Metabolic Studies in Mitral Valve Prolapse Syndrome

A Neuroendocrine–Cardiovascular Process

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SUMMARY Symptomatic patients with mitral valve prolapse (MVP) frequently mimic thyrotoxicosis, hyperadrenergic states or hypoglycemia. Twenty symptomatic patients with auscultatory and echocardiographic MVP were studied in the clinical research unit. T₃, T₄ and plasma cortisol were normal. Patients with MVP had normal responses to oral glucose administration but higher glucose levels than the controls (p < 0.05). Twenty-four-hour urinary epinephrine (E) and norepinephrine (NE) were greater than normal (E + NE excretion, 44 ± 2 vs 29.5 μg/g creatinine, p < 0.001). The short electromechanical systole corrected for heart rate (529 ± 3.9 vs normal 548 ± 2 msec, p < 0.01) also reflected high adrenergic tone. Frequent premature ventricular complexes (PVCs) with couples and triplets were found in 14 patients. Catecholamine excretion and frequency of PVCs were parallel and both decreased significantly at night (p < 0.001). Plasma catecholamine increase with exercise was greater in patients in whom the number of PVCs increased more than 10 per minute compared with patients in whom the number of PVCs remained relatively unchanged (620 ± 80 vs 98 ± 20 msec, p < 0.01).

We conclude that symptomatic patients with MVP have high adrenergic tone that may be responsible for or contribute to the multiple symptoms.

The anxiety, tachycardia, dysrhythmias, atypical chest pain, striking postural changes and echocardiographic findings of mitral valve prolapse were studied. Informed, written consent was obtained from each for study according to a protocol approved by the Institutional Human Research Committee. The patients were admitted to the clinical research center to standardize the environmental stimulation and placed on a caffeine-free diet. One week before the study, the patients' medications were discontinued. The frequency of symptoms and physical findings in the study patients are indicated in table 1. During the hospitalization the following procedures were performed.

Day 1

Epinephrine (E), norepinephrine (NE), 17-ketosteroids (17KS) and 17-hydroxycorticosteroids (17OHCS) excretions were measured in a 24-hour urine sample.

Day 2

Twenty-four-hour urinary E and NE excretion were repeated. In addition, phonocardiograms, systolic time intervals (STIs), echocardiograms, treadmill exercise tests and isometric handgrip exercises were performed between 10 a.m. and 12 o'clock noon. Blood for plasma catecholamine measurements was drawn before and immediately after treadmill exercise. Both specimens were obtained through a previously inserted heparinized needle with the patient in a supine position.

Day 3

Twenty-four-hour urine E and NE excretion were repeated. In addition, a 3-hour glucose tolerance test and thyroid function tests (T₆, T₄ and free thyroxin index) were performed.

Day 4

Total plasma catecholamines and plasma cortisol were measured at 0600, 1200, 1800 and 2400 hours. E and NE excretion were measured in urine samples collected between 0600 to 1200, 1200 to 1800, 1800 to 2400 and 2400 to 0600 hours. In addition, 24-hour ambulatory Holter monitoring was performed.
TABLE 1. Characteristics of Study Patients with Mitral Valve Prolapse (n = 20)

<table>
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<tbody>
<tr>
<td>Symptoms</td>
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<td>Palpitation</td>
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<td>Easy fatigability</td>
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<td>Dyspnea</td>
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<td>Syncope or near-syncope</td>
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<td>Anxiety</td>
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<td>Physical findings</td>
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<td>Midsystolic click and late systolic murmur</td>
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<td>Midsystolic click and no murmur</td>
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<td>No midsystolic click and late systolic murmur</td>
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STIs and echocardiograms were obtained using standard techniques.11-13 Total electromechanical systole corrected for heart rate (QS_{T}) was used as an additional index of adrenergic activity.14-17

Isometric exercise was performed with a hand dynamometer maintained at one-third of a predetermined maximum for 3-4 minutes.18 During this time, cardiac rhythm was monitored using ECG leads II, V_{2} and V_{6}.

After 30 minutes of recumbent rest, each subject underwent maximal exercise testing on a motorized treadmill according to the Bruce protocol.19-20 Electrocardiographic recordings were made with the patient in the supine, sitting and standing positions before, every minute during and for 10 minutes after exercise. Exercise and postexercise arrhythmias were recorded with a special delay circuit that permitted recording of events of 6 seconds. Twenty-four-hour ambulatory electrocardiographic recordings were obtained with a portable cassette tape (Avionics Model 600). The data were analyzed by playback (Avionics Model 445) as previously described.20

Urinary E and NE were measured fluorometrically.21 The interassay coefficient of variation was 13.4% for E, 12.8% for NE and 10.7% for total catecholamines. Plasma total catecholamine measurements were performed according to the method of Passon using a single-isotope assay.22 The interassay coefficient of variation was 12.6%.

