Autonomic Dysfunction in Women with Mitral Valve Prolapse Syndrome

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SUMMARY  Autonomic cardiovascular regulation was evaluated in 35 women, 19 with mitral valve prolapse and 16 healthy controls. Heart rate responses to the diving reflex and to phenylephrine infusion were diminished in patients. Noninvasive measures of cardiac output, heart rate, blood pressure, forearm flow and leg volume during lower body negative pressure (LBNP) showed that patients had less lower extremity pooling of blood and had lower forearm conductance. Blood pressures during LBNP rose or remained unchanged despite decreases in cardiac output of 20–25%. These data indicate that mitral valve prolapse patients have an increased venous and arterial vasoconstrictor activity. Cardiac output at rest and echocardiographic indices of contractility were normal. Patients with a history of significant ventricular arrhythmias had higher heart rates and lower forward stroke volumes than the other patients or controls.

The combined data demonstrate autonomic dysfunction in women with the mitral valve prolapse syndrome and suggest decreased parasympathetic, increased α- and normal β- adrenergic tone and responsiveness.

PATIENTS WITH MITRAL VALVE PROLAPSE syndrome (MVPS) may have a variety of cardiac and noncardiac abnormalities in addition to the characteristic valvular lesion with its mid-systolic click and late systolic murmur. Included are skeletal abnormalities such as pectus excavatum and scoliosis, an asthenic build, symptoms such as atypical chest pain, easy fatiguability, abnormal cardiovascular and electrocardiographic responses to exercise, ST- and T-wave changes on resting ECGs, and a variety of atrial and ventricular arrhythmias.1, 2 Attempts have been made to relate these findings with a single unifying concept, but no satisfactory explanation has been presented. The presence of chest pain, ST-T-wave abnormalities, and arrhythmias in the absence of hemodynamically significant valvular, myocardial or coronary artery disease suggests the possibility of a functional disorder involving the autonomic nervous system. Many of the clinical features of the MVPS are found in other conditions which have been attributed to some type of autonomic dysfunction, e.g., neurocirculatory or vasoregulatory asthenia.3 To test the hypothesis that autonomic dysfunction is present in patients with MVPS, we used a comprehensive set of noninvasive procedures to assess regulation of cardiovascular function.

Materials and Methods

Patients

The protocol was approved by the institutional Human Research Review Committee. The records of the Cardiographics Laboratory of the University of Texas Southwestern Medical School, Dallas, Texas were reviewed to obtain the names of patients with the diagnosis of mitral valve prolapse. Private cardiologists in the community were also contacted for names of patients who might enter the study. We studied only women because most of our MVPS patients are women and because we wished to avoid problems of data interpretation due to inherent cardiovascular differences between normal men and women. One patient was excluded because she required propranolol for control of arrhythmias. Four additional patients were taking propranolol at the time they agreed to participate, but all medications were discontinued for at least 72 hours before this study. Nineteen female patients (mean age 30 ± 1.8 years) were included.

The diagnosis of MVPS was confirmed by echocardiography using the criteria of DeMaria et al.4 or by phonocardiography demonstrating a nonejection systolic click-murmur complex which changed in the typical fashion in response to amyl nitrite inhalation or the Valsalva maneuver.5 The laboratory and clinical findings of the patients are summarized in table 1.

None of the patients had clinical findings suggestive of hemodynamically significant mitral regurgitation or echo- or electrocardiographic evidence of left atrial or ventricular enlargement.

