ORTHOSTATIC HYPOTENSION

C. Gunnar Blomqvist, M.D.

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University of Texas Southwestern Medical Center

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Orthostatic hypotension is a common and sometimes disabling condition. Its pathophysiology has been studied extensively. Likely causes include many different defects that singly or in combination affect major mechanisms controlling blood flow, vascular resistance, arterial pressure, and intravascular volume. The control systems are complex, and their interactions are poorly understood. As a consequence, obvious and straight-forward therapeutic approaches often prove ineffective, but seemingly paradoxical measures are sometimes helpful. These characteristics combine to make orthostatic hypotension a challenging topic. This review deals mainly with orthostatic hypotension occurring in the absence of structural neurological lesions.

Causes of Recurrent Episodic Arterial Hypotension.

Syncope is a common manifestation of orthostatic hypotension. The general clinical approach to the patient with syncope is the subject of an excellent recent Grand Round by Dr. Lynne M. Kirk (December, 1987).

The most frequent reason for syncope is a transient reduction in cerebral blood flow. 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 cerebral perfusion, particularly in patients with co-existing cerebrovascular disease. Mechanical obstruction of systemic or pulmonary blood flow may produce global cerebral ischemia with syncope. Such conditions include valvular aortic or pulmonary stenosis, idiopathic hypertrophic subaortic stenosis, atrial myxoma, and pulmonary embolic or vascular disease with pulmonary hypertension.

Vasodepressor (vasovagal) syncope. 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 portions of the autonomic nervous system. The typical psychological circumstances involve a perception of an actual or symbolic injury, 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 (Engel, 1978). Among the somatic mechanisms are carotid sinus hypersensitivity (Trout et al., 1979), and abnormal impact of afferent impulses from the ear, mouth, larynx, and pharynx (e.g. in glossopharyngeal neuralgia, Khero and Mullins, 1971). Simple swallowing (deglutition syncope, Wik and Hillestad, 1975) may precipitate vasodepressor syncope in some individuals.

The hemodynamic events have been well documented (Engel, 1978; Weissler and Warren, 1959; Epstein et al., 1968; Goldstein et al., 1982). A typical sequence includes an initial phase with moderate tachycardia followed by a marked fall in heart rate and arterial pressure. The depressor phase of the response has many features in common with orthostatic hypotension that progresses to syncope and will later be discussed in some detail.

PATHOPHYSIOLOGY OF ORTHOSTATIC HYPOTENSION

Principal features.

Orthostatic or postural hypotension may be defined as the inability to maintain adequate arterial pressure and tissue perfusion in the upright position. The brain is almost always the most vulnerable organ, but orthostatic angina pectoris has been described (Hines et al., 1981). Syncope is the obvious manifestation of inadequate cerebral blood flow. Lesser degrees of hypoperfusion cause only vague weakness, and postural dizziness or faintness. Many different clinical conditions are associated with orthostatic intolerance. Some patients have severe and widespread structural neurological and cardiovascular abnormalities. Others appear to have strictly functional disorders.

Two major mechanisms cause orthostatic intolerance:

1. Relative central hypovolemia with postural decreases in cardiac filling and stroke volume to subnormal levels.

2. Inadequate regulatory responses to the decrease in stroke volume and cardiac output.

The conventional terminology and nosology in this area are often inappropriate and confusing. It is based exclusively on the responses mediated by the sympathetic nervous system. It would be preferable to use dual descriptors referring to changes in intravascular volume and to regulatory responses. "Sympaticotonic orthostatic hypotension" may then be characterized as hypovolemic hypereactive orthostatic hypotension. The "asympaticotonic" variety would be referred to as normovolemic hyporeactive orthostatic hypotension.

Gravity, cardiovascular pressure-volume relationships, and Starling's law.

All intravascular pressures have a gravity-dependent hydrostatic component (Figure 1). The interactions between the gravitational field, the position of the body, and the functional characteristics of the blood vessels determine the distribution of intravascular volume. This, in turn, has major effects on cardiac filling and pump function.

