The Pathophysiology of Idiopathic Mitral Valve Prolapse

By Donald O. Nutter, M.D., Charles Wickliffe, M.D., Charles A. Gilbert, M.D., Carroll Moody, M.D., and Spencer B. King, III, M.D.

SUMMARY

Left ventricular structure, function, and the coronary circulation were studied in a subset of patients with mitral valve leaflet prolapse. This group of 26 patients (21 females, five males, with mean age of 46 years), had the syndrome identified as idiopathic mitral valve prolapse (IMVP), which was characterized by a systolic click-murmur, clinical symptoms that were highly variable in duration and intensity, angiographically-documented mitral prolapse, and no obvious associated systemic or cardiovascular disease. Mitral regurgitation was of moderate degree in four, mild in 14, and absent in eight. The left ventricular (LV) end-diastolic volume index was elevated in ten of 25 (40%), the LV mass index was elevated in six of 17 (35%), but the LV anterior wall thickness was increased in only one of 17. Three major patterns of ventricular contraction were identified: 1) normal in seven; 2) abnormal, usually an inferior deformity and/or anterior asynergy in eight; and 3) hyperkinetic in 11. Normal resting left ventricular function, assessed as an ejection fraction greater than 55%, was present in 17 of 25 (68%). Selective coronary arteriography was essentially normal in all 25 patients studied. An ischemic ECG response was detected during only one of 12 maximal treadmill exercise tests and in none of ten atrial pacing stress tests (AP). Myocardial lactate extraction did not change significantly during AP in six patients. We conclude that cardiomyopathy does not appear to be a primary cause or an important associated component of the IMVP syndrome. Abnormalities of the coronary circulation or of myocardial metabolism were not demonstrated by available methods. A proposed pathophysiological mechanism to explain the clinical and angiographic findings in IMVP is discussed.

SYSTOLIC PROLAPSE of the mitral valve leaflets is a common clinical syndrome of diverse etiology. A distinct subset of these patients is now recognized in whom no apparent cause exists for mitral prolapse and no associated cardiovascular disease can be identified. This subset can be appropriately termed idiopathic mitral valve prolapse when problems known to be responsible for mitral valve prolapse such as Marfan's syndrome, rheumatic valvular disease, and coronary atherosclerotic heart disease are excluded. Clinically these patients may demonstrate mid to late systolic clicks and murmurs, frequent and often atypical chest pain, various arrhythmias, and in many, a characteristic ECG abnormality (superiorly directed T vector). Some patients have shown a strong familial pattern with an autosomal dominant mode of inheritance.1,4

Two important questions concerning the pathophysiology of IMVP are at present unanswered. First, it is not clear whether these patients have a form of cardiomyopathy as an important component of the syndrome. Apparent left ventricular dysfunction and regional contractile abnormalities compatible with cardiomyopathy have been described in mitral prolapse patients by several investigators.5-9 A cardiomyopathic process, if present, might be the primary factor leading to mitral valve prolapse and mitral regurgitation or conversely the contraction abnormalities might represent secondary manifestations of dysfunction in the mitral apparatus. The second question concerns the existence of an abnormality in the coronary circulation with resultant ischemic heart disease or ischemic cardiomyopathy in many of the patients. Coronary insufficiency is suggested by the frequent occurrence of chest pain, arrhythmias,10-12 and ECG abnormalities, as well as the infrequent reports of sudden death in these patients and their families.1,4,10

The present study, in an attempt to answer these questions, investigated left ventricular dimensions, dynamic geometry, and function; coronary anatomy; and the cardiac response to stress testing in 26 patients with IMVP. These patients represented a spectrum of clinical involvement that included symptoms ranging from mild to severe, mild to moderate prolapse of one or both mitral leaflets, and mitral regurgitation ranging from none to moderate in degree.
Methods

The patient group included 21 women and five men with a mean age of 46 years (range 25 to 69 years). All 26 patients had a mid to late systolic click and/or murmur and had mitral valve leaflet prolapse demonstrated by left ventricular cineangiography. Twenty gave a history of chest pain, usually atypical in character, duration, and location and rarely associated with exertion. Ten had documented atrial or ventricular arrhythmias and nine showed a superior T vector on the resting ECG.

