Case Presentation

A 29-year-old white woman (weight, 121 lb; height, 5 ft 6 in.) was referred to the Hypertension Unit of Massachusetts General Hospital in December 1984. She had been athletic and apparently in excellent health until September 1979 when she contracted an upper respiratory tract infection associated with wheezing. She was treated with prednisone for 5 days with resolution of the symptoms but later noted a progressive decline in her exercise tolerance with shortness of breath. She lost 15 to 20 lb over the next 2 to 3 months, and then in November 1979 she began experiencing episodes of “faintness,” initially every 1 to 2 weeks but later at least daily. The episodes frequently occurred approximately 20 minutes after getting up from the supine position, at any time of the day, and were not related to eating. They consisted of a feeling of sudden fatigue followed by dizziness, pallor, and diaphoresis without nausea or vomiting. There were no premonitory signs or symptoms, no associated flushing, rhinorrhea, diarrhea, pruritus, palpitations, headaches, tremor, vertigo, respiratory difficulties, chest pain, urinary or fecal incontinence, paresthesias, or abdominal pain. The attacks occurred more commonly when she was physically fatigued, particularly after strenuous activity such as running or playing racquetball. They usually lasted from 5 to 15 minutes, although frequently she felt “washed out” for up to an hour or 2 after the attack.

Physical examination findings were unremarkable apart from a mild pectus excavatum and a soft systolic ejection murmur. She appeared to be a very pleasant, sensible, and intelligent person.

Results of initial investigations following the onset of her illness, including a chest roentgenogram and exercise tolerance test, were normal. In March 1980 she was admitted to her local hospital after a syncopal episode. She was placed on an electrocardiographic monitor, and during a subsequent episode, marked bradycardia to less than 30 beats/min was noted, leading to the insertion of a pacemaker. The syncopal spells ceased after implantation of the pacemaker, but the attacks of lightheadedness and fatigue continued. Mitral valve prolapse (MVP) was diagnosed on the basis of an echocardiogram. Other investigations included a blood count, sedimentation rate, biochemistries, urinalysis, serum B12 level, 5-hour glucose tolerance test, blood cultures, protein electrophoresis, a ventilation/perfusion scan, and 24-hour urinary excretion of vanillylmandelic acid and metanephrines, the results of which were all within normal limits. Respiratory function tests revealed mild reductions in functional residual capacity and residual volume with normal arterial oxygen tension at rest and with exercise.
Further evaluations were performed during a subsequent admission to another hospital in June 1980. Results of a repeat exercise tolerance test, Holter monitor, pulmonary function tests, and hemodynamic responses to 30-degree head-up tilting and carotid sinus pressure were all normal. Before this admission she had been treated with propranolol, 120 mg q.d., and fludrocortisone acetate (Florinef), 0.3 mg q.d., without improvement. The propranolol therapy was stopped at the time of this admission. Subsequently, therapy with a variety of anticholinergic drugs, β-blockers, metoclopramide, α-agonists, and salt tablets was tried without success.

In 1983 she had a normal pregnancy and gave birth to a healthy male infant. The attacks persisted unchanged throughout the pregnancy.

In February 1985 she underwent an exercise stress test with cardiopulmonary and biochemical evaluations (Table 1, Figure 1). Upright bicycle ergometry was performed to a work load of 100 W using a ramp protocol. The test was stopped because of leg fatigue. A first-pass radionuclide distribution study done at rest and at peak exercise indicated essentially normal left ventricular function. The heart rate increased from 90 at rest to 175 beats/min at peak exercise, and the blood pressure increased from 160/90 to 215/125 mm Hg. Six minutes after exercise she complained of feeling severely lightheaded and was noted to be markedly pale. The blood pressure fell to 80/40 but rose promptly to 125/65 mm Hg when she was placed in the supine position. She did not lose consciousness and was able to ambulate normally after resting for 30 minutes. Blood gas analysis revealed a mixed metabolic acidosis and respiratory alkalosis at rest, which became a compensated metabolic acidosis during exercise. Metabolic acidosis developed after exercise; the pH fell to 7.22, and the lactate rose to 9 mmol/L. The biochemical and neuroendocrine responses to exercise

