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Mitral Valve Prolapse Syndrome: The Effect of Adrenergic Stimulation

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Previous studies demonstrating increased adrenergic tone in symptomatic patients with mitral valve prolapse prompted a study of the response of symptomatic patients with mitral valve prolapse to adrenergic stimulation. Sixteen such patients had plasma catecholamines and 24 hour urinary epinephrine plus norepinephrine values that were greater than those of control subjects (473.3 ± 92.8 pg/ml versus 292 ± 15 and 44.7 ± 2.3 μg/g creatinine versus 29.8 ± 2.3; $p < 0.01$ and < 0.001, respectively). Twenty-four hour urinary sodium was lower in the patient group than in the control group (75 ± 7.4 versus 141 ± 11 mEq; $p < 0.01$), with an inverse relation between urinary sodium and norephinephrine in the patient group ($r = -0.78$) but not in the control group.

Isoproterenol infusions, 0.5, 1.0 and 2.0 μg/min for 6 minutes, produced a dose-related, greater increase in heart rate in the mitral valve prolapse group than in the control group (16.1 ± 2.3 versus 10 ± 2; 31.8 ± 3.5 versus 19.6 ± 3; 48 ± 4.1 versus 27 ± 3; $p < 0.01$ with 0.5, 1.0 and 2.0 μg, respectively). The greater increase in heart rate resulted in a significantly shorter diastolic time in the patient group than in the control group (26.4 ± 2 s/min versus 30.6 ± 2; 27 ± 1.5 versus 30.6 ± 2; 26.6 ± 2 versus 30.9 ± 2; $p < 0.01$ with 0.5, 1.0 and 2.0 μg, respectively). The QT interval was 25 ms shorter than electromechanical systole (QS_2) in the normal group and 26.5 ms shorter than QS_2 in the mitral valve prolapse group at rest; during isoproterenol infusion QT-QS_2 values were different in the mitral valve prolapse and control groups (3.3 ± 3 versus −7.0 ± 3; 31.9 ± 2.8 versus 10 ± 4; 52 ± 9.2 versus 29 ± 8; $p < 0.01$ with 0.5, 1.0 and 2.0 μg/min, respectively). Isoproterenol infusion also reproduced symptoms on a dose-related basis in 14 patients with mitral valve prolapse but not in control subjects (excluding palpitation).

Symptomatic patients with mitral valve prolapse and high rest values of catecholamines were hypersensitive to isoproterenol infusion, suggesting that some of the symptoms are catecholamine-related or mediated.

Symptomatic patients with mitral valve prolapse, currently referred to as the mitral valve prolapse syndrome, may present with anxiety, tachycardia, neurasthenia, arrhythmias, chest pain and posture-related phenomena (1–8). The autonomic nervous system has long been postulated as a potential source for these symptoms. Recent evidence (8–12) suggests that autonomic dysfunction, a hyperadrenergic state, or combinations thereof, associated with or occurring in the presence of mitral valve prolapse are a potential explanation for the diversity of behavior and clinical manifestations in the mitral valve prolapse syndrome.

We consider the mitral valve prolapse syndrome to be a constitutional neuroendocrine-cardiovascular process. Partly as a result of our earlier studies (10) showing that patients with this syndrome had high rest adrenergic activity, studies by other investigators (8,11,12) who presented evidence of autonomic dysfunction in patients with the mitral valve prolapse syndrome and, in particular, the many clinical observations during the past 120 years suggesting that individuals with irritable heart, soldier's heart and neurocirculatory asthenia had disorders of the sympathetic nervous system as a basis for their symptoms (1), the present study was undertaken to investigate the effect of adrenergic stimulation in symptomatic patients with mitral valve prolapse.

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Methods

Study patients. Sixteen symptomatic patients, 12 women with an age range of 21 to 54 years (mean ± standard deviation 35 ± 10.5) and 4 men ranging in age from 32 to 41 years (mean 38.5 ± 2.65) with auscultatory, phonocardiographic and echocardiographic findings of mitral valve prolapse were studied (2–5,13–15). Symptoms included chest pain (11 patients), palpitations, or irregular beats (10 patients), fatigue (8 patients), dyspnea (6 patients) and dizziness (3 patients). Auscultatory findings included a mid-systolic click and late systolic murmur in 13 patients and a mid-systolic click in 3 patients (4). Five of the patients participated in our previous study (10). Informed written consent was obtained from each patient according to a protocol approved by the Institutional Human Research Committee.