After obtaining informed consent complete right and left heart catheterization was performed in all patients. Catheterization studies included left ventricular cineangiography in the 30\(^\circ\) right anterior oblique (RAO) projection in all patients and in the 45\(^\circ\) left anterior oblique projection in 17. Twenty-five of the patients had selective right and left coronary cinearteriography. Measured and calculated data obtained from cardiac catheterization in the majority of patients included pulmonary artery pressure, left ventricular end-diastolic pressure (LVEDP), and the forward cardiac index by the Fick technique. Angiographic left ventricular end-diastolic and end-systolic volumes and ejection fraction were calculated by a modified Dodge area-length method, and left ventricular mass was calculated by the method of Kennedy et al. Left ventricular anterior wall thickness was measured and volume and mass calculations were performed on contractions showing sinus rhythm and occurring at least two cycles removed from ectopic contractions. The following normal values from the work of Kennedy et al. were used: LV end-diastolic volume index (LVEDVi) in men or women: 50-90 ml/m\(^2\); LV anterior wall thickness (LAVWT) in men: 10.3-13.3 mm; and LV mass index (LVMi) in men: 80-111 g/m\(^2\). Normal values for women were determined in our laboratory from calculations performed on seven women below the age of 50 years without evidence of coronary artery disease or significant left heart disease. These values included LAVWT: 6.3-10.1 mm; and LVMi: 45-86 g/m\(^2\). The over-all pattern of ventricular contraction and the geometry of ventricular ejection were assessed from the 30\(^\circ\) RAO ventriculograms. This analysis included the calculation of systolic percent shortening of the ventricular long axis, measured from the aortic valve midplane to the apex, and of three minor axes constructed as perpendicular chords that trisected the long axis.

Atrial pacing was performed during cardiac catheterization in ten IMVP patients after the administration of atropine sulfate (0.75-1.5 mg). Sequential pacing rates of 100, 120, 140, 160, and 180 beats/minute were maintained for two minutes unless atrioventricular dissociation developed. The patients were monitored for the development of pain, arrhythmias, or "ischemic" ST segment displacement on ECG leads II and V\(_6\). The LVED pressure was obtained at the end of each pacing interval and for the first ten beats immediately upon termination of pacing. In six patients coronary arterial and venous lactate levels were measured, as coronary sinus pacing and blood sampling were performed using the Gorlin bipolar catheter.

Maximal treadmill exercise testing was performed in 14 IMVP patients using a modified Bruce protocol. Patients were monitored for the development of chest pain or for "ischemic" ST segment responses (> 1.0 mm) using a four lead (Frank scalar leads X, Y, Z, and a bipolar lead CM\(_{4}\)) ECG system. Treadmill performance was quantitated by oxygen consumption, heart rate, a five minute postexercise capillary lactate level, and the treadmill duration score (TDS) in minutes of exercise.

A group of 12 patients, six female and six male with a mean age of 46 years, who had unexplained and often atypical chest pain, normal coronary arteriography, and no demonstrable abnormalities of the mitral valve were selected as a control group for comparison with IMVP patients. This group also underwent diagnostic right and left heart catheterization with atrial pacing in all 12, five of whom had pacing from the coronary sinus and lactate studies. Treadmill exercise testing was performed in nine of the control group.

Results

IMVP Group

Prolapse of a mitral valve leaflet was demonstrated in either or both the RAO and LAO projection during left ventriculography in all patients with the IMVP syndrome. Mitral regurgitation was detected in the absence of ectopic contractions in 18 patients and was of mild degree in 14, and of moderate degree in four. None had severe mitral regurgitation. All patients were in sinus rhythm at the time of catheterization.

Left ventricular end-diastolic volume indices were normal in 15 of 25 patients and increased in the remaining ten. The left ventricular anterior wall thickness was increased in only one of the 17 patients in whom this measurement could be obtained. Left ventricular mass was increased in six of these 17 patients.