**Table 1. Hemodynamic and Metabolic Data of Exercise Study I, February 1985**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Rest</th>
<th>Peak Exercise</th>
<th>Postexercise (min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>VO2 (ml·kg⁻¹·min⁻¹)</td>
<td>5.8</td>
<td>19.6</td>
<td>—</td>
</tr>
<tr>
<td>Work load (W)</td>
<td>0</td>
<td>100</td>
<td>0</td>
</tr>
<tr>
<td>Heart rate (beats/min)</td>
<td>90</td>
<td>175</td>
<td>145</td>
</tr>
<tr>
<td>MAP (mm Hg)</td>
<td>113</td>
<td>155</td>
<td>95</td>
</tr>
<tr>
<td>LVEF (%)</td>
<td>65</td>
<td>63</td>
<td>—</td>
</tr>
<tr>
<td>pHi</td>
<td>7.36</td>
<td>7.31</td>
<td>7.24</td>
</tr>
<tr>
<td>HLa (mmol/L)</td>
<td>1.2</td>
<td>5.0</td>
<td>9.8</td>
</tr>
<tr>
<td>HCO3 (mEq/L)</td>
<td>18.6</td>
<td>17.0</td>
<td>14.5</td>
</tr>
</tbody>
</table>

VO2 = systemic oxygen uptake; MAP = mean arterial pressure; LVEF = left ventricular ejection fraction (from radionuclide ventriculography); HLa = plasma lactate concentration.

**Figure 1.** Biochemical and neuroendocrine responses to two exercise stress tests (Study I and II). Blood samples for the various determinations were obtained from an arterial catheter at rest and at peak exercise, while the patient was sitting on the bicycle ergometer, and at the time of the syncopal episodes, while she was standing. See Case Presentation for details. NE = norepinephrine; EPI = epinephrine; PRA = plasma renin activity; AG = anion gap.
are shown in Figure 1 (Study I). With exercise the serum K⁺ increased by 2.0 mEq/L to 6.1 mEq/L but fell to 3.8 mEq/L at the time of her syncopal episode. The HCO₃⁻, which fell by 4 mEq/L to 15 mEq/L at the time of peak exercise, fell further to 11 mEq/L at the time of the syncopal episode. The plasma catecholamines increased with exercise but fell toward the resting values after exercise, despite a marked fall in arterial pressure. Respiratory gas analysis indicated exercise tolerance at the lower normal limit with a maximal oxygen uptake of 1.54 L/min or 28 ml·kg⁻¹·min⁻¹.

In April 1985 the exercise stress test was repeated. On this occasion a pulmonary artery catheter was inserted for continuous monitoring of pressures and measurement of cardiac output. Upright bicycle ergometry was performed for 7 minutes to a work load of 87.5 W (Table 2). The heart rate increased from 130 at rest to 190 beats/min at peak exercise, and the blood pressure increased from 105/65 to 140/80 mm Hg. Two minutes after exercise, she again experienced severe lightheadness and the blood pressure fell to 90/55 mm Hg but rose promptly when she was placed in the supine position. Cardiac output rose with exercise, from 4.9 to 11.5 L/min, but fell to 8.6 L/min at the time of the syncopal symptoms. The calculated total peripheral resistance fell progressively with exercise by 722 dyn·sec·cm⁻⁵ from 1592 and fell further after exercise to 775 dyn·sec·cm⁻⁵. Similar, though less marked changes in the blood gases were noted with this study. A marked metabolic acidosis occurred with exercise, which became more severe after exercise. The biochemical and neuroendocrine responses to exercise (see Figure 1, Study II) were also qualitatively similar with this exercise test. Respiratory gas analysis demonstrated lower exercise tolerance on this occasion with a maximal oxygen uptake of 1.2 L/min (59% of predicted) and an anaerobic threshold of 0.68 L/min.

Other measurements included plasma acetoacetate, which was negative, and a plasma β-hydroxybutyrate level of 2.1 mM (normal, 2.2 mM) after a 48-hour fast. Serum carnitine levels, performed because a recent report suggested low levels in patients with MVP and dysautonomia, were normal on several occasions. The urinary pH of an early morning specimen was 5.4. Analysis of a spot urine sample obtained on a different occasion was negative for organic acids.

In June 1985 a repeat echocardiogram was obtained, with a two-dimensional study. A false tendon was observed in the left ventricular cavity, but the examination results were otherwise normal. There was no evidence of MVP. Plasma volume, determined by the dye dilution technique, was low at 2750 ml (82% of predicted value).

The patient currently is being treated with sodium bicarbonate tablets, 1.8 g/day, and metoclopramide, 60 mg/day, with some improvement in her symptoms.

Case Discussion

This is an intriguing case history of a young woman who was in excellent health until 6 years ago. An upper respiratory tract infection was then treated with a short course of prednisone. She lost 15 lb and noticed a decrease in exercise tolerance, increased shortness of breath, and episodes of faintness in the upright position, particularly following physical activity. Syncope in March 1980 prompted the implantation of a cardiac pacemaker. There has been no further syncope, but postexercise hypotension has been recorded. Daily episodes of faintness, dizziness, pallor, and diaphoresis have persisted. Therapy with a sodium supplement and a dopaminergic antagonist has been only marginally successful.