Protocol. The patients were admitted to the Clinical Research Center to standardize the environmental stimulation and placed on a caffeine-free, ad lib sodium diet. Medications were discontinued at least 1 week (beta-blocking agents at least 3 weeks) before the study. During hospitalization, the following procedures were performed:

Day 1. Epinephrine, norephinephrine and sodium were measured in a 24 hour urine specimen.

Day 2. Twenty-four hour urinary epinephrine, norepinephrine and sodium measurements were repeated. A phonocardiogram, systolic time interval determinations and M-mode echocardiogram were performed between 10:00 and 11:00 a.m. Serial isoproterenol infusions were performed between 12:00 and 1:00 p.m. A maximal treadmill exercise test was performed between 2:00 and 3:00 p.m. Forty-five to 60 minutes before the exercise, a heparinized needle was inserted in a forearm vein. After the patient had been supine for 30 minutes, blood was drawn for the preexercise plasma epinephrine, norepinephrine and total plasma catecholamine measurements. The patient then completed the exercise protocol. Immediately thereafter, with the patient again supine, blood was drawn for a postexercise plasma epinephrine, norepinephrine and total plasma catecholamine determination.

Day 3. Twenty-four hour urinary epinephrine, norepinephrine and sodium measurements were repeated.

Day 4. Twenty-four hour urinary epinephrine, norepinephrine and sodium measurements were repeated. In addition, 24 hour ambulatory monitoring was performed.

Systolic time intervals and echocardiograms were obtained using standard techniques (13–18).

Measurements. The duration of electrical systole (QT) and electromechanical systole (QS_2) was measured from the simultaneous recordings of the electrocardiogram and phonocardiogram at a paper speed of 100 mm/s. The QS_2 interval was measured from the onset of ventricular depolarization to the first high frequency vibration of the aortic component of the second heart sound. The QT interval was measured from the beginning of the Q wave to the end of the T wave. In rare instances when the end of the T wave was not precise, the end of the T wave was taken at the point where a line of most rapid descent of the T wave transected the baseline. At least 10 cardiac cycles were averaged to obtain the QS_2 and QT intervals (19). Diastolic time was measured from the cardiac cycle length (RR), subtracting the total electromechanical systolic time (QS_2) (20).

Maximal treadmill exercise testing was perfomed according to the Bruce protocol (21,22). Heart rate was increased by at least 100% in all patients during exercise. Twenty-four ambulatory electrocardiographic recordings were obtained with a portable cassette tape (Avionics model 600). The data were analyzed by playback (Avionics model 445) as described previously (22).

Urinary epinephrine and norepinephrine were measured fluorometrically (23). The interassay coefficient of variation was 13.4% for epinephrine, 12.8% for norepinephrine and 10.7% for total catecholamines. Plasma catecholamine measurements were performed according to the method of Passon using a single isotope assay (24). The interassay coefficient of variation was 12.6%. Urinary creatinine measured by the Jaffee reaction had a coefficient of variation of 2.2% (25).

Isoproterenol infusion protocol. After 30 minutes of recumbent rest, normal saline solution was infused for 30 minutes. Then 6 minute isoproterenol infusions of 0.5, 1.0 and 2.0 μg/min were alternated with normal saline solution infusions using a Harvard infusion pump. This duration of isoproterenol infusion was based on a previous study (26) in which serial measurements helped establish that a steady state is reached after 6 minutes of isoproterenol infusion. Changes in heart rate, blood pressure, relation between QT and QS_2 intervals and diastolic time were analyzed before and during each isoproterenol infusion; the patient's symptoms were recorded for each infusion.

Control groups. Control values for 24 hour urinary epinephrine, norepinephrine and sodium excretion levels were obtained from 29 normal ambulatory subjects (24 women and 5 men, mean age 32.1 ± 4 years) in no obvious stress (10). In addition, 35 hospitalized patients (23 women and 12 men, mean age 39 ± 6 years) with normal cardiovascular function undergoing minimally stressful diagnostic studies were used as control subjects for epinephrine and norepinephrine determinations (10). Control values for plasma epinephrine and norepinephrine were obtained from 30 normal ambulatory subjects. The ages of control patients were comparable with those of patients with mitral valve prolapse syndrome. Postexercise values were obtained with maximal treadmill exercise. Heart rate was increased by at least 100% in all subjects. Control values for changes due to isoproterenol infusion were obtained from 12 normal volunteers without cardiovascular disease and no obvious stress in whom

JACC Vol 2, No. 4
October 1983.638–44

isoproterenol infusions were performed during their admission in the Clinical Research Center for 2 days.

