platelet function studies. In 19 patients all of these studies were normal. Laboratory abnormalities were found only in 5 patients, all of whom had evidence of hypercholesterolemia with blood cholesterol levels ranging from 300 to 350 mg% as the sole clinical laboratory abnormality.

Neurologic disability was substantial among patients in this series. Two, both with multiple brain infarctions, are greatly disabled. Eight others have moderate disability and could not independently return to their former life roles. The others have minimal or mild disabilities in the form of mild hemiparesis, visual defects, ataxia and the like, but are fully independent. No patient in the series has died.

Cardiac Findings (Table 2)

In 20 of these 24 patients, the diagnosis of MVP was made at the time of onset of the neurologic disorder or up to 3 years subsequent to it. In only 4 patients was MVP known prior to neurologic illness. Half of the group (12 patients) had symptoms referable to the heart. Nonanginal, sharp retrosternal chest pain and palpitations were the most common complaints. Three patients had experienced one or more episodes of syncope. The remaining half of the patient group was free of any cardiac symptoms.

Thirteen patients had auscultatory findings ordinarily associated with MVP. Three of these had only a non-ejection middysstolic click. Eight patients were found to have a non-ejection click and mid-to-late systolic murmur. Two patients had only a mid-to-late systolic murmur without a middysstolic click. Eleven patients had normal cardiac physical examinations on one or more occasions. The resting electrocardiogram
was available in all patients. In 22 instances it was normal. One patient had a left anterior hemiblock and another had frequent unifocal premature ventricular contractions. Holter electrocardiography was performed in only 8 of our patients. It was normal in 3, and in 4, episodes of paroxysmal atrial arrhythmias and/or frequent ventricular premature beats were noted. One patient experienced episodes of paroxysmal atrial flutter and ventricular tachycardia.

Cardiac catheterization was performed in 6 of 24 patients and was abnormal in all of them. Three of these studies disclosed prolapse without mitral regurgitation and in 3, prolapse of the mitral leaflets was associated with mitral regurgitation. All 24 of our patients had echocardiography, and in only one was it normal. In this patient the prolapse was documented by left heart catheterization. In 23 of 24 of our patients, the echocardiogram was diagnostic of MVP. In 5, echocardiographic studies disclosed pansystolic prolapse of both leaflets of the mitral valve. The remainder of the echocardiograms showed mid-to-late systolic prolapse, late systolic prolapse, prolapse of the posterior leaflet only or were simply designated as "diagnostic of mitral valve prolapse".

Discussion

Beginning in the late 19th century, physicians began to describe patients with peculiar systolic auscultatory cardiac findings which were not easily classified and were generally thought to be of extra cardiac origin. Sir William Osler\(^{16}\) described a systolic whoop or honk. Subsequently, Gallavardin\(^{17}\) described a mid-systolic click which he thought to be of pericardial origin. During systole the heart was thought to pull against pericardial adhesions, producing a clicking sound. In 1961, Reid\(^{18}\) suggested that these systolic noises may have their origin within abnormal mitral valves. Barlow and his colleagues in 1963\(^{19}\) proved by phonocardiography and angiocardiology that these clicks and murmurs were associated with disordered movement of an abnormal mitral valve. Since that time a number of synonyms have been applied to this common phenomenon including Barlow's or Reid-Barlow's syndrome, billowing mitral valve leaflet syndrome, floppy mitral valve syndrome, midsystolic click-late systolic murmur syndrome,\(^{20}\) and more recently mitral valve prolapse.\(^{21}\) Mitral valve prolapse exists when one or both leaflets abnormally protrude...
and balloon into the left atrium during systole. Since Barlow's description, a large body of literature has emerged which bears on the pathology and pathogenesis of the disorder, its clinical and laboratory features, incidence, complications and prognosis.

Only in recent years has the true frequency been appreciated. One study by Markiewicz et al. found phonocardiographic evidence of MVP in 18 percent of 100 presumably healthy young women. Another, larger prospective series of 1169 women by Procacci et al. found 6 percent to have auscultatory findings attributed to MVP. This is more consonant with Brown's findings of 6 percent in 520 women. It is generally accepted that 6 to 10 percent of "normal" women and 0.5 percent of men have MVP. In very large clinical series women predominate over men by a 3 to 2 ratio in the younger ages but this sex difference becomes less evident in older age groups. The common occurrence of MVP is also borne out by postmortem studies where approximately 1 to 5 percent of routine autopsies will show myxomatous (mucoid) degeneration of the mitral valve ("floppy" mitral valve).