Direct observation and quantitative data document...
Causes of Recurrent Episodic Arterial Hypotension

Causes of recurrent episodes of arterial hypotension include cardiac dysrhythmias, bradyarrhythmias, tachyarrhythmias, and intermittent atrioventricular conduction blocks can cause reductions in cardiac output of sufficient magnitude to impair tissue perfusion.

There is no evidence that the patient had primary dysrhythmias.

Mechanical obstruction of blood flow may cause global cerebral ischemia with syncope. Such conditions include valvular aortic pulmonary stenosis, idiopathic hypertrophic subaortic stenosis, atrial myxoma, and pulmonary embolic or vascular disease with pulmonary hypertension. These diagnoses have also been effectively ruled out.

A wide range of emotional and somatic afferent stimuli can precipitate vasodepressor, or vasovagal, syncope. Neither term is strictly accurate. The cardiovascular response includes both bradycardia and vasodilatation, and impulse flow is altered in both the parasympathetic and sympathetic systems. The typical psychological circumstances involve a perception of injury, actual or symbolic, that the victim feels that he or she should be able to face without fear. Obligation to submit to painful or unfamiliar diagnostic or therapeutic procedures is a prime example. Included among the somatic mechanisms are carotid sinus hypersensitivity and afferent impulses from the ear, mouth, larynx, and pharynx (e.g., in glossopharyngeal neuralgia). Simple swallowing (deglutition syncope) may precipitate vasodepressor syncope in some individuals.

The hemodynamic events have been studied extensively. A typical sequence includes an initial phase with moderate tachycardia followed by a marked fall in heart rate and arterial pressure. There is little or no increase in plasma norepinephrine in response to the hypotension. The cutaneous circulation usually is vasoconstricted, but there is a large decrease in systemic resistance caused by vasodilatation in skeletal muscle. The efferent mechanism — β-adrenergic or cholinergic vasodilatation versus α-adrenergic inhibition — has been controversial. However, recent data obtained by direct nerve recording techniques have documented a strong inhibition of impulse traffic in the α-adrenergic vasoconstrictor fibers supplying skeletal muscle. The depressor phase of the response has many features in common with orthostatic hypotension that progresses to syncope.

Orthostatic or postural hypotension may be defined in a general sense as the inability to maintain adequate arterial pressure and tissue perfusion in the upright position. Many different conditions are associated

<table>
<thead>
<tr>
<th>Variable</th>
<th>Preexercise control</th>
<th>Postexercise (min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart rate (beats/min)</td>
<td>60</td>
<td>105*</td>
</tr>
<tr>
<td>Mean arterial pressure (mm Hg)</td>
<td>94</td>
<td>90*</td>
</tr>
<tr>
<td>Central venous pressure (mm Hg)</td>
<td>6</td>
<td>4*</td>
</tr>
<tr>
<td>[HCO₃] (mmol/L)</td>
<td>24</td>
<td>15*</td>
</tr>
<tr>
<td>Plasma volume (%)</td>
<td>100</td>
<td>84*</td>
</tr>
</tbody>
</table>

* indicates p < 0.05, compared with control values.
Heart rate and contractility and vasoconstriction, with increases afferent nerve activity and releases inhibitory adrenergic sympathetic activity result in increased sympathetic drive and increased \( \alpha \)-adrenergic and \( \beta \)-activity in the cardiovascular centers. Release of para-spinal cord pathways. A fall in arterial pressure decreases venous return, ventricles, arterioles, and veins by vagal and tic, and cardiopulmonary mechanoreceptors are involved.14 These receptors respond to deformation accomplished by neural mechanisms. Carotid, aortic, and cardiopulmonary mechanoreceptors are involved.14 These receptors respond to deformation (e.g., stretch caused by increased transmural pressure). Afferent impulses travel with the vagus and the glossopharyngeal nerve to the cardiovascular centers. Efferent fibers reach the sinus and atrioventricular nodes, ventricles, arterioles, and veins by vagal and spinal cord pathways. A fall in arterial pressure decreases afferent nerve activity and releases inhibitory activity in the cardiovascular centers. Release of parasympathetic drive and increased \( \alpha \)-adrenergic and \( \beta \)-adrenergic sympathetic activity result in increased heart rate and contractility and vasoconstriction, with reduced blood flow to the skin and skeletal muscle, the kidney, and the splanchnic region. The renin-angio-
tensin system is activated, and plasma levels of atrial natriuretic peptide decrease while arginine vasopressor levels increase.