Data on human blood volume, its distribution, and vascular pressure-volume relationships have been reviewed by Blomqvist and Stone (1983). Total blood volume in mammals is a linear function of body weight. Mean values in normal adult humans cluster around 75 ml/kg, corresponding to a total of 5-5.5 liters in a 70 kg person. High levels of physical activity and adaptation to a hot climate cause expansion of the blood volume with balanced increases in red cell mass and plasma volume.

Figure 1.

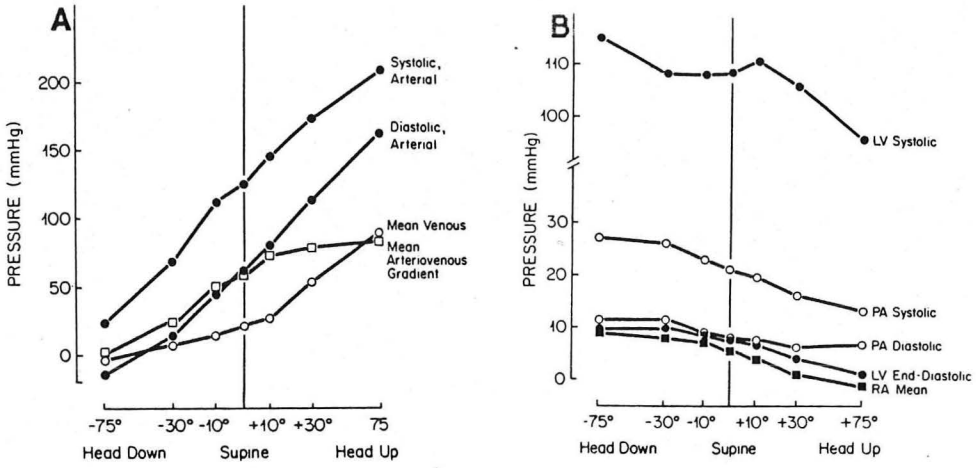

Figure 1. Responses to graded head-up tilt in 10 young normal men. LV, left ventricle; PA, pulmonary artery; RA right atrium. Intravascular pressures in foot (A) and in central circulation (B). Angle of tilt (horizontal axis) plotted as sine function to provide linear scale for primary hydrostatic effects of body-position changes. Based on data from Katkov and Chestukhin, 1980. From Blomqvist and Stone, 1983.

Approximately 70% of the total blood volume is contained in the systemic veins; the heart and the lungs account for 15%, the systemic arteries for 10% and the capillaries for 5%. Effective total vascular compliance represents the summed compliances of the various vascular compartments. It is dominated by the systemic veins. Measurements are derived by monitoring central venous pressure during acute changes in blood volume. Normal human compliance values are of the order 2-3 ml/mm Hg/kg body weight. Effective compliance is an empirical measurement, complicated by reflex hemodynamic adjustments with secondary redistribution of venous volume, by delayed compliance (viscoelastic creep of the vessel walls), and by loss of plasma volume to the interstitial space by tissue filtration. Nevertheless, it provides a useful measure of the impact on right-sided cardiac filling pressures of acute hypo- and hypervolemia.

A simple Frank-Starling relationship (stroke volume as a function of endiastolic volume or pressure) is a reasonably accurate descriptor of cardiac performance during postural changes in healthy individuals at rest. There are normally no major changes in arterial blood pressure. Afterload, expressed as end-systolic wall stress is usually slightly reduced in the upright position. The normal left ventricle ejects more than half of its endiastolic volume, usually between 2/3 and 3/4 (Table 1).

Figure 2.