We graded the severity and frequency of each patient’s symptoms and ventricular and supraventricular arrhythmias on a scale of 0–4+ (as defined in table 1) on entry to the study, and used the sum of
Table 1. Clinical Information

<table>
<thead>
<tr>
<th>Pt no</th>
<th>Age/race</th>
<th>Skeletal abnormalities</th>
<th>Chest pain</th>
<th>SOB</th>
<th>Palpitations</th>
<th>Arrhythmias</th>
<th>Ventricular</th>
<th>Supraventricular</th>
<th>Rest ECG</th>
</tr>
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<tr>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>34/W</td>
<td>Pectus</td>
<td>4+</td>
<td>2+</td>
<td>3+</td>
<td>Recurrent V Tach</td>
<td>0</td>
<td>Minor IVCD</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>31/W</td>
<td>Pectus, scoliosis</td>
<td>3+</td>
<td>3+</td>
<td>4+</td>
<td>Frequent bigeminy V tach</td>
<td>Frequent S Tach</td>
<td>Inferior Ts flat</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>30/W</td>
<td>Pectus, scoliosis</td>
<td>2+</td>
<td>0</td>
<td>4+</td>
<td>Continual bigeminy</td>
<td>Rare V Tach</td>
<td>0</td>
<td>Diffuse NSSTTW changes</td>
</tr>
<tr>
<td>4</td>
<td>36/W</td>
<td>0</td>
<td>2+</td>
<td>2+</td>
<td>4+</td>
<td>Frequent PVCs with couplets</td>
<td>0</td>
<td>Early repolarization</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>26/W</td>
<td>Pectus</td>
<td>2+</td>
<td>3+</td>
<td>4+</td>
<td>Frequent PVCs</td>
<td>Rare V Tach</td>
<td>Frequent S Tach</td>
<td>Inferior ST changes</td>
</tr>
<tr>
<td>6</td>
<td>28/W</td>
<td>Pectus</td>
<td>0</td>
<td>2+</td>
<td>3+</td>
<td>Frequent bigeminy</td>
<td>Frequent S Tach</td>
<td>Inferior ST changes</td>
<td></td>
</tr>
<tr>
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<td>4+</td>
<td>3+</td>
<td>3+</td>
<td>Occasional PVCs</td>
<td>Frequent S Tach</td>
<td>Inferior Ts flat</td>
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<tr>
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<td>3+</td>
<td>1+</td>
<td></td>
<td>Occasional PVCs</td>
<td>0</td>
<td>Early repolarization</td>
<td></td>
</tr>
<tr>
<td>Group 2</td>
<td></td>
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<td></td>
<td></td>
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<td></td>
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<tr>
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<td>2+</td>
<td>3+</td>
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<td>Frequent S Tach</td>
<td>Normal</td>
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<td>2+</td>
<td>2+</td>
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<td>Frequent S Tach</td>
<td>Inferior Qs</td>
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<td>37/W</td>
<td>Scoliosis</td>
<td>2+</td>
<td>1+</td>
<td>2+</td>
<td>Rare PVCs</td>
<td>0</td>
<td>Inferior ST-T changes</td>
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<td>2+</td>
<td>2+</td>
<td>2+</td>
<td>0</td>
<td>Frequent S Tach</td>
<td>Early repolarization</td>
<td>Inferior Ts flat</td>
</tr>
<tr>
<td>14</td>
<td>41/W</td>
<td>0</td>
<td>2+</td>
<td>1+</td>
<td>2+</td>
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<td>0</td>
<td>Incomplete RBBB</td>
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<tr>
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<td>2+</td>
<td>3+</td>
<td>2+</td>
<td>0</td>
<td>Rare S Tach</td>
<td>—</td>
<td></td>
</tr>
<tr>
<td>16</td>
<td>31/W</td>
<td>0</td>
<td>2+</td>
<td>2+</td>
<td>2+</td>
<td>0</td>
<td>Frequent S Tach</td>
<td>Normal</td>
<td></td>
</tr>
<tr>
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<td>2+</td>
<td>2+</td>
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<tr>
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<td>0</td>
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<td></td>
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<tr>
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<td>1+</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>Inferior Ts flat</td>
<td></td>
</tr>
</tbody>
</table>

Patients are ranked in order of clinical severity. Group 1 patients had significant ventricular arrhythmias and generally more severe symptoms. Group 2 patients were characterized by an absence of ventricular arrhythmias and had less severe symptoms. Symptoms were scored: 0 = never, 1+ = rarely and 2+ = occasionally mild symptoms, 3+ = frequent or moderately severe symptoms, and 4+ at times disabling symptoms.