Statistical evaluation was performed using the Student's *t* test and analysis of variance.

Results

Noninvasive cardiac tests. All patients had normal left ventricular systolic function as measured by systolic time intervals and echocardiography, and normal left and right ventricular and left atrial sizes as determined by echocardiography. Six patients had a normal electrocardiogram, six had nonspecific ST and T wave changes, two had right bundle branch block, one had increased anterior forces and one had premature ventricular beats. During the 24 hour ambulatory monitoring period, frequent premature ventricular beats (> 10/min) were recorded in five patients, occasional premature ventricular beats were recorded in two patients and atrial tachycardia was recorded in one patient. In two patients, inappropriate sinus tachycardia (140 to 150 beats/min) was recorded with minimal physical activity.

Urinary and plasma epinephrine plus norepinephrine. The 24 hour urinary excretion of epinephrine, norepinephrine and epinephrine plus norepinephrine were significantly higher in patients than in normal ambulatory control subjects (44.7 ± 2.3 μg/g creatinine versus 29.8 ± 2.3 for combined epinephrine plus norepinephrine) (Fig. 1). In addition, combined 24 hour urinary epinephrine and norepinephrine excretion was significantly higher (probability [p] < 0.001) in the study patients than in the 35 hospitalized patients used as control subjects (44.7 ± 2.3 versus 31.2 ± 2 μg/g creatinine). The 24 hour epinephrine, norepinephrine and epinephrine plus norepinephrine excretion measurements were not significantly different in the study patients from day to day during the hospitalization period.

Plasma epinephrine and norepinephrine and total plasma catecholamines before exercise were significantly higher in symptomatic patients with mitral valve prolapse compared with normal control subjects (Fig. 2). These values did not differ immediately after exercise in the two groups. Increased 24 hour urinary epinephrine and norepinephrine excretion and high plasma catecholamines have been reported previously from this institution in another separate study (10) involving 20 symptomatic patients with mitral valve prolapse.

Urinary sodium excretion. Twenty-four hour urinary sodium excretion was lower in patients with mitral valve prolapse compared with control subjects (75 ± 7.4 versus 141 ± 11 mEq, $p < 0.01$). There was an inverse correlation between urinary norepinephrine and urinary sodium excretion for patients with mitral valve prolapse ($r = -0.78$) but not for control subjects ($r = -0.05$) (Fig. 3). The 24 hour sodium excretion was not significantly different in the study patients from day to day during the hospitalization period. There was no relation between urinary epinephrine and urinary sodium excretion, and plasma norepinephrine and urinary sodium excretion in patients with mitral valve prolapse.

Isoproterenol Infusions

Heart rate and pulse pressure (Fig. 4). Baseline heart rate and pulse pressure measurements were not significantly different in symptomatic patients with mitral valve prolapse compared with control subjects (74 ± 2.6 versus 71 ± 5 beats/min and 49.1 ± 2.2 versus 53 ± 3 mm Hg, respectively). During isoproterenol infusion, the increase in heart rate and pulse pressure was dose-related. The increase in heart rate during isoproterenol infusion was significantly greater in symptomatic patients with mitral valve prolapse compared with normal control subjects, whereas changes in

Figure 1. Twenty-four hour urinary epinephrine (E), norepinephrine (NE) and epinephrine plus norepinephrine excretion. Patients with mitral valve prolapse syndrome (MVPS) had higher levels than did normal control subjects.