In the past 15 years the clinical features of patients with MVP have been well defined. Between 50 and 75 percent of such patients will have symptoms referable to the cardiovascular system. Palpitations are common. More serious cardiac symptoms include prolonged, atypical, boring, nonanginal chest pain unrelated to exercise which waxes and wanes and is associated at times with dyspnea and chronic fatigue, but without overt congestive heart failure. Syncope occurs in approximately 4 percent of individuals with MVP. Certain auscultatory findings, while not always present, are highly characteristic of MVP. These findings include nonejection systolic clicks occurring alone or in association with mid-to-late systolic murmurs which begin shortly after the click. These can best be heard while listening with the patient in several positions and after provocative maneuvers such as amyl nitrite inhalation and the Valsalva maneuver. In spite of this, some 15 percent of patients have "silent" MVP, i.e., normal auscultatory findings with definite echocardiographic and/or angiographic confirmation of MVP. In our series, nearly one-half of the patients had "silent" MVP but not all had cardiac examinations on more than one occasion utilizing the aforementioned provocative measures; the findings were not routinely confirmed by phonocardiography.

A characteristic body habitus has been observed in patients with MVP suggesting "forme fruste" of Marfan's syndrome. None of our patients, however, had evidence of Marfan's syndrome or any similar genetic disturbance of connective tissue.

Ancillary cardiac studies have been of considerable interest. The resting electrocardiogram is often normal. However, about 15 to 30 percent of patients will demonstrate ST segment and T-wave changes which are similar to the pattern and distribution of posterior-inferior wall ischemia in the absence of coronary artery disease. Another finding has been multifocal premature ventricular contractions which are increased after exercise.

Continuous Holter electrocardiographic monitoring has shown a substantial incidence of both atrial and ventricular arrhythmias in MVP and are probably the most common manifestation of this syndrome. Winkle et al. recorded an incidence of 50 percent of patients with ventricular arrhythmias and 60 percent with atrial arrhythmias. What has been most striking is the lack of correlation of clinical symptoms with the presence or absence of these arrhythmias, a finding confirmed repeatedly by many cardiologists.

The echocardiogram is currently believed to be the most sensitive noninvasive technique for the diagnosis of MVP. In Procacci's study of 1169 women, the echocardiogram was diagnostic in 81 percent of women with the auscultatory findings of MVP. DeMaria et al. found echocardiogram evidence of MVP in 26 out of 27 patients with documented prolapse by left ventricular cine angiography. The echocardiography pattern was consistent with either mid-systolic or pansystolic prolapse. Only 15 of 24 patients in this study had the auscultatory findings on phonocardiography generally associated with MVP.

As judged by the high incidence of MVP in the general population and the paucity of reported serious complications, it is not surprising that MVP has been felt to be a "benign" condition. Reliable, long term prospective studies documenting the natural history of MVP are lacking. Nevertheless, at least 4 recognized complications are accepted by most authorities and include: 1) sudden death, 2) bacterial endocarditis, 3) progressive mitral regurgitation, and 4) rupture of the chordae tendineae. Sudden death must be, fortunately, rare. As of 1979 only 25 deaths have been reported in patients with documented MVP. In Mills's retrospective analysis of 53 patients followed for a mean of 13.7 years, only 2 instances of sudden death related to mitral valve disease were noted. Bacterial endocarditis is well documented in MVP, occurring in about 3 percent of patients.

Approximately 9 percent of the patients in Mills's series developed progressive mitral regurgitation and left ventricular failure. Spontaneous rupture of the chordae tendineae is a well recognized, but uncommon, event and is due to the progressive thinning of the chordae tendineae secondary to weakening by abnormal tension on these structures. Some patients will be found to have unsuspected rupture of the chordae tendineae at the time of mitral valve replacement.

Neurologic complications of MVP have been neither widely appreciated nor readily accepted. Faintness and syncope are recognized as part of the clinical profile and are easily attributed to generalized cerebral ischemia either from cardiac dysrhythmia or hyperventilation. Focal cerebral ischemic events are believed to occur largely on the background of embolization in the course of infective endocarditis, a well recognized neurologic complication of bacterial endocarditis. Focal cerebral ischemic events as a consequence of noninfected emboli have not been emphasized.
Perhaps the first mention of this phenomenon was Barlow's description of a 23-year-old woman with transient episodes of left arm weakness. Little significance was attached to this.

Barnett and his colleagues drew attention to the possibility of cerebral ischemia secondary to non-infected cerebral emboli. They identified 12 patients, 7 men and 5 women, whose only identifiable risk factor was MVP. All of their patients had cardiac cine angiography establishing the diagnosis. Of interest is the fact that 4 of 12 patients had normal echocardiographic studies. Ten patients had one or more episodes of cerebral hemispheric ischemic events and 2 had infarction in the vertebrobasilar territory. None of their patients had seizures. Four of their patients had angiograms showing evidence of branch arterial occlusion without evidence of atheromatous disease in the major cervical vessels. On the basis of their clinical and laboratory assessment they concluded that these cerebral ischemic events were most likely due to emboli from adherent fibrin and red cells on the roughened, myxomatous, degenerated mitral valve. They cited the pathological studies of Pomerance to support this contention.