The sympathetic activation during orthostatic stress is clearly nonuniform. Vasoconstriction is manifest before heart rate or contractility is measurably affected. Forearm flow and conductance decrease markedly before splanchnic flow is affected. The differential effects on limb flow and splanchnic flow probably are related to a predominance of low pressure baroreceptor effects at mild degrees of orthostatic stress and increasing effects on the carotid sinus with progressive pooling and decreasing arterial pressures and pulse pressure. Nonuniform regional vasoconstrictor responses may also be related to differential effects of changes in the impulse flow from ventricular and arterial baroreceptors and to unequal levels of basal vasoconstrictor activity.

Local reflex mechanisms may contribute to the response to orthostatic stress. Henriksen and Sejrsen16, 17 have demonstrated vasoconstriction with decreased limb blood flow in response to local venous distention. Blocking studies indicated that the vasoconstriction was mediated by a local (axonal) sympathetic reflex mechanism. Activation of venous afferent fibers producing reflex-induced leg muscle activity may also counteract postural pooling.18, 19

### Normal Response to Orthostatic Stress

The normal physiological adjustments to changing from a supine to an upright position have recently been reviewed by Ziegler13 and Blomqvist and Stone.14 Venous volume of the legs increases by about 500 ml. Most of the volume translocated from the thoracic area is contained in the deep intramuscular and intermuscular leg veins. Additional volume, probably 200 to 300 ml, is transferred to the veins in the buttocks and the pelvic area. Reflex-induced vasoconstriction also produces a passive decrease in splanchnic venous volume. The altered blood volume distribution causes a significant decrease in cardiac filling pressures and a negative Starling effect (Table 4).15 Stroke volume decreases by about one third. In the absence of any reflex adjustments, this change would cause an equally large decrease in cardiac output and arterial pressure. The new level of cerebral perfusion pressure would often be below the autoregulatory range and would cause cerebral ischemia.

Short-term regulation of blood pressure is mainly accomplished by neural mechanisms. Carotid, aortic, and cardiopulmonary mechanoreceptors are involved.14 These receptors respond to deformation (e.g., stretch caused by increased transmural pressure). Afferent impulses travel with the vagus and the glossopharyngeal nerve to the cardiovascular centers. Efferent fibers reach the sinus and atroventricular nodes, ventricles, arterioles, and veins by vagal and spinal cord pathways. A fall in arterial pressure decreases afferent nerve activity and releases inhibitory activity in the cardiovascular centers. Release of parasympathetic drive and increased \( \alpha \)-adrenergic and \( \beta \)-adrenergic sympathetic activity result in increased heart rate and contractility and vasoconstriction, with reduced blood flow to the skin and skeletal muscle, the kidney, and the splanchnic region. The renin-angio-

### Orthostatic Intolerance

Two principal mechanisms cause orthostatic intolerance: 1) abnormal degree of central hypovolemia and 2) inadequate cardiovascular regulatory responses. The terminology and nosology in this area are often confusing. Use of dual descriptors referring to volume and autonomic state may be helpful.

Hypovolemic hyperadrenergic orthostatic intolerance (arterial circulatory anemia and sympathetico-tonic orthostatic hypotension) is caused by an abnormally large reduction in cardiac filling, linked to a decrease in total blood volume or an abnormal volume distribution during orthostatic stress. The regulatory and hemodynamic patterns exaggerate the normal response. The hypovolemia-induced large decrease in stroke volume is counteracted by increased adrenergic drive with elevated plasma catecholamines, marked tachycardia, and vasoconstriction. Variations in total blood volume well within the physiological range may affect orthostatic tolerance.20, 21 Patients with massive venous varicosities or a congenital absence of the venous valves have postural hypotension and decreased exercise capacity in the upright position.22 Ambient temperature also may affect the degree of peripheral pooling, probably by altering skeletal muscle tone. Heat markedly reduces, and cold increases, orthostatic tolerance.23, 24

Normovolemic dysregulatory orthostatic intolerance (postural, orthostatic, or asympatheticotonic hypotension) includes a variety of conditions that abolish or attenuate the normal regulatory responses to a redistribution of intravascular volume.13, 14 It can be caused

### Table 4: Left Ventricular Dimensions and Performance at Rest

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Supine</th>
<th>Sitting</th>
<th>( p )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Volume (ml)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>End diastolic</td>
<td>107 ± 10</td>
<td>85 ± 6</td>
<td>&lt;0.02</td>
</tr>
<tr>
<td>End systolic</td>
<td>34 ± 4</td>
<td>32 ± 5</td>
<td></td>
</tr>
<tr>
<td>Stroke</td>
<td>76 ± 8</td>
<td>55 ± 5</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Ejection fraction (%)</td>
<td>76 ± 2</td>
<td>72 ± 4</td>
<td></td>
</tr>
<tr>
<td>Heart rate (beats/min)</td>
<td>71 ± 6</td>
<td>89 ± 5</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Arterial pressure (mm Hg)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systolic</td>
<td>125 ± 8</td>
<td>125 ± 5</td>
<td></td>
</tr>
<tr>
<td>Diastolic</td>
<td>76 ± 4</td>
<td>84 ± 4</td>
<td></td>
</tr>
</tbody>
</table>