Plasma thyroid hormone and cortisol were measured by standard radioimmunoassay techniques.23, 24 Urine 17KS was measured by the method of Klendshyt and 17OHCs was measured according to the method of Silber.25, 26 Urine creatinine measured by the Jaffé reaction had a coefficient of variation of 2.2%.27

Controls

Control values for the 24-hour urinary E and NE excretion were obtained from 29 normal, ambulatory subjects (24 females and five males, mean age 32.1 ± 4 years) in no obvious stress, who were within 10% of their ideal weight. In addition, 35 hospitalized patients (23 females and 12 males, mean age 39 ± 6 years) with normal cardiovascular function undergoing minimally stressful diagnostic studies were used as controls for E and NE.

Control values for STIs were obtained from 200 normal ambulatory subjects.11, 12

Control values for the 24-hour urine 17KS and 17OHCs were obtained from the 29 normal subjects used as controls for the E and NE excretion. The control values for the thyroid function test and plasma cortisol were obtained from the same normal subjects.

Control values for the glucose tolerance tests were obtained from 20 other ambulatory subjects (16 females and four males, mean age 28 ± 4 years) with no apparent disease who were within 10% of their ideal weight.

The QT interval before, during and after the treadmill exercise was compared with that in 25 normal subjects undergoing similar exercise testing.

Statistical analysis was performed using the t test and analysis of variance.

Results

All patients had normal left ventricular systolic function as measured by the STI and echocardiograms and normal left and right ventricular and left atrial sizes as determined by echocardiography. Electrocardiographically, seven patients were normal, eight had nonspecific ST- and T-wave changes, two had poor R-wave progression, one had a right intraventricular conduction defect, one had increased anterior forces and one had a short PR interval.

The 24-hour urinary excretion of E and NE shown in figure 1 was significantly higher (p < 0.001) in patients than in normal, ambulatory controls. In addition, combined 24-hour urinary E and NE excretion was significantly higher (p < 0.001) in the study patients than in 35 hospitalized patients used as controls (38.6 ± 4 vs 72 ± 3 µg). The 24-hour E and NE excretion was not significantly different in the study patients from day to day during the hospitalization period (43 ± 1.9 µg/g creatinine day 1, 42 ± 2.5 µg/g creatinine day 2, 44 ± 2 µg/g creatinine day 3).

FIGURE 1. Twenty-four-hour urinary epinephrine (E) and norepinephrine (NE) excretion. Patients with mitral valve prolapse syndrome (MVPS) had higher levels than normal controls.
The QSI was significantly shorter in patients with mitral valve prolapse compared with our normal value (529 ± 3.9 vs 548 ± 2 msec) (fig. 2).

Significant dysrhythmias were recorded in 15 patients. Frequent premature ventricular complexes (PVCs), i.e., more than 10 per minute, were present in 14 patients (uniform in 10 and multiform in four). Two PVCs in a row were recorded in four patients and three or more PVCs in a row were recorded in two patients. Ectopic atrial rhythm was recorded during ambulatory monitoring in one patient. Dysrhythmias were detected by ambulatory monitoring in all 15 patients, by isometric handgrip exercises in 10 patients, by treadmill exercise in nine patients and by resting ECG in only one patient (fig. 3).

The frequency of PVCs decreased during treadmill exercise compared with the preexercise levels, but increased significantly immediately after exercise (p < 0.01). In contrast, the number of PVCs increased significantly during isometric handgrip exercise and decreased significantly after exercise (p < 0.01, fig. 4).

Plasma E and NE increased significantly (p < 0.01) after exercise compared with preexercise levels. Moreover, the plasma E plus NE increase was greater (p < 0.01) in patients whose number of PVCs with exercise increased more than 10 per minute compared with patients in whom the frequency of PVCs remained relatively unchanged (fig. 5).

The QT interval in patients with mitral valve prolapse was identical to that in normal subjects before, during and after exercise.

The number of PVCs per hour paralleled urinary E plus NE excretion (fig. 6). At night, the number of PVCs and the catecholamine excretion both decreased significantly.