Abbreviations: Pectus = pectus excavatum; SOB = shortness of breath; V Tach = ventricular tachycardia; IVCD = intraventricular conduction delay; S Tach = sinus tachycardia; PVCs = premature ventricular contractions; NSSTTW = non-specific ST- and T-wave changes; RBBB = right bundle branch block; + = present; 0 = absent; — = information not available.

Controls

Sixteen healthy female volunteers (medical school personnel, students and physicians' wives, mean age 28 ± 1.3 years) served as controls. Neither patients nor controls had hypertension, congestive heart failure or diabetes mellitus. No one was taking neuroactive medication and all were asked to avoid products containing caffeine for at least 12 hours before the study. Six of the patients and two of the controls smoked, but no smoking was allowed within 12 hours of the study.

Monitoring ECGs (Frank's orthogonal leads) were recorded and displayed continuously. Beat-to-beat heart rate was displayed by a Quinton Cardiotachometer (Model 611). Indirect arterial blood pressure was determined automatically with a Narco Biosystems Electro-Sphygmomanometer (PE-300). Performance data derived in our laboratory have been published elsewhere.

We measured forearm blood flow by occlusion plethysmography using the techniques of Siggaard-Andersen with a specially designed air-filled latex cuff. Correct application of this cuff in each case was verified by the presence of the usual vasoreactive responses to deep respiration and the Valsalva maneuver. Forearm conductance was calculated as

\[
\text{Forearm flow (ml/min/100 g tissue)} = \frac{\text{Mean arterial pressure (mm Hg)}}{4} - 1
\]

Leg volume changes were determined by a mercury-in-silastic Whitney strain gauge. The silastic tubing was doubled with 1-cm spacers separating the two sec-
tions of the strain gauge. This assembly was then placed around the calf at its maximum girth and changes in calf circumference were converted to the equivalent volume change in the 1-cm-thick section of calf under the strain gauge. Changes are reported in percent change from resting volume.

We obtained cardiac outputs with an acetylene rebreathing technique based on mass spectrometer measurements, as described previously by this laboratory.\(^1\) Comparison of the results to simultaneously obtained dye dilution measurements over the range of 5-19 1/min demonstrated no systematic difference and a linear correlation coefficient of 0.94.

Lower body negative pressure (LBNP) was produced with an airtight box sealed immediately below the level of the iliac crests. The methods and cardiovascular effects of LBNP have been reviewed elsewhere.\(^5\), \(^8\)

**Protocol**

Informed written consent was obtained from each subject. Care was taken to familiarize each person with the laboratory personnel, equipment and procedures to avoid the confounding effects of excessive psychological stress.\(^9\) Each person was asked to eat a light meal at least 2 hours before being studied.

No attempt was made to randomize the order of testing. However, patients and subjects were tested concurrently and the order of tests was varied at times to accommodate requirements for optimal scheduling of patients and controls, computer time, laboratory space, etc. Serial resting measurements of heart rate, cardiac output, blood pressure and oxygen uptake were performed before each intervention to establish a steady or basal resting state. A basal state was felt to exist when successive determinations of these parameters varied by less than 10% and (for tests in the supine position) were within 10% of the patient’s data from previous tests performed as part of this study.

**LBNP**

Subjects were placed in the LBNP device and resting measurements of heart rate, blood pressure, forearm flow, calf volume, oxygen uptake and cardiac output were obtained as described above. LBNP was then begun according to the standard NASA protocol\(^10\) at levels of -8, -16, -32, and -40 mm Hg, with repeat measures of heart rate, blood pressure and calf volume at each level and determination of cardiac output and forearm flow at levels of -16 and -40 mm Hg. In no case did syncope occur and there were no complications.