Values are mean ± SE for seven normal subjects. Scintigraphic data reprinted from Poliner et al.,15 by permission of the American Heart Association, Inc.
by 1) abnormal baroreceptor function, 2) peripheral or central lesions of the nervous system interrupting afferent or efferent neural pathways or causing dysfunction of the medullary cardiovascular control centers, or 3) end-organ failure to respond to autonomic stimuli. Such failure may be caused by nonneural lesions, such as the lack of postural heart rate response in patients with sick sinus syndrome or complete heart block. High and low pressure baroreceptor function is altered in many different cardiovascular disorders, but the efferent rather than the afferent limb usually is involved in patients with severe orthostatic hypotension. The response pattern is hypoadrenergic, with a lack of tachycardia and vasoconstriction. Parasympathetic involvement may also be a factor. The inability to regulate blood pressure may also be manifest as arterial hypertension in the supine position.

Autonomic dysfunction with hypoadrenergic orthostatic hypotension may be idiopathic or one of several clinical manifestations of systemic or neurological disorders, such as diabetic neuropathy, tabes dorsalis, amyloid disease, syringomyelia, traumatic lesions of the spinal cord, cerebrovascular disease, tumors, or degenerative or demyelinating diseases of the central nervous system. Idiopathic orthostatic hypotension and the Shy-Drager syndrome are relatively rare forms. They are diseases of late middle age with general signs of autonomic nervous system dysfunction, such as bowel and bladder disturbances, inability to sweat, and impotence, or as in the Shy-Drager syndrome, signs of extrapyramidal tract involvement (Parkinson’s disease). Humoral abnormalities can also be demonstrated. The catecholamine response to orthostatic stress is attenuated or absent, and postural changes in plasma renin levels are often but not always subnormal, consistent with an efferent autonomic block. Some patients also have diminished aldosterone responses and a decreased ability to conserve sodium.13, 14

The hypovolemic hyperadrenergic and the normovolemic hypoadrenergic varieties of postural hypotension cannot always be clearly distinguished. Some patients with idiopathic orthostatic hypotension have a reduced blood volume and vasoconstriction during supine rest with increased arterial pressure and total peripheral resistance. The present patient clearly belongs to the group with hypovolemic hyperadrenergic orthostatic intolerance. Total blood volume is reduced. There is no evidence for any disease of the central nervous system. The neuroendocrine responses to exercise show an intact regulatory apparatus. Furthermore, there are no signs of any major abnormality affecting the regulation of body fluids and electrolytes or of marked anatomical cardiovascular lesions. The original diagnosis of MVP was rejected. The patient was found to have anomalous chordae tendineae. A recent study in our laboratory by Beattie et al. demonstrated chordae in 4% of a series of more than 2000 routine clinical echocardiograms. About 5% of the patients with chordae had systolic murmurs, and another 5% had atypical chest pain with orthostatic hypotension or any other associated symptoms.

Episodes of marked bradycardia in the course of syncope in the upright position are not unusual. An uncompensated episode of orthostatic hypotension will often turn into vasodepressor syncope. The activation of multiple sets of receptors may explain not only the relative lack of compensatory tachycardia when venous pooling has caused large decreases in stroke volume and cardiac output and falling arterial mean and pulse pressures, but also the paradoxical bradycardia during actual syncope. Presyncopal heart rates rarely exceed 130 beats/min (i.e., they remain at least 40 beats below normal maximal heart rate). This relatively slow rate may be the result of opposing chronotropic drives originating in the cardiac and in the arterial (carotid sinus and aortic) receptors. A reduction of ventricular dimensions during the presyncopal state may progress until the end-systolic volume approaches zero. Left ventricular endocardial receptors, which normally are activated by high ventricular pressure and wall tension, are then stimulated by direct compression during systole. The normal adjustments to a reduced cardiac output and arterial pressure are negated, and bradycardia and vasodilatation are produced.