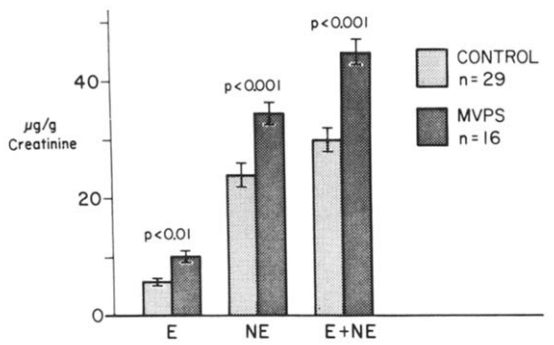
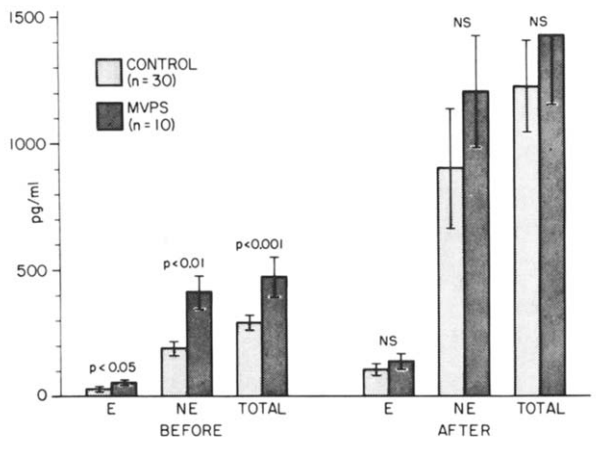


Figure 2. Plasma epinephrine (E), norepinephrine (NE) and total plasma catecholamines before exercise were significantly higher in patients with mitral valve prolapse syndrome (MVPS) compared with control subjects but were not different immediately after exercise.



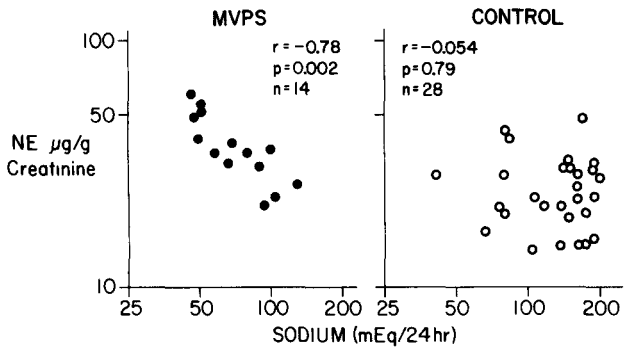


Figure 3. An inverse relation is present between 24 hour urinary norepinephrine (NE) and sodium (Na^+) excretion in patients with the mitral valve prolapse syndrome (MVPS) but not in control subjects.

pulse pressure during isoproterenol infusion were not significantly different.

QT-QS_2 relation (Fig. 4). Changes in QT-QS_2 relation during isoproterenol infusion were dose-related. Before isoproterenol infusion, the QS_2 interval was greater than the QT interval. During an infusion of 0.5 μg/min, the QS_2 interval was almost equal to the QT interval; during a 1.0 μg/min infusion, it was significantly shorter than the QT interval ($p < 0.01$) (QT prolongation relative to QS_2); and during a 2.0 μg/min isoproterenol infusion, the QT prolongation relative to QS_2 was even greater ($p < 0.01$). QT-QS_2 values were similar in both groups before isoproterenol infusion (-26.5 ± 2.9 versus -25 ± 3). However, during isoproterenol infusion, QT-QS_2 differences were significantly different in patients with mitral valve prolapse compared with control subjects.

The duration of diastolic time before and during each isoproterenol infusion in symptomatic patients with mitral valve prolapse and in control subjects is shown in Figure 5. Before isoproterenol infusion, the diastolic time per beat and per minute was the same in patients with mitral valve prolapse and control subjects. Diastolic time per beat and per minute decreased significantly in both groups ($p < 0.05$) during isoproterenol infusion. However, the decrease in diastolic time with each isoproterenol infusion was significantly greater in the patients than in the control subjects.