Independent assessment of the left ventricular cineangiograms by two of the authors (D.N. and C.W.) divided the patients into three patterns of contraction: 1) Seven patients demonstrated a normal pattern of contraction; 2) Eight patients had abnormal contraction patterns. In two of these eight there were no regional abnormalities but the ventricle showed moderate, diffuse hypokinesis accompanied in one by an akinetic area on the anterior wall. The remaining six ventriculograms showed a contraction deformity of the inferior wall in the middle or basilar portion of the ventricle accompanied by anterior wall hypokinesis, or accentuated relaxation of the anterior wall during the isovolumic relaxation phase; 3) Eleven patients demonstrated a hyperkinetic contraction pattern with obliteration of the ventricular cavity distal to the papillary muscles.

Graphic illustrations of the ventricular contraction patterns encountered in these patients are presented in figure 1. The systolic percent shortening of the left ventricular major and minor axes are shown in relation to ventricular volume and mass, contraction patterns, and ventricular function indices in table 1.

Resting left ventricular function was normal, as assessed by an ejection fraction greater than 55%, in 17 patients with IMVP. The ejection fraction in three patients lay between 50 and 55% and in the remaining five was less than 50%. Only two of 25 patients had a LV end-diastolic pressure greater than 12 mm Hg and
two of 14 had a cardiac index less than 2.5 ml/min/m². Two of these four patients with an abnormal cardiac index or LVEDP also had a depressed ejection fraction (< 55%). Only one of the nine patients with an abnormality of left ventricular function (low cardiac index) was in the group showing a hyperkinetic contraction pattern. The average mean pulmonary artery pressure in 20 patients was 15 mm Hg and only two of 20 had mild pulmonary hypertension.

Coronary arteriography demonstrated a normal distribution and anatomy of coronary vessels in all 25 patients studied although six arteriograms showed minor luminal irregularities not felt to be of clinical significance. A right dominant coronary pattern was present in 21 arteriograms, the circulation was balanced in one, and was left dominant in three.

Treadmill exercise tests were judged to be maximal or near maximal in 12 of 14 patients tested and showed an average TDS of 6.2 min and an average heart rate of 165 beats/min. One patient was unable to perform an acceptable test due to extreme anxiety on two occasions. Seven of these tests were interpreted to indicate decreased exercise performance when compared to age and sex related normal values in our Exercise Laboratory. Only three of 12 patients developed chest pain, all episodes were atypical in nature and commenced after termination of the exercise. One of these patients did show an ST-segment depression of 2.0 mm at a heart rate of 148 beats/min during exercise (before the onset of postexercise chest pain). None of the other patients had ST-segment responses considered positive for ischemia. Premature ventricular contractions occurred in four patients during or after exercise and one developed a paroxysm of ventricular tachycardia.

Sequential atrial pacing reached a rate of 200 beats/min in one patient, 180 beats in two patients, 160 beats/min in five patients, and 140 beats/min in two patients. Two of these ten developed atypical

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**Figure 1**

Drawings of left ventricular end-diastolic and end-systolic cine frames in the 30° right anterior oblique projection obtained from one representative patient in each of the three major contraction pattern groups seen with IMVP. The calibration factors differ for each of these drawings. The abnormal contraction pattern shown in (B) is characteristic of the regional deformities seen on the inferior and anterior walls. The ventricular long (major) and short (minor) axes are drawn on the chamber outlines and measurements or calculations of ventricular structure and function are shown on the right side. The shaded areas are felt to represent portions of prolapsing mitral leaflets. In this hyperkinetic ventricle (C) prolapse was observed only in the left anterior oblique projection.
Table 1

Measurements of Left Ventricular Structure and Function: Idiopathic Mitral Valve Prolapse