A similar sequence of events is likely to occur in vasovagal or vasodepressor syncope. Echocardiographic studies support this mechanism by demonstrating a trend toward smaller end-systolic volumes with progressive venous pooling. An unstable autonomic state is sometimes seen during presyncope with large oscillations in heart rate and arterial pressure. This state may reflect variations in the balance between opposing drives from ventricular and arterial receptors (i.e., deformation of the ventricular receptors in an empty heart falsely signaling high left ventricular pressures at a time when the carotid and aortic receptors sense a low arterial pressure).13 Activation of ventricular deformation receptors by high ventricular transmural pressure or direct contact is also likely to be the principal cause of syncope in aortic stenosis and in idiopathic hypertrophic subaortic stenosis. Paradoxical vasodilatation and bradycardia are also surprisingly common features of hemorrhagic shock.26

**Mitral Valve Prolapse and Related Conditions**

The clinical data put the present patient into a fairly large but poorly defined group with functionally important circulatory abnormalities in the absence of any structural, neurological, or major cardiovascular lesions. Symptoms suggesting orthostatic intolerance are common. Other complaints include atypical chest pain, palpitations, fatigue, and poor exercise tolerance. In the absence of MVP, these patients are often given the diagnosis of dysautonomia, vasoregulatory asthenia,27 or hyperkinetic heart syndrome.28

A series of recent studies in our laboratory by Gaffney, Schutte, and associates29-31 have dealt with the nature of the autonomic dysfunction in prolapse patients and its relationship to similar functional abnormalities in patients without valvular dysfunction. The
characteristic click-murmur complex is only a marker that reflects an abnormal relationship between valvular and ventricular anatomy. Prolapse can be a consequence of a redundant valve or of a reduced left ventricular size. At one extreme is a group of patients with a large valve and associated skeletal defects including pectus excavatum and scoliosis. Schutte et al. reported a distinctive habitus in women with MVP. A discriminant function equation that used only height, arm span, and anteroposterior chest diameter allowed correct classification of 75 to 85% of patients with MVP and controls. The combination of prolapse and certain anthropomorphic features is inherited in a dominant fashion. On the opposite side of the spectrum are patients who may be symptomatic with chest pain, palpitations, fatigue, exercise intolerance, and near syncope but who have normal valvular anatomy and a small left ventricle. There is only a tenuous relationship between the degree of anatomical abnormality and symptomatology; however, most symptomatic patients have at least some degree of orthostatic intolerance.

It has been suggested that patients with prolapse often have a primary hyperadrenergic state, manifested particularly as increased β-adrenergic activity that produces a hyperkinetic circulatory state. We have not been able to confirm this view. Our data indicate that most patients with MVP have normal levels of plasma catecholamines during supine rest. Systemic hemodynamic data are also normal. The heart rate response to exogenous β-adrenergic stimulation by infusion of isoproterenol is also within normal limits, but heart rate changes caused by changes in arterial pressure are attenuated, as is the response to the diving reflex. Some but not all patients show a large orthostatic increase in norepinephrine level. These patients also tend to have a large postural decrease in ventricular volume and stroke volume. A massive sympathetic activation with tachycardia and vasoconstriction is necessary to maintain blood pressure and cerebral perfusion. However, some patients have an exaggerated vasocostrictror response and produce blood pressures above control values even in the presence of an abnormally low cardiac output in the upright position.

The α-adrenergic hyperactivity in the upright position may eventually lead to a chronic state of vasoconstriction. The fact that orthostatic intolerance develops in some patients with pheochromocytoma provides support for the hypothesis that a neuroendocrine postural response that is beneficial on a short-term basis may gradually produce orthostatic intolerance. Chronic vasoconstriction may be particularly unfavorable in patients with prolapse in whom the valvular abnormality would tend to enhance the negative Starling effect on standing. A vicious circle may be established. Substantial mitral regurgitation is not a prerequisite. The increasing volume contained by the ballooning leaflets with decreasing ventricular size may produce, for any given reduction in left ventricular filling pressure, an exaggerated decrease in resting fiber length, fiber shortening, and forward stroke volume. The finding of a marked reduction in left ventricular end-diastolic volume in MVP patients with upright rest or exercise supports the concept that decreased ventricular filling in the upright position is a prominent feature in the pathophysiology of this syndrome.

This relationship between MVP, reduced blood volume, and chronic vasoconstriction may well provide an explanation for the confusing overlap of MVP and a variety of functional and psychiatric syndromes. An excessive vasoconstriction caused by chronic anxiety in patients with elevated catecholamines, high resting heart rates, and diminished plasma and ventricular volumes could produce functional MVP; that is, abnormal mitral valve motion but a structurally normal mitral valve. Similarly, autonomic dysfunction in patients with myxomatous MVP could be expected to increase the frequency of symptoms such as palpitations, easy fatigability, near syncope, and resting tachycardia that are interpreted as signs of psychoneurosis.

**Orthostatic Intolerance Caused by Prolonged Bed Rest**

Prolonged bed rest is another common cause of orthostatic intolerance and decreased exercise performance. The hemodynamic syndrome is of the hypovolemic hyperadrenergic variety. There is generally only a modest loss of blood volume, and the degree of hemodynamic abnormality tends to be greater than predicted from the magnitude of the hypovolemia. The reasons for this syndrome remain poorly understood.