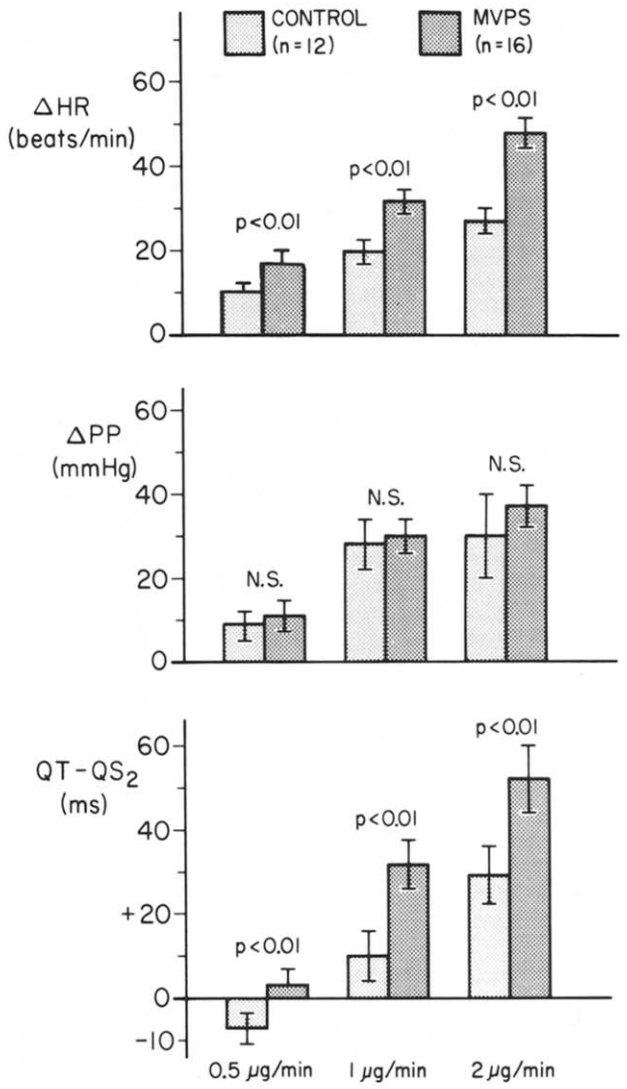
Symptoms. Isoproterenol infusions reproduced symptoms in 14 of 16 symptomatic patients with mitral valve prolapse. Infusion of saline solution did not reproduce the symptoms. All the symptoms produced by isoproterenol disappeared during saline infusion. Patients usually were not aware if saline solution or isoproterenol was infused.

Symptom reproduction during isoproterenol infusion was dose-related. Three of 16 patients developed symptoms with a 0.5 μg/min infusion, 5 of 13 developed symptoms with a 1.0 μg/min infusion and 9 of 11 developed symptoms with a 2.0 μg/min infusion. Seven patients experienced chest pain, six patients became extremely fatigued during and for up to 60 minutes after the infusion, six experienced dyspnea, four became dizzy, two felt numbness and two had a panic attack. Hyperventilation was observed in only two of the patients. Four patients had cool hands during isoproterenol infusion and *one each* had ectopic atrial rhythm and junctional rhythm. None of the control patients developed symptoms excluding palpitation during isoproterenol infusion.

Discussion

Increased adrenergic activity. If one accepts the premise that many patients with mitral valve prolapse syndrome were previously considered to have irritable heart, soldier's

Figure 4. Effect of isoproterenol infusions on heart rate (HR), pulse pressure (PP) and QT-QS_2 relation. Changes (△) in heart rate and QT-QS_2 with each isoproterenol infusion were significantly greater in patients with mitral valve prolapse syndrome (MVPS) compared with control subjects; changes in pulse pressure were not different in patients with mitral valve prolapse compared with control subjects. N.S. = not significant.