<table>
<thead>
<tr>
<th>Patients</th>
<th>Age/sex</th>
<th>MR</th>
<th>LVEDV (mL/m²)</th>
<th>LVMI (g/m²)</th>
<th>LVAWT (mm)</th>
<th>EF (%)</th>
<th>Long</th>
<th>Base</th>
<th>Mid</th>
<th>Apex</th>
<th>CI (mL/min/m²)</th>
<th>LVEDP (mm Hg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. ES</td>
<td>54, F</td>
<td>moderate</td>
<td>105</td>
<td>92</td>
<td>7</td>
<td>55</td>
<td>19</td>
<td>42</td>
<td>38</td>
<td>38</td>
<td>2.9</td>
<td>8</td>
</tr>
<tr>
<td>2. AM</td>
<td>41, F</td>
<td>mild</td>
<td>78</td>
<td>93</td>
<td>9</td>
<td>65</td>
<td>27</td>
<td>42</td>
<td>45</td>
<td>38</td>
<td>3.3</td>
<td>19</td>
</tr>
<tr>
<td>3. LO</td>
<td>53, F</td>
<td>mild</td>
<td>98</td>
<td>—</td>
<td>—</td>
<td>65</td>
<td>19</td>
<td>40</td>
<td>41</td>
<td>55</td>
<td>—</td>
<td>7</td>
</tr>
<tr>
<td>4. MB</td>
<td>33, F</td>
<td>0</td>
<td>72</td>
<td>69</td>
<td>7</td>
<td>60</td>
<td>21</td>
<td>28</td>
<td>40</td>
<td>44</td>
<td>—</td>
<td>7</td>
</tr>
<tr>
<td>5. AB</td>
<td>49, F</td>
<td>0</td>
<td>104</td>
<td>142</td>
<td>12</td>
<td>51</td>
<td>26</td>
<td>38</td>
<td>26</td>
<td>42</td>
<td>—</td>
<td>2</td>
</tr>
<tr>
<td>6. MC</td>
<td>39, F</td>
<td>0</td>
<td>72</td>
<td>69</td>
<td>7</td>
<td>60</td>
<td>21</td>
<td>28</td>
<td>40</td>
<td>44</td>
<td>—</td>
<td>7</td>
</tr>
<tr>
<td>7. CT</td>
<td>54, M</td>
<td>0</td>
<td>125</td>
<td>86</td>
<td>6</td>
<td>30</td>
<td>20</td>
<td>21</td>
<td>37</td>
<td>36</td>
<td>—</td>
<td>8</td>
</tr>
<tr>
<td>Mean</td>
<td></td>
<td></td>
<td>97</td>
<td>96</td>
<td>8</td>
<td>38</td>
<td>22</td>
<td>35</td>
<td>38</td>
<td>42</td>
<td>3.2</td>
<td>9</td>
</tr>
</tbody>
</table>

Normal Contraction

| 8. LM    | 25, F   | moderate | 138 | 94 | 6 | 33 | 16 | 13 | 21 | 12 | 3.9 | 8 |
| 9. JG    | 41, F   | moderate | 111 | —  | — | 68 | 29 | 23 | 43 | 55 | —  | 5 |
| 10. FK   | 51, F   | mild    | 106 | 91 | 7 | 38 | 6  | 16 | 35 | 24 | 2.6 | 8 |
| 11. OW   | 45, F   | mild    | 59  | 77 | 9 | 53 | 13 | 37 | 27 | 52 | 3.6 | 10 |
| 12. SM   | 40, F   | mild    | 48  | —  | — | 61 | 13 | 46 | 48 | 52 | —  | 11 |
| 13. EM   | 43, F   | 101     | —  | —  | — | 31 | 10 | 21 | 31 | 26 | 2.3 | 12 |
| 14. MH   | 55, F   | 0      | 80  | 84 | 8 | 25 | 13 | 25 | 26 | 19 | —  | 10 |
| 15. CH   | 28, M   | 0      | 50  | 59 | 8 | 25 | 16 | 23 | 21 | 14 | 2.8 | 7 |
| Mean     |         |         | 87  | 81 | 8 | 42 | 14 | 26 | 32 | 32 | 3.0 | 10 |