The development of cardiovascular dysfunction following bed rest has generally been attributed to prolonged physical inactivity. A series of recent studies performed in our laboratory suggest that a rapid response to the redistribution of body fluids is the primary mechanism.

Head-down tilt at moderate degrees was introduced by the Russians as a means of simulating the redistribution of fluids that occurs at zero gravity. A 20- to 24-hour period of tilt at −4 to −6 degrees produces a marked central shift of intervascular and interstitial fluid. Central venous pressure, left ventricular end-diastolic volume, and stroke volume all increase transiently, but the increased central volume activates various compensatory mechanisms. There is inhibition of vasopressin, renin, and aldosterone and increased levels of atrial natriuretic factor (P. Norsk, personal communication, 1985).

A negative fluid balance is established, and filling pressures, stroke volume, and cardiac dimensions decrease to a level below the supine baseline within 24 hours. In fact, at that time the hemodynamic state in the supine position is similar to that normally prevailing in the upright position. This adaptation, consistent with Gauer’s view, is the normal operating point for the human cardiovascular system. Once this adaptation has been achieved, however, there is no capacity to deal with the fluid shift that occurs during the transition from supine to upright position, and orthostatic intolerance becomes manifest.

A similar sequence of events is likely to occur dur-
ing adaptation to weightlessness. Postflight orthostatic intolerance is present to some extent in virtually all returning astronauts. The degree of orthostatic intolerance and the loss of exercise capacity following space flight are also significantly greater than would be predicted from the total blood volume loss. It has also been shown that blood volume loss during bed rest can be prevented by the administration of fludrocortisone or corrected by intravenous fluid administration without completely restoring normal hemodynamics.14 Similarly, exercise in the supine position during bed rest does not prevent the development of orthostatic intolerance, whereas spending a few hours per day in the standing or sitting position is an effective countermeasure.14 The regulatory adaptations that are responsible for the disproportionately large effect of the hypovolemia remain to be defined. On the other hand, there seems to be little doubt that the fluid shift is the primary stimulus to the changes that develop during bed rest. This point has clinical relevance and provides a rationale for the reemphasis of the 40-year-old armchair approach to the treatment of acute cardiovascular disorders, including myocardial infarction, as described by Levine and Lown.45

Therapeutic Aspects

The large variety of therapeutic agents that have been used to treat orthostatic intolerance in general and the hyperadrenergic variety in particular is a certain indicator that our understanding of the pathophysiology is incomplete. Management often includes a combination of pharmacological agents designed to expand blood volume and to enhance compensatory reflex adjustments. A high salt diet is often prescribed as an initial step.46 An appropriate second step is fludrocortisone therapy, which is effective in many different forms of orthostatic hypotension. The mechanism of action is a combination of salt and water retention and increased vascular responsiveness to norepinephrine and angiotensin,47 an effect also produced by indomethacin.48 β-Adrenergic blocking agents and a dopaminergic antagonist have been used in hyperadrenergic orthostatic hypotension with the rationale of opposing active neurogenic vasodilatation, but there is little evidence that this mode of therapy is effective.

Gaffney et al.33 treated eight patients with dysautonomia (including 5 with MVP) with clonidine. All had symptomatic orthostatic intolerance. Treatment with clonidine, up to 0.4 mg/day for at least 1 month, reduced standing plasma norepinephrine levels and total peripheral resistance. A smaller postural decrease in cardiac output occurred after treatment, which also increased plasma volume by 12%. The objective improvement was paralleled by marked relief of symptoms. The mode of action is not entirely clear, but it seems likely that clonidine interrupted the link between chronic vasoconstriction, hypovolemia, and orthostatic intolerance.

Nonpharmacological treatment regimens have also been employed. Pressure garments to prevent excessive peripheral pooling have generally been of limited value. Most patients with hyperadrenergic orthostatic hypotension do not pool excessively. Garments that affect blood volume distribution are uncomfortable and restrict movements to a degree that is unacceptable to most patients.49

Nighttime head-up tilt at 5 to 20 degrees has been particularly successful in patients with normovolemic hypoadrenergic syndromes and supine hypertension46 but also should be tried in patients with the hypovolemic hyperadrenergic syndrome. The rationale is to prevent the transient postural increase in central blood volume and the nocturnal diuresis. The approach has not been widely used but is simple and rational, as discussed in the section on prolonged bed rest.