JACC Vol 2, No 4
October 1983 638–44

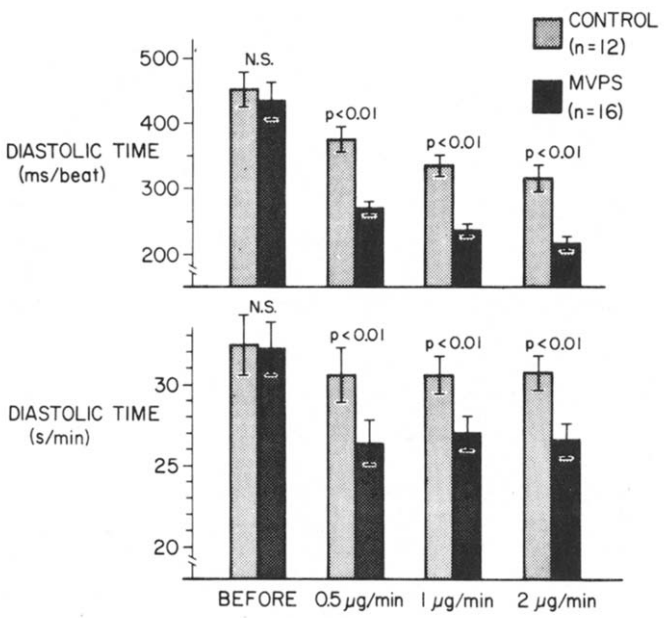


Figure 5. Effect of isoproterenol infusions on diastolic time per beat (**upper panel**) and per minute (**lower panel**). The decrease in diastolic time with each isoproterenol infusion was significantly greater in patients with mitral valve prolapse syndrome (MVPS) than in control subjects.

heart, systolic gallop sounds or neurocirculatory asthenia, then physicians have been attempting to unravel the basis for symptoms for more than a century (1). Throughout the earlier studies (10,12), metabolic factors, autonomic dysfunction and sympathetic nervous system hyperactivity were all considered as possible causes or mechanisms for symptoms in this disorder.

Fraser and Wilson (27), working in the Heart Section at the Military Hospital, Hampstead, England during World War I, investigated the sympathetic nervous system in the "irritable heart of soldiers" in order to better understand the mechanism by which symptoms were produced. Minute doses of intravenous adrenalin and apocodeine produced greater heart rate and blood pressure responses and symptoms in their patients with irritable hearts than in control subjects, which led to the conclusion that in some respects the sympathetic nervous system was "relatively unstable (in the irritable heart patients) in that it appears to be more susceptible to the stimulating and depressing influences respectively of these drugs" (27).

Peabody and his colleagues (28), at the U.S. Army General Hospital No. 9, Lakewood, New Jersey, evaluated the effects of the intramuscular injection of epinephrine in soldiers with irritable heart using the Goetsch test (28,29). A positive reaction after 0.5 cc of 1:1,000 epinephrine administration was described as "production of an early rise in the systolic blood pressure of greater than 10 mm Hg (10 to 50) or the pulse rate of over 10 or 15 points accompanied by the production of rather typical symptoms, such as flushing, sweating, increased vascular pulsation, increased tremor of the hands and often of the arms, restlessness and more or less marked general nervousness" (28). Sixty-five patients in the irritable heart group were compared with control subjects; 60% of the patients had a positive Goetsch test, with a doubtful or suggestive result in an additional 10%. A subgroup of 12 patients had electrocardiograms taken during the provocative test; 10 of these had symptoms (dizziness, blurred vision, palpitation and precordial pain) that "bore a close resemblance to the symptoms prominent in their histories." Peabody et al. (18) concluded "it is distinctly interesting, therefore, that so large a proportion should be hypersensitive to epinephrine, and one should at least consider carefully whether an unusually excitable sympathetic nervous system may not play a part in determining their condition."

The results of our present study show that symptomatic patients with mitral valve prolapse with high rest adrenergic tone have hypersensitivity to isoproterenol administration as manifested by dose-related reproduction of symptoms, greater heart rate response, shorter diastolic time and greater QT interval prolongation relative to QS_2 interval when compared with control subjects. Increased 24 hour urinary epinephrine and norpinephrine excretion and high plasma catecholamines in symptomatic patients with mitral valve prolapse have been reported previously from this and other institutions (9,10).

Adrenergic receptors. The precise explanation for hyperresponsiveness to adrenergic stimulation in our patients with mitral valve prolapse syndrome is not well understood. According to the receptor theory, the number of active adrenergic receptors should be low in the presence of high catecholamines, and the response to adrenergic stimulation should be diminished (26,30–33). The hyperresponse to isoproterenol infusion in our patients would suggest increased beta-receptor function. If beta-receptor function is increased, then either a defective autoregulatory mechanism at the catecholamine receptor level or transient increases of plasma catecholamines during the day may be responsible for this phenomenon. The observation that the number of active beta-adrenergic receptors increases with short duration (up to 60 minutes) of isoproterenol infusion (34) and our previous observation that the excretion of urinary epinephrine and norepinephrine decreases significantly during the night (10) support the hypothesis that symptomatic patients with mitral valve prolapse have frequent, transient and possibly inappropriate increases of catecholamines during the day with activity, postural changes and stressful situations. Thus, an inappropriate increase of endogenous catecholamines during isoproterenol infusion might be responsible for the hypersensitivity noted during isoproterenol infusions. Nevertheless, the precise catecholamine-receptor

inter-relation in symptomatic patients with mitral valve prolapse has yet to be defined.