Abnormal Contraction

| 16. CMcL | 60, M   | moderate | 125 | 130| 10| 90 | 37 | 56 | 66 | 77 | —  | 6 |
| 17. EB    | 52, F   | mild    | 65  | 83 | 9 | 78 | 22 | 52 | 59 | 60 | —  | 9 |
| 18. RD    | 53, F   | mild    | 55  | 84 | 10| 78 | 45 | 31 | 50 | 64 | 3.8 | 5 |
| 19. JS    | 25, M   | mild    | 67  | —  | — | 64 | 25 | 39 | 54 | 45 | 2.6 | 11 |
| 20. LF    | 27, M   | mild    | 34  | 65 | 11| 85 | 50 | 41 | 52 | 62 | 3.4 | 8 |
| 21. EMcC  | 48, F   | mild    | 68  | 86 | 9 | 84 | 36 | 53 | 59 | 57 | 2.6 | 9 |
| 22. EH    | 38, F   | mild    | 45  | —  | — | 78 | 31 | 39 | 47 | 72 | 3.5 | 10 |
| 23. MY    | 69, F   | mild    | 60  | —  | — | 72 | 29 | 9  | 51 | 69 | —  | 11 |
| 24. LY    | 46, F   | mild    | 184 | —  | — | 74 | 28 | 18 | 62 | 55 | 3.7 | 8 |
| 25. IC    | 60, F   | 0      | 39  | 55 | 8 | 84 | 38 | 47 | 65 | 68 | 2.4 | 5 |
| 26. EK    | 41, F   | 0      | 67  | 61 | 6 | 69 | 36 | 23 | 31 | 25 | —  | 8 |
| Mean     |         |         | 74  | 81 | 9 | 78 | 36 | 37 | 54 | 60 | 3.1 | 8 |

Hyperkinetic Contraction

Mitral regurgitation (MR) assessed from left ventricular cineangio-grams.

Abbreviations: LVEDVI = left ventricular end-diastolic volume index; LVMI = left ventricular mass index; LVAWT = left ventricular anterior wall thickness; EF = ejection fraction; axis shortening = percent systolic shortening of four axes (long, base, mid, and apex) described in text. CI = cardiac index; LVEDP = left ventricular end-diastolic pressure. m² = square meters of body surface area.

chest pain during pacing but none developed "ischemic" ST-segment depression or elevation. Four of the ten manifested an abnormal LVEDP response (an immediate post-paced LVEDP value 6 mm Hg or more above the initial value) at pacing rates of 160–200 beats/min. One of these patients with an abnormal LVEDP response also had the single positive ECG response to exercise testing. All six patients with coronary lactate studies demonstrated myocardial lactate extraction in the unstressed state and responded normally to pacing stress (i.e., lactate extraction remained above 10%). The responses to treadmill exercise or atrial pacing coronary stress tests are summarized in Table 2.

Control Group

The results of left ventricular catheterization studies in the 12 control patients are tabulated in Table 3. Six of these patients showed mild to moderate generalized hypokinesis on left ventricular cine-angiography. Two patients had a hyperkinetic contraction pattern similar to that observed in 11 of the IMVP patients. Abnormal left ventricular function, as manifest by a LVEDP > 12 mm Hg, an ejection fraction < 55%, or a cardiac index < 2.5 L/min/m², was present in ten of the 12 controls. One man in this group showed an increase in left ventricular volume and calculated mass and one woman had an increased anterior wall thickness.

Selective coronary arteriography was normal in all 12 patients. Exercise electrocardiography was normal in all nine of the controls tested on the treadmill. Four of these patients showed impaired exercise performance and two developed premature contractions during or following exercise. All controls underwent atrial pacing and three showed an abnormal LVEDP response immediate post pacing. One of these patients also developed atypical chest pain and ST-segment depression in ECG lead V₅ with pacing. Two other patients experienced pain with pacing (one typical
angiographic, and left ventricular angiographic features of patients with the mitral valve prolapse syndrome have been well documented in the cardiovascular literature. A major difficulty inherent in dealing with a heterogeneous syndrome is the possibility that diverse pathogenetic mechanisms may lead to the same end point, in this case, mitral valve prolapse. We have attempted to evaluate a distinct and more homogeneous group, identified as idiopathic mitral valve prolapse, by eliminating from consideration all patients with recognized cardiac disease associated with their mitral prolapse. In addition, we have attempted to define cardiac and coronary structure and function in these patients in a more comprehensive manner by studying patients with a variable duration of symptoms and signs that ranged from mild to severe in intensity.