It does not necessarily follow from the experience with bed rest that superior physical fitness is associated with a high level of orthostatic tolerance. Subjects with superior aerobic fitness tend to have relative orthostatic intolerance, perhaps caused by attenuated baroreflex function with diminished tachycardia and vasoconstrictor responses.50 On the other hand, static exercise may have a beneficial effect.51,52 Increased muscle mass and increased muscle tone are likely to decrease the amount of orthostatic pooling in the leg. Most of the total volume pooled in the leg is contained in the deep veins, which are thin-walled and have little autonomic innervation. The effective compliance is determined by skeletal muscle (J.C. Buckey, R.M. Peacock, and C.G. Blomqvist, unpublished data, 1986). A balanced program of physical activity designed to improve both aerobic fitness and muscle tone generally should be tried in patients with hyperadrenergic orthostatic intolerance. The relative impairment of reflex regulation seems to occur only in subjects with very high levels of maximal oxygen uptake (e.g., champion long-distance runners). Moderate enhancement of physical fitness may be particularly appropriate in a patient with postexercise hypotension to which metabolic acidosis is likely to be a contributing factor. The outstanding metabolic effects of exercise training are to enhance the use of free fatty acids and to decrease the dependence on carbohydrates, which are in limited supply and also are likely to produce metabolic acidosis at high loads.53 Physical training is also likely to produce an increased blood volume.

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Questions and Answers

Dr. Arthur E. Weyman (Massachusetts General Hospital, Boston, Massachusetts): How did you define mitral valve prolapse in the patients you studied?

Dr. Blomqvist: Most of the patients we have studied have had the physical findings of prolapse with at least a click and a murmur. They were also evaluated by two-dimensional echocardiograms. The degree of prolapse was quantitated by measuring the amount of pro-
lapse past the plane of the mitral valve, usually using two- and four-chamber views.

Dr. Weyman: When you compared the patients with prolapse to the normal group, did the control subjects have the same symptomatology as the patients with prolapse?

Dr. Blomqvist: Our normal controls have generally been asymptomatic subjects of the same age and body build. In the study involving clonidine therapy, three of the eight patients had a symptomatology indistinguishable from the patients with prolapse, but they had no prolapse by echocardiogram or by any other criteria.

Dr. Mark Casey (Massachusetts General Hospital, Boston, Massachusetts): You talked about drug treatment in the management of patients with prolapse. What is the role of β-blocking agents?

Dr. Blomqvist: In some patients one might suspect that any beneficial effects of β-blocking agents are nonspecific and attributable to blockade of cardiac manifestations of anxiety. It is also possible that by abolishing the heart rate response you may produce augmented vasoconstriction. In general, however, I find it difficult to conjure up any rational explanation as to why β-blocking agents are effective.

Dr. Robert Levine (Massachusetts General Hospital, Boston, Massachusetts): Could the association of the orthostatic syndrome you described in your patients with autonomic abnormalities merely be a statistical association? In other words, is it possible that the mitral valve prolapse just happens to occur in these people without being causally related?

Dr. Blomqvist: It is possible, but you have to differentiate between symptomatic and asymptomatic patients in considering the autonomic abnormalities I described. It is more likely that the common denominators are symptoms and a hyperadrenergic state. On one hand, there are patients who because of their valvular lesion, tend to have an enhanced negative Starling effect, and as a result, a hyperadrenergic state develops. This compensatory response is needed to maintain cerebral perfusion in the erect position. On the other hand, there are patients in whom a hyperadrenergic state is the primary abnormality that secondarily leads to a vicious circle, with vasoconstriction and decreased blood volume and so on. Because of the hypovolemia and high contractile state, these patients end up with a small left ventricle. The prolapse results from the reduced left ventricular size rather than from a large, redundant valve.

Dr. Robert M. Graham (Massachusetts General Hospital, Boston, Massachusetts): In response to a report suggesting that carnitine levels were low in all patients with mitral valve prolapse, I measured the carnitine levels in this patient on several occasions and they were always normal. I also measured her acetocetate and β-hydroxybutyrate levels after she had undergone a prolonged fast. These were normal, suggesting that her carnitine acetyltransferase activity was normal.

Dr. Blomqvist: That is interesting because carnitine is involved in skeletal muscle disease associated with abnormalities of cardiovascular control. We have used well-defined single-enzyme metabolic defects to study cardiovascular control during exercise. Both Mcardle’s syndrome and carnitine-deficient patients have an abnormal degree of vasodilatation, but they also have a primary defect in cardiovascular control that results in blood pressure elevation despite extremely low systemic resistance. Their primary defect is actually increased skeletal muscle flow.

Dr. David Preston (Harvard Medical School, Boston, Massachusetts): Have you ever tried using elastic support stockings in these patients?

Dr. Blomqvist: Yes, different kinds of elastic garments have been used in a variety of ways. In general, the type of support that is most effective hemodynamically is the professional-type G suit. However, these suits are so uncomfortable that most patients cannot tolerate them. They may also lead to actual nerve damage because of excessive pressure on superficial nerves.

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