**Diving Reflex**

Resting heart rate was recorded in the sitting position after a recovery period with repeat heart rate, blood pressure and cardiac output determinations to verify return to a steady resting state. The subject was then asked to dunk her face in a basin of 0° C water. Each subject was told to take a deep breath before immersion but to avoid performing a Valsalva maneuver. The heart rate before immersion and maximal and minimal heart rates during immersion were noted. Response to the dive is biphasic: A tachycardia caused by anticipation of the test is followed by a bradycardia caused mainly by increased vagal tone but also by withdrawal of sympathetic tone.\(^11\)

**Phenylephrine Infusion**

After another recovery period and the return of heart rate, blood pressure and cardiac output to steady state resting levels, an infusion of phenylephrine HCl (40 μg/ml) was begun intravenously. Blood pressure and heart rate were measured at 30-second intervals and the infusion rate was adjusted to produce a rise in systolic blood pressure of 20–40 mm Hg. Heart rate (beats/min) and RR intervals (msec) were each plotted against systolic, diastolic, mean and pulse pressures. The plots of RR intervals vs mean arterial pressures \([1/3 (systolic – diastolic) + diastolic]\) yielded the highest correlation coefficient (mean 0.76 for patients and 0.79 for controls). For this reason, we used those regression lines instead of the RR intervals vs systolic pressure plots used by other authors.\(^12\) An example from one of our patients is shown in figure 1. The slope of each regression equation was considered to be an index of baroreflex sensitivity and vagal responsiveness.\(^12\), \(^13\)

All electrocardiographic, forearm flow, blood pressure and leg volume data were recorded on an Elema-Schonander Mingograf eight-channel recorder. Cardiac outputs were computed with an on-line computer

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**FIGURE 1.** An example of heart rate response to phenylephrine infusion in patient 5. Linear regression. BP = blood pressure.
(PDP-12) or stored on magnetic tape for subsequent processing.7

We obtained echocardiographic estimates of mean left ventricular velocity of circumferential fiber shortening (Vcf) at supine rest using procedures described by Cooper et al.14

All data were entered on punch cards and group differences were analyzed with unpaired t-test or the nonparametric Mann-Whitney U test. Both tests are included in the Statistical Package for the Social Sciences program (SPSS 7.0).15 The slopes of regression lines obtained during the phenylephrine infusion were also calculated with the appropriate SPSS program.

Results

Three of the patients had significant ventricular arrhythmias before and during the tests, two requiring temporary treatment with antiarrhythmics after the formal test procedure. One of the control subjects developed ventricular bigeminy during the phenylephrine infusion and after the diving reflex but returned to normal sinus rhythm spontaneously. This occurred at heart rates of 38-48 and probably represented an escape mechanism. No other complications were encountered, and all patients and subjects completed the study protocol.

To determine whether patients with MVPS represented a relatively homogenous group or whether subgroups were present, various statistical analyses were performed using the hemodynamic results and the clinical data obtained before admission to the experimental part of the study.

We found correlations between overall clinical severity and resting heart rate and the degree of vasoconstrictor responsiveness, suggesting that subgroups did exist. The first nine patients (group 1) are those with a greater frequency of both ventricular and supraventricular arrhythmias as well as more severe clinical symptoms. Patients in group 2 had no significant ventricular arrhythmias and presented most often with complaints of chest pain only. Because of both hemodynamic and clinical homogeneity, data from the two groups are presented separately. The hemodynamic data from the LBNP studies are presented in figure 2. There were no significant differences between mean values of cardiac index, stroke index or blood pressure at rest. Group 1 patients had higher resting heart rates and group 2 patients had lower forearm conductances. At −16 mm Hg, LBNP patients in both groups had significantly less venous pooling than controls (p < 0.002) as measured by changes in calf volume, but group 2 patients nevertheless had lower forearm conductance (p < 0.05). At −40 mm Hg, LBNP, mean blood pressure of the patients rose (group 2) or remained stable (group 1) while that of the controls fell. Calf volume changes remained less marked in patients than in controls (p < 0.01). Measurements of forearm conductance at this level showed a marked vasoconstrictor effect in all groups, but the controls still showed greater conductance than the patients (p < 0.05). Thus, the patients in both groups had significantly less venous pooling of blood in the legs during LBNP at any given pressure level, but greater arterial vasoconstriction as measured by forearm conductance and blood pressures. The low