A number of these patients were found to have elevated left ventricular end-diastolic volumes, accompanied in some by an increase in ventricular mass, despite the fact that only four of 26 had angiographically demonstrated moderate mitral regurgitation. A majority of patients with IMVP had normal resting left ventricular function as assessed by LVEDP, cardiac index, and angiographic ejection fraction. The majority also exhibited a normal or supranormal extent of left ventricular major and minor axis systolic shortening (table 1) when compared to published studies of left ventricular dynamic geometry. There is, however, an apparent difference in ventricular function between the 18 patients with normal or hyperkinetic ventricular contraction patterns and the eight patients with some form of contraction deformity. Only four of the former had evidence of ventricular dysfunction and one of these (MB), with a LVEDP of 19 mm Hg, may be explained by the mild to moderate, chronic, essential

**Table 2**

<table>
<thead>
<tr>
<th>Summary of Coronary Stress Testing</th>
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<tbody>
<tr>
<td><strong>IMVP</strong></td>
</tr>
<tr>
<td><strong>Treadmill Exercise</strong> (N = 12)</td>
</tr>
<tr>
<td>TDS (minutes)</td>
</tr>
<tr>
<td>Maximal heart rate</td>
</tr>
<tr>
<td>Chest pain</td>
</tr>
<tr>
<td>Positive ECG</td>
</tr>
<tr>
<td><strong>Atrial Pacing</strong> (N = 10)</td>
</tr>
<tr>
<td>Maximal paced rate</td>
</tr>
<tr>
<td>Chest pain</td>
</tr>
<tr>
<td>Positive ECG</td>
</tr>
<tr>
<td>Abnormal LVEDP</td>
</tr>
<tr>
<td>Positive coronary lactate</td>
</tr>
</tbody>
</table>

*Atypical pain with onset postexercise.

TDS = treadmill duration score during a modified Bruce protocol.

Positive ECG responses refer to ST-segment depression greater than 1.0 mm.

Abnormal LVEDP = a left ventricular end-diastolic pressure response to pacing characterized by a post-paced value 6 mm Hg or greater than the pre-paced value.

Positive coronary lactate responses were seen in the myocardial lactate extraction below 10% or the presence of myocardial lactate production.

**Discussion**

The typical clinical, electrocardiographic, echo-
hypertension also present. On the other hand, six of the eight patients with contraction deformities had at least one abnormal measurement of LV function. The duration and intensity of clinical symptoms (e.g., atypical pain, dyspnea, and palpitations) did not correlate well with ventricular size, contraction pattern, or function.

We conclude that a hyperkinetic pattern of left ventricular contraction is present in many cases of IMVP when representative patients are studied whose clinical signs and symptoms range from mild to severe, and whose mitral dysfunction assessed angiographically ranges from mild to moderate. When the contraction pattern is hyperkinetic or normal, resting ventricular function and contraction geometry is often normal, although the ventricular volume may be increased. Contraction deformities are often accompanied by ventricular dysfunction. In the absence of severe mitral regurgitation few patients with IMVP show more than a small increase in ventricular mass.

Left ventricular studies did not demonstrate dilatation or hypertrophy in the control patient group with chest pain, normal coronary arteriography, and normal mitral valves. The presence of a diffuse hypokinetic ventricular contraction pattern with ejection fractions below 55 percent (34-54%) in eight of the 12 does however suggest the possibility of a latent cardiomyopathy in this group. On the other hand, coronary arteriography, exercise testing, and atrial pacing did not suggest coronary artery disease as a likely cause for the ventricular dysfunction in the control patient group.

Several investigators have performed hemodynamic studies in IMVP and in most instances have reported normal resting left ventricular function.5, 7, 9, 20, 21 A recent report by Gulotta and associates describes left ventricular dysfunction at rest or with exercise in 26 patients with IMVP associated with severe symptoms or moderate to severe mitral regurgitation.8 Nevertheless, normal resting ventricular function (EF > 55%; CI > 2.5 ml/min/m²; and LVEDP < 12 mmHg) was present in 16 of Gulotta’s 26 patients and in ten the ejection fraction was above 75%. Abnormal cardiac responses to exercise defined by a diminished forward cardiac output to oxygen consumption index were present in only nine of the group. In addition, 54% of this series had left ventricular hypertrophy based on angiographic measurements of left ventricular anterior wall thickness.