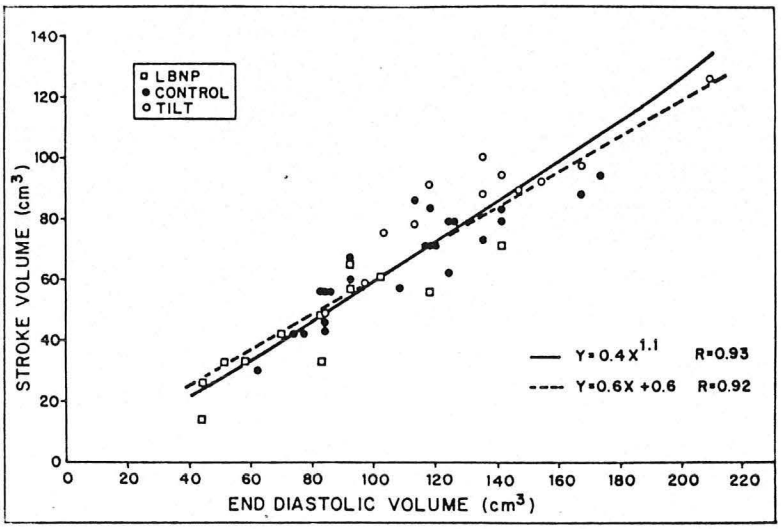

Figure 2. Relationship between left ventricular stroke volume and endiastolic volume. Echocardiographic measurements in 12 normal young men. Large variations in preload were introduced by head-down tilt at 5° and lower body negative pressure (LBNP) at -40 mm Hg. From Nixon et al., 1982.

Table 1. Postural Cardiovascular Adjustments in Normal Human Subjects.

Parameter	Supine	Sitting	p
Left ventricular volume (ml)*			
End-diastolic	107 ± 10	85 ± 6	<0.02
End-systolic	34 ± 4	32 ± 5	
Stroke	76 ± 8	55 ± 5	<0.05
Ejection fraction (%)*	76 ± 2	72 ± 4	
Heart rate, beats/min	73 ± 4	84 ± 4	<0.001
Pressure, mmHg			
Brachial artery	96 ± 3	99 ± 4	
Systolic	130 ± 5	132 ± 5	
Diastolic	76 ± 3	82 ± 3	<0.05
Pulmonary artery	13 ± 1	13 ± 1	
Pulmonary capillary wedge	6 ± 1	4 ± 1	<0.001
Left ventricular end diastolic	8 ± 1	4 ± 1	<0.001
Stroke index, ml/m^2	50 ± 5	35 ± 3	<0.001
Cardiac index, liters/min/m^2	3.5 ± 0.3	2.8 ± 0.2	<0.001

*Left ventricular scintigraphic data (mean ± standard error) from 7 young normal subjects studied by Poliner et al. (1980). Hemodynamic measurements from 10 sedentary men, age 32-58 (Thadani and Parker, 1978).

Stroke volume varies in direct proportion to changes in filling and endiastolic volume (Figure 2, Nixon et al., 1982). Increases in ejection fraction with secondary increases in stroke volume, mediated by positive inotropism, are of only minor functional significance during acute interventions that primarily affect ventricular filling. Arterial pressure is maintained by adjustments in heart rate and systemic vascular resistance.

Cerebral perfusion.

Cerebral blood flow is normally tightly controlled by autoregulation. It remains stable over a wide range of mean arterial pressure at any given level of arterial carbon dioxide partial pressure (Figure 3). Cerebral blood flow usually starts to decrease significantly when driving pressure (mean arterial pressure at the eye level) falls below 50 mmHg. Consciousness may be lost when blood flow falls below 1/4 of normal which usually occurs at a mean pressure of about 40 mmHg (Hainsworth, 1988). The hydrostatic gradient between the levels of the heart and the brain in the upright position adds another 30 mmHg to the required pressure as measured at the heart level. A mean arterial threshold pressure of 70 mmHg corresponds to systolic and diastolic pressures of about 80/65 mmHg. A significant shift of the autoregulatory range to the left is likely to occur in autonomic function (Bannister and Mathias, 1988).

Figure 3.