The results of our study would be in agreement with Barnett's assessment. Our patient population differed somewhat from Barnett's due to methods of patient selection. Our patients were somewhat older but the sex distribution accurately reflects the overall incidence of MVP in an unselected population. In our series, the diagnosis was established by echocardiography in all patients. This would tend to underestimate its true frequency since the echocardiogram may be normal in 10-20 percent of patients with proven MVP. The distribution of brain ischemic events was similar in the 2 series. Most had either infarction or transient ischemic attacks in the carotid distribution while a smaller proportion had posterior circulation disturbances. Cerebral angiography was not performed in all of our patients, but the results of those done were similar to Barnett's. Most were normal but 3 showed evidence of branch arterial occlusion and none had evidence of atheromatous disease in the cerebral vasculature.

Other observations are consonant with Barnett's hypothesis. Each year in our hospital, several patients have a mitral valve replacement for progressive mitral regurgitation and/or rupture of the chordae tendineae in which the pathologic diagnosis of the specimen is usually designated "fibrous valvulitis." Careful review of these patients invariably shows they have myxomatous degeneration of the mitral valve and thin, attenuated and frayed chordae tendineae. In several instances we have observed collections of fibrin-platelet thrombi and red cells loosely adherent to the valve surface similar to those described by Pomerance (figs. 1 and 2). While none of our patients has come to postmortem, we believe these observations provide indirect evidence of the capability of embolization from the damaged valves. The present medical literature is bereft of autopsied patients with brain disorders associated with a prolapsed mitral valve. Correlative

Figure 1. Gross specimen of myxomatous degeneration of mitral valve showing areas of hemorrhage and thrombi.

Figure 2. Low power view of myxomatous mitral leaflet showing partially adherent thrombi.
It is clear that MVP is a common condition and that within the MVP cohort, stroke and other brain disorders are uncommon events. Why this is so may be reflected in a study of platelet survival time in MVP patients recently published by Steele et al. These investigators showed that patients with MVP and thromboembolic disease have shortened platelet survival times when compared to patients with MVP and no thromboembolic disorders. It may be that within the population of patients with MVP, stroke and similar disorders occur in that subset of patients who are inordinate platelet consumers. While MVP may be an uncommon cause of stroke, its role in stroke in the younger patient has been clearly supported by recent epidemiologic studies furnished by Barnett’s group.

**References**


**Figure 3.** High power view of myxomatous mitral leaflet showing thrombus material.
Butanediol Induced Ketosis Increases Tolerance to Hypoxia in the Mouse

Jeffrey R. Kirsch, B.S., Louis G. D'Alecy, D.M.D., Ph.D., and Peter B. Mongroo, B.S.

SUMMARY In previous studies from our laboratory a positive correlation between elevated blood ketone levels and the survival time (ST) during hypoxia (4-5% oxygen) was observed in fasted and alloxan diabetic mice. To test the hypothesis that ketosis was somehow increasing the tolerance of mice to hypoxia, we induced ketosis by either oral (PO), intraperitoneal (IP), or intravenous (IV) 1,3-butanediol (BD). Blood beta-hydroxybutyrate increased from 0.33 ± 0.06 mM to 3.32 ± 0.08 mM for PO, 1.2 ± 0.2 mM for IV and 0.83 ± 0.15 mM for IP. BD was associated with an increase in ST to 458% (n = 19) when given PO, 217% (n = 12) by IP route, and 560% (n = 13) by the IV route. The effect of ambient temperature (T_a) on this phenomenon was evaluated at 12, 22, 32, and 34°C. At each T_a, IV BD at 1.4 mmole/mouse was associated with an increase in ST to 525, 559, 151, and 145% of control, respectively. The absolute ST of both control and treated mice was greater at T_a of 12 and 22°C than at 32 and 34°C. Rectal temperature was continuously recorded and no differences were detected between control and treated groups just prior to hypoxia except for the group treated at T_a of 12°C. Hypoxia, however, was associated with a decrease in body temperature in each group. It is concluded that the artificial induction of ketosis by BD is associated with an increase in ST of mice exposed to hypoxia.

Increased blood ketone levels and hypoxic tolerance. In other studies, in which elevated blood ketones could be predicted, an increased tolerance to hypoxia or ischemia has been noted. On the basis of this correlation, it was desirable to determine if an intentional elevation in blood ketone levels could produce an increased tolerance of the brain for hypoxia. A wide variety of procedures can elevate blood ketone levels (i.e., fasting, ketogenic diet, uncontrolled diabetes). For this study we have chosen the non-toxic alcohol 1,3-butanediol (BD). BD is converted in the body to beta-hydroxybutyrate (BHB) by alcohol dehydrogenase and aldehyde dehydrogenase. Although present in the brain, alcohol and
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