Although many patients with mitral valve prolapse have demonstrated normal left ventricular angiographic patterns, attention has been drawn to a considerable number of patients who manifest regional contraction abnormalities on left ventriculography. Ehlers and associates8 have described “postero-inferior bulging” into the left ventricular cavity during systole and similar findings are present on the ventriculograms in other reports.21 Scampardonis et al.7 found a posterior-inferior systolic contraction deformity, often associated with early diastolic relaxation of the anterior ventricular wall, in 49 of 87 patients who had some form of the mitral prolapse syndrome. Twenty of the 26 patients studied by Gulotta et al.8 had evidence of anterolateral wall hypokinesis and two showed postero-inferior contraction deformities. Six of our eight patients with an abnormal ventricular contraction pattern had some combination of postero-inferior and anterior wall deformity. The hyperkinetic pattern present on 11 of our angiograms has been observed in a few cases from two series of angiographic studies.7, 22

The pathophysiology of the postero-inferior and anterior contraction abnormalities has not been adequately defined. Two mechanisms are readily suggested from an analysis of the angiographic data: 1) an asynchronous ventricular contraction or a regional area of hypercontraction of unknown etiology may be responsible for an inferior inward bulge, and perhaps for anterior asynergy as well; and 2) an unusually prominent or malpositioned papillary muscle or muscles may cause the deformity. After reviewing the ventriculograms from our patients with contraction abnormalities, as well as the illustrations accompanying many of the published reports, we favor the latter explanation. At least two mechanisms may lead to papillary muscle induced deformities of the ventricular contraction pattern. First, one or both papillary muscles may be subjected to excessive chordal “pull” from the tense prolapsed leaflets and become malaligned along with a portion of ventricular wall during the late stages of systole.23 Secondly, the deformity may represent asynchronous, i.e., delayed or incomplete, contraction of the papillary muscle(s) with malposition during systole. The primary case for this asynergistic or inadequate papillary muscle contraction might be regional ischemia or chronic excessive stress imposed by the prolapsed leaflet(s). Liedtke et al. have described an altered systolic relation of the inferior papillary muscle tip to the mitral valve ring in patients with idiopathic mitral prolapse and have attributed this to incomplete papillary muscle contraction.8 The late systolic hypokinesis or outward bulging of the anterolateral ventricular wall is most likely due either to an accentuation of normal asymmetric early diastolic relaxation as described by Altieri et al.24 or to early relaxation of the papillary muscle and underlying ventricular wall.

Large vessel coronary artery anatomy was normal in the 25 patients studied in our laboratory and in vir-
tually all of the reported experience with coronary arteriography in the mitral prolapse syndrome.\textsuperscript{7, 9} Treadmill exercise stress testing did not reveal evidence of myocardial ischemia in the 12 patients we tested. Gooch et al. also failed to find "ischemic" ST-segment changes or chest pain in 24 patients with mitral prolapse who were treadmill tested.\textsuperscript{10} Atrial pacing in ten of our patients, including six who had coronary arterio-venous lactate measurements, also failed to provide convincing evidence of myocardial ischemia. The occurrence of abnormal LVED pressure responses to pacing (four of ten patients) may reflect incomplete relaxation and decreased compliance of the left ventricle associated with the high pacing rates (160–200 beats/min) achieved. Exercise testing was also negative in the control group of patients with chest pain and normal coronary arteriography and the majority did not have a positive ischemic response to atrial pacing. Normal pacing and treadmill exercise stress tests do not, of course, exclude the possibility of regional myocardial ischemia. LeWinter and associates have recently reported that chest pain could be induced by phenylephrine infusion in eight of nine patients with mitral valve prolapse and a history of spontaneous atypical chest pain.\textsuperscript{26} The authors postulate that a pressor stress may result in excessive wall tension and localized ischemia at the base of papillary muscles already overstressed by the abnormal systolic tension of prolapsed mitral leaflets. These observations are of particular interest since normal coronary arteriography and treadmill exercise tests were present in their patients.