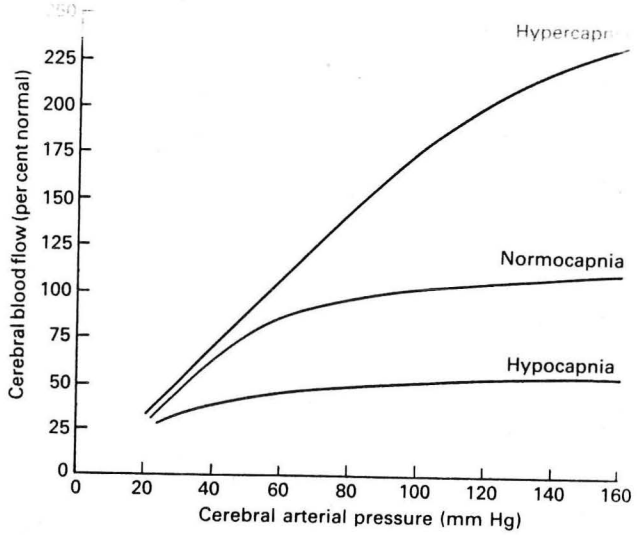

Figure 3. Autoregulation of cerebral blood flow. The flow at normal perfusion pressure and arterial P_{CO2} is taken as 100 per cent. Cerebral perfusion pressure (cerebral arterial pressure minus intracranial pressure) is 5-10 mm Hg less than cerebral arterial pressure. Above an arterial pressure of about 60 mm Hg the flow is largely independent of pressure. During hypercapnia the autoregulation is lost. During hypocapnia blood flow is only about 50 per cent of normal at all levels of CO_2. From Hainsworth, 1988.

Normal responses to orthostatic stress.

A change in body position from supine to standing or sitting initiates a well-defined sequence of events (Ziegler 1980; Blomqvist and Stone 1983; Rowell 1986):

1. Blood volume is redistributed away from the heart. About 500 ml are removed from the intrathoracic region to the legs. An additional volume of 200-300 ml is transferred to the veins in the buttocks and the pelvic area.

2. Cardiac filling pressures fall, and stroke volume decreases, usually by 20-30%.

3. An equally large acute decrease in arterial pressure is prevented by rapid baroreflex-induced increases in heart rate and systemic vascular resistance. Additional neurohumoral mechanisms are activated within minutes to preserve adequate intravascular volume, and to help maintain arterial pressure.

4. Cerebral perfusion pressure is kept within the autoregulatory range.

The principal features of the human cardiovascular response to orthostatic stress are shown in Figure 4. The data represented in the figure were collected during lower body negative pressure (LBNP). Application of LBNP produces a redistribution of intravascular volume similar to that which occurs during a transition from supine to sitting or standing. Pressure gradients between the ambient atmosphere and the intravascular space are created, but by a controlled local decrease in atmospheric pressure rather than by a postural hydrostatic increase in intravascular pressures.

The use of LBNP facilitates many measurements. LBNP also gives the experimenter better control of the stimulus by minimizing skeletal muscle activity that has major effects on the blood volume distribution, and on the dynamic cardiovascular response. Furthermore, in the microgravity environment of space, LBNP provides a means of studying the equivalent of gravitational postural shifts of intravascular volume.

Figure 4 shows a progressive decrease in right atrial pressure, left ventricular endiastolic volume, stroke volume, and cardiac output. Aortic pressure is during the early stages maintained by vasoconstriction only. This initially involves the skin and skeletal muscle (forearm) but later also the splanchnic region. Further decreases in stroke volume are partially offset by increasing heart rate. Plasma levels of norepinephrine increase, representing overflow from vascular receptors, and plasma renin activity levels are also elevated in response to large decreases in cardiac filling.

Figure 4.