![Graphs](http://circ.ahajournals.org/downloadable/897_f2.jpg)

**Figure 2.** Hemodynamic data from lower body negative pressure studies. Values are mean ± SEM.
proaching the mean $-2 SEM$ of the control patients' values. No statistical relationship between slope and age or resting blood pressure was found among controls or patients, indicating that these factors did not influence the results. Groups 1 and 2 had virtually identical mean slopes.

The patients' response to facial immersion (diving reflex) was also different from that of the normals. Both patients and normals were able to maintain immersion for an average of 21 seconds and no one had an immersion time of less than 14 seconds. The results are given in table 2. The difference between maximal and minimal heart rates during this procedure was smaller in the patients ($37 \pm 4$ beats/min for the groups 1 and 2 combined, compared with $57 \pm 5$ in the control group, $p = 0.005$). Baseline and peak rates were similar in the control group and in group 1. Both maximal and minimal heart rates were lower in group 2 but the difference between the rates was of the same magnitude in both patient groups whether measured as beats/min (table 2) or as percent of pre-dive heart rate. The difference corresponded to 41.9% in group 1 and 43.8% in group 2 compared with 62.6% in the control group ($p < 0.02$ and $p < 0.01$). Minimal heart rates tended to be lower in the control group, but the difference between patients and controls only approached significance ($p < 0.07$) when rates were expressed as percent of pre-dive heart rates.

Echocardiography demonstrated that the patients' Vcf's and shortening fractions were within normal limits for this laboratory and did not differ significantly from those of the controls. Patients' mean Vcf was $0.90 \pm 0.08$ diameters/sec and mean shortening fraction was $32 \pm 2\%$.

**Discussion**

The present study examined vasoregulatory function in patients with MVPs. Because vasoregulatory responses often involve activation and/or inhibition of both major components of the autonomic nervous system, it is difficult in the intact human subject to attribute a response exclusively to a single component. However, the various test procedures will be categorized, whenever possible, by their major autonomic effect.

The patients' response to phenylephrine infusion is consistent with diminished vagal responsiveness. The patients showed significantly less heart rate decrease for a given rise in blood pressure. Sympathetic withdrawal may contribute to the response, but
human data supporting a major parasympathetic component have been presented by Pickering et al. This procedure has not been previously studied in patients with MVPS but has been used as a test of vagal function in a variety of other cardiac disease states. Bristow et al. demonstrated diminished baroreflex sensitivity in patients with hypertension. Eckberg et al. examined patients with congestive heart failure of diverse etiologies and similarly showed markedly diminished baroreflex sensitivity which they interpreted as evidence of abnormal parasympathetic function. The younger normal controls in those studies had a heart rate response to phenylephrine similar to that of our controls, but their older controls (considerably older than our subjects) had diminished responsiveness. Age, hypertension and congestive heart failure can be excluded as causes of the findings in our patients. Patients and controls had nearly identical mean ages. There were no signs of congestive heart failure, and the blood pressures of both the patients and controls were in the low-normal range.