The pathogenesis of idiopathic mitral valve prolapse remains uncertain. The data presented do not support the concept that some form of cardiomyopathy or a generalized ischemic disorder of the ventricle is primarily responsible for mitral leaflet prolapse, chest pain, arrhythmias, or the angiographic contraction abnormalities seen in many of the patients with this syndrome. The variable duration and intensity of symptoms and the mild degree of mitral regurgitation found in most of the patients studied in our laboratory is probably quite characteristic of IMVP since the clinical experience in our own and other institutions\textsuperscript{48} indicates that the syndrome of mitral prolapse is an extremely common problem, is often asymptomatic, and in the majority of cases is benign over many years of clinical observation. It seems quite likely that a primary defect of the mitral apparatus, probably of the valve leaflets and/or chordae tendineae, is present in these individuals. In view of the high familial incidence of mitral prolapse this may be a heritable genetic defect in many cases. Relatively little pathological material has been available to permit definition of this primary lesion in the mitral apparatus. Postmortem examinations and the examination of mitral valve structures resected at the time of surgical replacement of the mitral valve for severe mitral regurgitation have shown myxomatous degeneration in a few patients.\textsuperscript{4, 21, 27, 28} Until further studies are available there is no reason to assume that myxomatous changes are the underlying factor in the majority of patients with IMVP. An additional mechanism may be necessary to allow development of a clinical picture that includes mitral regurgitation, atypical chest pain, ECG abnormalities, arrhythmias, and ventricular dysfunction or an angiographic contraction deformity. This mechanism or accelerating factor may simply be the magnitude of leaflet redundancy, chordal length, or papillary muscle damage; the extent of progression in a myxomatous process; or a ventricular factor such as the hyperkinetic contraction pattern observed in many of our patients. A hyperkinetic ventricular contraction would favor prolapse of a defective mitral apparatus and this in turn could result in additional stress being applied to the defective leaflet, chordae or papillary muscle with further prolapse. Of considerable interest in this respect is the observation that mitral leaflet ballooning may occur in the small, hyperkinetic ventricle of patients with idiopathic hypertrophic subaortic stenosis.\textsuperscript{29} In both of these conditions, i.e., our patients with hyperkinetic contraction and patients with IHSS, the ventricle is disproportionally small in comparison to the mitral valve apparatus.

When mitral prolapse becomes established the prolapsed leaflet(s) presents a greater than normal surface area for the development of pressure stress and therefore permits excessive stress on the chordae and papillary muscles. As previously described this chronic overload on the papillary muscle and adjacent ventricular wall may result in local ischemia and/or asynergy with the production of a contraction abnormality, pain, arrhythmias, and T vector abnormalities on electrocardiography. The presence of significant mitral regurgitation in addition to regional asynergy may in a few patients lead to ventricular dilatation, hypertrophy, and dysfunction. The proposed relationships between factors that may be operative in the pathogenesis of IMVP are summarized in figure 2.

In conclusion, we feel that IMVP is a common, usually benign abnormality of the mitral valve apparatus that in selected individuals may progress to a stage involving significant mitral regurgitation, ventricular dilatation, and severe stress with mid to late systolic displacement and dysfunction of a papillary muscle(s). The characteristic ventriculographic deformity, the "ischemic" electrocardiogram, and many of the recurrent arrhythmias, sometimes life threatening, are the result of regional ventricular dysfunction.
A proposed pathophysiological mechanism for the development of the IMVP syndrome, including most of the important clinical features. The heritable and acquired primary factors are unknown and might include myxomatous degeneration, although a myxomatous process could also be the result of long term stresses on leaflets, chordae, and papillary muscles. A majority of this population may reside at the two levels marked stable and may therefore avoid clinical detection. A hyperkinetic ventricular contraction pattern and other unidentified factors are considered to play a potentiating role. The tricuspid valve apparatus may be involved in a similar manner in an unknown number of these patients.

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