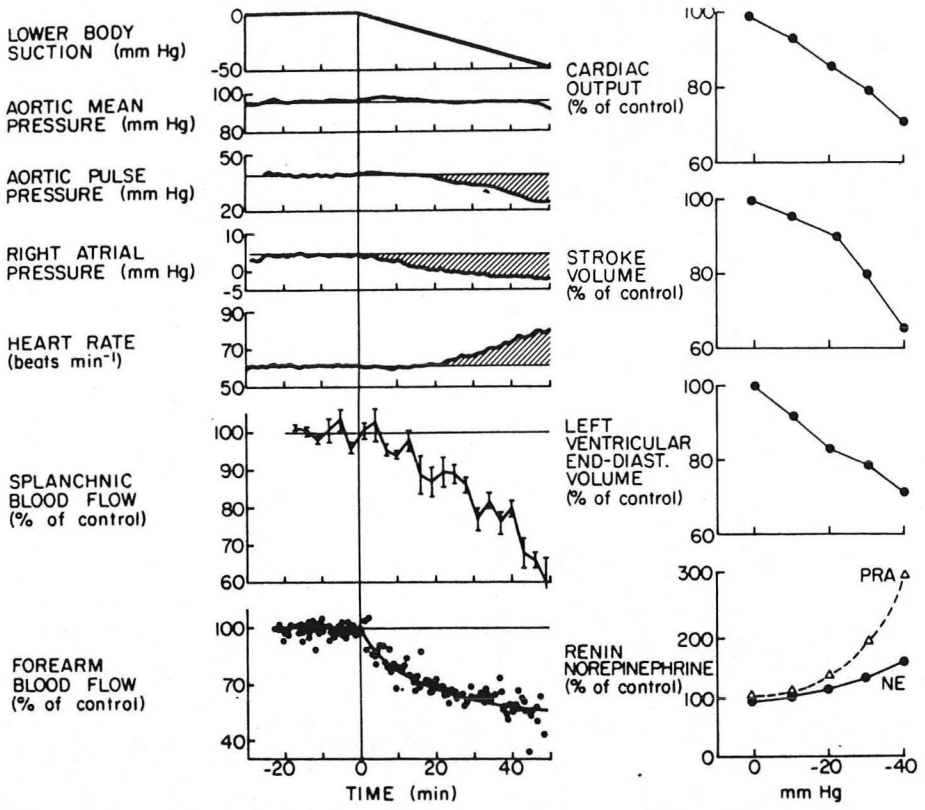

Figure 4. Cardiovascular responses to graded lower body negative pressure. Panels on the left show average responses to suction applied at a continuous rate of -1 mm Hg min^{-1} for 50 min (Johnson et al., 1974). Panels on the right show central circulatory responses to 10-mm Hg steps in negative pressure down to -40 mm Hg (Ahmad et al., 1977). From Rowell, 1986.

Total blood volume and mechanisms controlling its distribution.

Variations in total blood volume well within the physiological range may affect orthostatic tolerance (Murray et al., 1967; Bergenwald et al., 1977). Patients with massive venous varicosities or a congenital absence of the venous valves have postural hypotension and decreased exercise capacity in the upright position (Bevegard and Lodin, 1962). Ambient temperature also affects the degree of peripheral pooling, probably by altering skeletal muscle tone. Heat markedly reduces, and cold increases, orthostatic tolerance (Raven et al., 1981).

Relative rather than absolute magnitude probably determines the hemodynamic impact of peripheral redistribution of blood. Subsets of patients (e.g. mitral valve prolapse syndrome) with orthostatic hypotension and reduced total blood volume may pool no more or even less than normal controls in terms of absolute volume (Gaffney et al. 1979). Other patients with intact autonomic function have a combination of increased absolute peripheral venous pooling and reduced total blood volume (Streeten et al., 1988).

Considerable controversy exists regarding the extent to which active reflex-mediated venomotor changes contribute to cardiovascular homeostasis during changes in posture (Shepherd and Vanhoutte, 1975; Rothe, 1983; Rowell, 1986). In general, active venoconstriction may occur in the skin and in the splanchnic region. Veins supplying skeletal muscle are poorly innervated, and plasma concentrations of norepinephrine rarely reach levels that would produce venoconstriction. Effective neurohumoral control is unlikely. Furthermore, the deep veins in the leg have very thin walls. Venous compliance is largely determined by the characteristics of skeletal muscle.

Mayerson and Burch (1940) measured intramuscular pressures in young individuals who had had multiple episodes of orthostatic hypotension progressing to syncope. Fainters had lower intramuscle pressures in the leg at rest and subnormal pressure increases during head-up tilt. Buckey et al. (1988) recently used a combination of magnetic resonance imaging (MRI) and occlusion plethysmography to examine the capacity of the deep leg veins. At distending pressures equivalent to the hydrostatic venous pressures in the upright position, more than 1/2 of the increase in leg volume was accommodated by the deep veins (Figure 5). This finding implies that the properties of skeletal muscle are likely to affect significantly the distribution of venous volume and cardiac filling also at rest when the muscle pump is inactive. Smith et al. (1987) have shown that low level skeletal muscle activity in the legs and trunk improves orthostatic tolerance. They controlled the activity by a myographic biofeedback system.

Figure 5.