Figure 7 shows the glucose levels during the glucose tolerance test. Although patients with mitral valve prolapse had a normal response to oral glucose, plasma glucose levels were higher at 2 and 3 hours in patients than in controls.

The thyroid function tests were similar in patients with mitral valve prolapse and in the controls, respectively: T₄ 8.6 ± 0.8 vs 8.2 ± 0.9 μg/dl; T₃ resin uptake 0.9 ± 0.3 vs 0.85 ± 0.2 μg/dl; free thyroxin index 7.8 ± 0.4 vs 7.2 ± 0.3. The 24-hour urine 17KS and 17OHCS were also similar in mitral valve prolapse patients and in the controls, respectively: 17KS 8.2 ± 1 vs 9.6 ± 0.9 mg/g creatinine; 17OHCS 5.1 ± 1 vs 4.3 ± 0.7 mg/g creatinine. The diurnal rhythm of cortisol secretion was normal in the patients with mitral valve prolapse: 0600 hours 16.4 ± 1.8 μg/dl; 1200 hours 10 ± 0.6 μg/dl; 1800 hours 8.5 ± 1.5 μg/dl; 2400 hours 4.9 ± 0.7 μg/dl.

Discussion

If one accepts the premise that many patients with what is currently designated as the mitral valve prolapse syndrome were previously considered to have irritable heart (J.M. DaCosta, 1864), soldiers' heart (Thomas Lewis, James MacKenzie 1916–1940), systolic gallop sounds (W.P. Thompson, S. Levine,
1935), or neurocirculatory asthenia (P.D. White, M. Cohen, 1931–1972), then physicians have been attempting to unravel the bases for symptoms for more than a century. Throughout this earlier literature runs the suspicion that metabolic factors, autonomic dysfunction or sympathetic nervous system hyperactivity must play a role in the genesis of signs and symptoms in this disorder. In fact, our response to these earlier observations and suggestions prompted the present study.

The results of this study show that symptomatic patients with mitral valve prolapse have high adrenergic tone as manifested by the high catecholamines and shortening of the total electromechanical systole.

The mean 24-hour urinary catecholamine excretion was significantly greater in the symptomatic patients with mitral valve prolapse than in a group of normal, ambulatory volunteers and a group of hospitalized patients undergoing minimally stressful studies. The mean 24-hour catecholamine excretion in the study subjects was the same from day to day of the study, indicating that the findings are not the result of variations in the schedule of activity or stresses induced by the experiments. For individual patients, the day-to-day variation in catecholamine excretion was not greater than 10%.

A diurnal rhythm of E and NE excretion occurs in

**Figure 5.** Total plasma catecholamines — epinephrine plus norepinephrine (E + NE) — before and immediately after exercise. Plasma catecholamines increased significantly with exercise (panel A). However, plasma catecholamines increased significantly more in patients in whom the number of premature ventricular complexes (PVCs) with exercise increased more than 10 per minute compared with patients in whom the number of PVCs with exercise was relatively unchanged (panel B). MVPS = mitral valve prolapse syndrome.

**Figure 6.** Number of premature ventricular complexes (PVCs) per hour (upper panel) and the urinary epinephrine (E) plus norepinephrine (NE) excretion (lower panel). The frequency of PVCs and the urinary catecholamine excretion were parallel. At night, both the number of PVCs and the E + NE excretion decreased. MVPS = mitral valve prolapse syndrome.

**Figure 7.** Plasma glucose levels during the glucose tolerance test (n = 20). Patients with mitral valve prolapse (MVP) had normal response to oral glucose administration but higher glucose levels than the controls.
normal subjects: Catecholamine excretion is higher during the day and decreases with sleep.\textsuperscript{28} The same diurnal rhythm of catecholamine excretion was found in symptomatic patients with mitral valve prolapse in the present study.

The short QS\textsubscript{2}I in this group of patients provides additional evidence of increased adrenergic tone.\textsuperscript{14-17} Previous studies demonstrated that subjects with increased urinary catecholamine excretion have a short QS\textsubscript{2}I. In addition, there is an inverse relationship between shortening of the QS\textsubscript{2}I and catecholamine excretion.\textsuperscript{14} Shortening of the QS\textsubscript{2}I caused by infusion of epinephrine or isoproterenol is directly related to the amount of drug administered in normal subjects.\textsuperscript{29, 30}