Sodium excretion. Low sodium excretion in symptomatic patients with mitral valve prolapse has not been observed previously. Urinary sodium excretion appears to be inversely related to norepinephrine excretion (35–37). The low urinary sodium excretion in the present study may be secondary to preferential low sodium intake (38,39). Symptomatic patients with mitral valve prolapse may consume less sodium and thus excrete less sodium than the control subjects. Catecholamine levels may be influenced by the amount of sodium intake. The cause and effect basis for low sodium-high catecholamine excretion was not established, however, in the present study and obviously requires further evaluation.

Electrical systole-electromechanical systole relation. The duration of electrical systole (QT) in normal subjects is shorter (mean ± 1 standard deviation = − 26 ± 13 ms) and parallels the duration of electromechanical systole (QS_2) throughout the normal range of rest heart rate (40,41). The QT-QS_2 intervals represent a basic cardiac electrical-mechanical relation; synchrony or parallel behavior appears to be a normal phenomenon. Dyssynchrony of these intervals as a response to adrenergic stimulation in symptomatic patients with mitral valve prolapse is an interesting observation because this electrical-mechanical dyssynchrony may be related to the production or occurrence of arrhythmias. Animal studies by Brooks et al. (42) indicated that the autonomic nervous system exerted a substantial influence on the protective zone in the cardiac cycle, and that these effects were mediated largely by the action of catecholamines released at localized myocardial sites. Spontaneous transient appropriate or inappropriate increases in catecholamines during daily activities or stressful situations in patients with mitral valve prolapse syndrome may produce transient QT prolongation relative to the QS_2 interval. To further support this postulate, our earlier studies (10) showed that 24 hour catecholamine excretion and frequency of premature ventricular beats were parallel, and both decreased significantly at night ($p < 0.001$). Beta-adrenergic blockade has been shown to abolish QT prolongation relative to QS_2 produced by isoproterenol infusion in normal subjects (19). The potential role of beta-blockade in abolishing QT prolongation relative to QS_2 and ventricular irritability in symptomatic patients with mitral valve prolapse has yet to be defined.

Diastolic time. Diastolic time has a nonlinear relation with heart rate. Therefore, small changes in heart rate may result in significant changes in diastolic time (20). The diastolic time during isoproterenol infusion was significantly shorter in patients with mitral valve prolapse compared with control subjects. This was due to the greater increase in heart rate. These changes in diastolic time under certain circumstances may be of clinical significance because the greater proportion of coronary blood flow occurs in diastole and subendocardial flow is almost totally diastolic (43). A sudden significant decrease in diastolic time may result in subendocardial ischemia (44,45). Spontaneous or inappropriate sinus tachycardia in patients with mitral valve prolapse results in a significant decrease in diastolic time, which under certain conditions may produce subendocardial ischemia (46,47).

Mitral valve prolapse-mitral valve prolapse syndrome. The cause of adrenergic hyperactivity and hyperresponsiveness to adrenergic stimulation in symptomatic patients with mitral valve prolapse is not well understood. The relation or association between the anatomic entity (mitral valve prolapse) and the mitral valve prolapse syndrome (anatomic mitral valve prolapse and the symptom complex) requires further definition. An independent, biochemically-mediated anxiety state existing in an individual with the anatomic entity (mitral valve prolapse) is one potential explanation for the syndrome. Equally plausible is that the anatomic entity (mitral valve prolapse) is a specific marker in certain individuals for the constitutional, neuroendocrine-cardiovascular process that is currently designated as the mitral valve prolapse syndrome.

In conclusion, symptomatic patients with mitral valve prolapse and high rest adrenergic tone have hypersensitivity to isoproterenol infusion as manifested by reproduction of symptoms, greater heart rate response, shorter diastolic time and greater QT prolongation relative to the QS_2 interval compared with control subjects. Stress-mediated or activated biochemical mechanisms that alter adrenergic tone may provide a basis for the multiple symptoms in patients with mitral valve prolapse syndrome.

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