The patients' response to facial immersion supports the hypothesis of altered vagal function. The diving reflex evokes an extremely potent vagal response and can be used clinically to treat supraventricular tachyarrhythmias. The typical bradycardic response can be elicited even during the strong β-adrenergic drive present during near-maximal exercise. MVPS patients were less responsive to the diving maneuver, with substantially less decrease in heart rate suggesting diminished vagal responsiveness. However, the results are not as clear-cut as those from the phenylephrine infusion because group 2 patients also had an attenuated initial tachycardic response to the dive. Diminished vagal response to the diving reflex has also been reported in patients several weeks after myocardial infarction.

While the responses to phenylephrine infusion and facial immersion are likely to be primarily vagally mediated, the response to LBNP is considerably more complex. The primary hemodynamic stimulus during LBNP is peripheral venous pooling with an acute decrease in circulating blood volume. Previous studies have shown that increasing levels of LBNP cause a progressive decrease in left ventricular end-diastolic volume and stroke volume. Arterial blood pressure, left ventricular contractile state and heart rate are normally unchanged during moderate levels (−10 to −30 mm Hg). The fall in cardiac output is initially compensated for by peripheral vasoconstriction, manifest as decreasing forearm conductance and later by splanchnic vasoconstriction as well. Presumably, the initial vasoconstrictor responses are primarily mediated by activation of low pressure baroreceptors and occur before any measurable changes in arterial pressure are induced. Pressures beyond −40 mm Hg are likely to cause a fall in arterial pressure, activate the carotid sinus mechanism and produce a compensatory tachycardia.

Baseline hemodynamic values for the two groups were similar except for a relative tachycardia in group 1 patients. Significant differences developed during LBNP. The patients had less lower extremity venous pooling and lower forearm conductance values and had a paradoxical rise in arterial blood pressure. Samueloff et al. have shown that there is very little acute change in venous compliance in response to LBNP stress, so the diminished pooling in the patient group probably resulted from lower basal venous compliance caused by either structural vascular differences or increased α-adrenergic tone in MVPS patients.

Patients with ventricular arrhythmias (group 1) had changes in stroke index and cardiac index similar to those in controls, but had significantly higher heart rates despite enhanced peripheral vasoconstrictor responses. Group 2 patients had a smaller stroke volume reduction and less tachycardia. The mechanisms are not clear but the differences may be the result of a complex interaction between changes in the left ventricular contractile state and in the degree of prolapse and mitral regurgitation related to the decrease in preload and left ventricular end-diastolic volume during LBNP. Actual chamber size was not measured during this study.

Although the findings of an enhanced arterial vasoconstrictor response and decreased venous compliance suggest abnormal α-adrenergic activity, there is evidence suggesting normal β-adrenergic activity. There were no significant differences in resting blood pressure, cardiac output or stroke volume between patients and controls and the patients' resting echocardiographic indices of contractility were normal. It is unlikely that excessive psychological stress among the patients caused the abnormal response to LBNP, since most of the patients had been in the laboratory several times before the study and were familiar with the laboratory equipment and personnel. Many of the patients and controls dozed frequently during the testing and appeared relaxed most of the time (the diving reflex was a notable exception).

Our findings indicating abnormal autonomic function are supported in part by a preliminary report of Coghlan et al. They examined MVPS patients' heart rate response to the Valsalva maneuver and to 90° head-up tilting. The patients had less tachycardia than control subjects early after return to the supine position during the tilt test and a prolonged and more pronounced phase of bradycardia after the Valsalva maneuver. These results may at first seem to contradict ours. Differences between the studies in methods and patient selection may account for the different results. However, the combined data may also be interpreted as suggesting that some patients may be vagally hypersensitive to low or moderate levels of cardiovascular stimulation, but hyperreactive to higher levels of stimulation, at least in terms of the duration of the response and perhaps also the magnitude. This type of abnormality would tend to create an inefficient homeostatic control system characterized by a high threshold and underdamping, or a vagal stimulus-response curve displaced to the right with an abnormally steep slope. The presence of both sinus and ectopic tachyarrhythmias and severe
bradyarrhythmias\textsuperscript{23} in MVPS patients appears to be consistent with this explanation. None of the patients in this study suffered from bradyarrhythmias and therefore would not be expected to show the excessive vagotonia which may have been present in some of Coghlan's patients.