The oral glucose tolerance test results are also compatible with higher catecholamine activity. Mean blood glucose values are significantly greater in mitral valve prolapse patients than in our normal controls. Catecholamine effects on the pancreatic $\beta$ cell are primarily $\alpha$-adrenergic inhibition of insulin release. In contrast, the effects of catecholamine on the pancreatic $\alpha$ cell are primarily $\beta$-adrenergic augmentation of glucagon secretion. Accordingly, catecholamine excess is ordinarily associated with increased glucose concentrations as a result of decreased insulin and augmented glucagon secretion.\textsuperscript{31, 32}

According to the receptor theory, the number of active adrenergic receptors should be low in the presence of high catecholamines and the response to catecholamines should be diminished.\textsuperscript{33-38} Indeed, in patients with congestive heart failure who have high plasma catecholamine concentrations, the number of $\beta$-adrenergic receptors is low.\textsuperscript{39} This would explain why patients with congestive heart failure have a normal QS\textsubscript{2}I despite the high catecholamine levels.\textsuperscript{11} The shorter QS\textsubscript{2}I and the high glucose blood levels in our patients with mitral valve prolapse would suggest normal $\beta$-receptor function. If $\beta$-receptor function is normal, then either a defective autoregulatory mechanism at the catecholamine receptor level or transient increases of plasma catecholamines during the day may be responsible. The observation that the number of active $\beta$-adrenergic receptors remains unchanged during isoproterenol infusions given over short periods supports the latter possibility. The number of adrenergic receptors appears to decrease with longer periods of isoproterenol administration.\textsuperscript{55} We have shown that the response to isoproterenol on QS\textsubscript{2}I, heart rate and blood pressure does not change significantly in normal subjects given the drug over 10 minutes on multiple occasions during a 24-hour period.\textsuperscript{16} The significant decrease in urinary epinephrine excretion at night further supports our hypothesis that the increase in total catecholamines in our patients is due to multiple, transient, secretory catecholamine peaks during the day.

The cause of adrenergic hyperactivity in these patients is not clear. The patients in the present study were symptomatic, with auscultatory and echocardiographic mitral valve prolapse. Hospitalized patients without mitral valve prolapse had lower catecholamine levels than mitral valve prolapse patients.\textsuperscript{15, 17, 38} Left ventricular function as determined by echocardiograms and STIs was normal in the symptomatic mitral valve prolapse patients, so the excessive sympathetic stimulation was not a compensatory mechanism to left ventricular dysfunction. Thyroid function and plasma cortisol concentrations were normal, so the increased adrenergic tone was not due to thyroid or adrenal cortical dysfunction. Hypoglycemia, which has been shown to be associated with high plasma catecholamine concentrations, was not found in patients in this study.\textsuperscript{31, 32}

The frequency of PVCs and the elevation of plasma and urinary catecholamines were parallel both during the day and in response to exercise testing in this study. Thus, at night, the urinary E and NE excretion and the frequency of PVCs decreased significantly. Likewise, plasma E plus NE increased significantly more in patients in whom the increase of PVCs was greater than 10 per minute than in patients in whom the frequency of PVCs remained relatively unchanged. The precise relationship between the frequency of PVCs and catecholamine levels is unclear.

In the majority of patients, PVCs were initiated with isometric exercise. Thus, handgrip exercise may provide a simple technique to detect ventricular dysrhythmias in patients with mitral valve prolapse. The increase in peripheral resistance with isometric exercise may in part be responsible for the recorded dysrhythmias. Previous studies have shown that infusion of phénylprènilne in patients with mitral valve prolapse produced symptoms associated with increased arterial pressure.\textsuperscript{39}

The pathogenesis of multiple symptoms, such as awareness of rapid heart beat, shortness of breath, left breast or chest aching, palpitations, syncope or presyncope, morning fatigue and easy exhaustion, is not understood fully. Stress-mediated or stress-activated biochemical mechanisms that increase adrenergic tone may provide a basis for multiple symptoms. With better understanding of the central and peripheral biochemistry of anxiety and stress, the relationship of symptoms in mitral valve prolapse to anxiety and tension will become clearer.\textsuperscript{40}

In summary, symptomatic patients with mitral valve prolapse have high adrenergic tone. Adrenergic hyperactivity may be responsible for or contribute to the multiple symptoms and clinical manifestations in symptomatic patients with mitral valve prolapse.

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Metabolic studies in mitral valve prolapse syndrome. A neuroendocrine--cardiovascular process.
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Circulation. 1980;61:1200-1205
doi: 10.1161/01.CIR.61.6.1200

Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0009-7322. Online ISSN: 1524-4539

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