The common occurrence of ST-T abnormalities at rest and during stress in MVPS patients is consistent with the concept of autonomic dysfunction. It is well known that both central and peripheral autonomic alterations can produce these electrocardiographic changes. The autonomic origin of ST- and T-wave changes seen in cerebrovascular accidents has been well documented.\textsuperscript{24} Orthostatic ST-T abnormalities often occur in patients with other functional cardiovascular abnormalities\textsuperscript{25} and can be produced by small intravenous doses of epinephrine.\textsuperscript{26} ST-T abnormalities may reflect inhomogeneities with respect to electrical recovery and state of excitation, i.e., conditions promoting the development of ventricular arrhythmias.\textsuperscript{27} Several investigators have attempted to link the presence of ST-T abnormalities with a high incidence of arrhythmias in patients with MVPS.\textsuperscript{28-30} Indirect support for a relationship between autonomic dysfunction and arrhythmias in MVPS patients may be derived from the data of Combs et al., who studied the electrocardiographic responses to a standardized psychological stress situation.\textsuperscript{31} Several patients developed significant arrhythmias.

Most authors have attributed the arrhythmias and chest pain of MVPS to localized papillary muscle ischemia created by excessive tension of the mitral chordae tendineae\textsuperscript{32} or to a diffuse cardiomyopathy.\textsuperscript{33} Our thallium-201 perfusion studies\textsuperscript{35} and those of Massie et al.\textsuperscript{36} probably rule out significant ischemia caused by a fixed perfusion deficit, but these studies do not exclude intermittent spasm. The presence of excessive peripheral vasoconstrictor activity in MVPS patients raises the possibility of coronary artery spasm, but the exact relationship has not been determined. LeWinter et al. produced the typical chest pain in MVPS patients, but infused phenylephrine in doses substantially larger than used in this study.\textsuperscript{37} They interpreted this as being caused by increases in myocardial tension causing ischemic pain. A direct $\alpha$-adrenergic coronary vascular response is an alternate explanation. The patients in our study with the most severe chest pain (group 1) did not seem to have higher vasoconstrictor activity than the other patients (group 2) in response to acute volume depletion during LBNP, but other stimuli may produce more powerful $\alpha$-adrenergic responses.

The clinical symptoms of MVPS resemble those of the "vasoregulatory asthenia" patients of Holmgren et al.\textsuperscript{38, 39} Their patients were hyperkinetic and had large cardiac outputs and narrow arteriovenous $O_2$ differences at rest and during exercise. While MVPS patients clearly do not have these hyperkinetic changes, both groups commonly complain of atypical chest pain, shortness of breath, easy fatigueability and palpitations. Holmgrens' patients showed substantial improvement after treatment designed to increase vagal and decrease sympathetic tone, i.e., physical training.\textsuperscript{40} Whether MVPS patients would respond favorably to physical training remains to be studied. Further tests, including both vagal and $\alpha$- and $\beta$-adrenergic blockade, are needed before the clinical symptomatology and electrocardiographic abnormalities of MVPS can be attributed to malfunction of specific components of the autonomic nervous system.

In conclusion, the results provide strong evidence for autonomic dysfunction in patients with MVPS, probably involving both the sympathetic and parasympathetic systems. The exact nature of the autonomic defects remains to be established. Whether these defects occur simply as another aspect of the syndrome, i.e., as an expression of a generalized growth disorder, also manifest as skeletal abnormalities and an anthropometrically distinct MVPS habitus (Schutte JE, Gaffney FA, Blomqvist CG: unpublished data), or as an abnormal response to the valvular regurgitation itself is not known. These autonomic abnormalities may be a result of defective sensing, inadequate central processing and output or altered end-organ responsiveness, with or without underlying structural abnormalities of the nervous system.

References

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