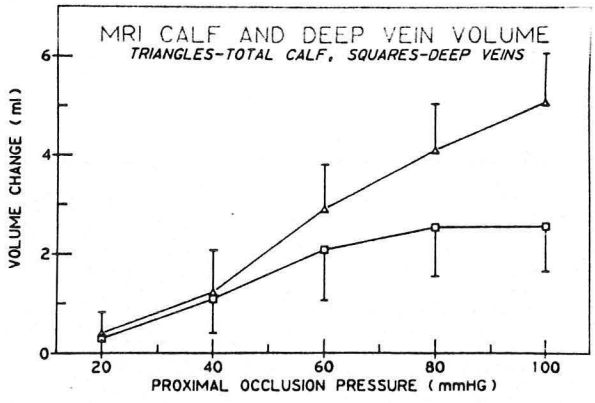

Figure 5. Changes in deep venous volume and total leg volume with increasing venous occlusion pressures. Measurements derived by quantitative analysis of crossectional magnetic resonance images of the lower leg. From Buckey et al., 1988.

Local reflex mechanisms may contribute to the vascular response to orthostatic stress. In experimental animals, activation of venous afferent fibers by distension produces reflex-induced leg muscle activity that may counteract postural pooling. However, attempts in our laboratory to demonstrate a similar reflex in humans have been unsuccessful (Thompson et al., 1982; Thompson and Yates, 1983). Henriksen (1977) and Henriksen and Sejrsen (1977) 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.

Cardiac pressure-volume characteristics. Cardiac pressure-volume characteristics are likely to modulate the systemic effects of any given decrease in intrathoracic blood volume. In the supine position in normal sedentary subjects, the left ventricle appears to be operating close to its maximal functional diastolic volume. Increases in filling pressure during exercise or intravenous fluid loading, or during the two interventions combined, produces only minor increases in endiastolic volume and stroke volume (Parker and Case, 1979; Poliner et al., 1980; Blomqvist and Saltin, 1983).

Figure 6.

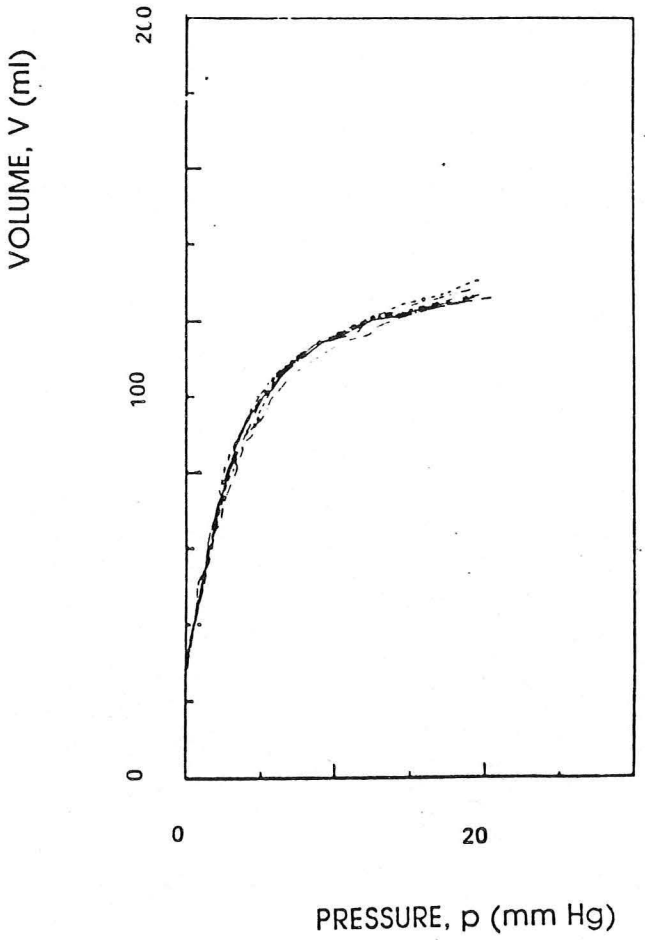

Figure 6. Diastolic pressure volume characteristics of the normal left ventricle. Sedentary subjects operate at near-maximal volume in the supine position, i.e. on the relatively flat portion of the curve. Hypovolemia with a decrease in filling pressure will cause a shift to the steep portion and potentiate the effects on ventricular volume of further decreases in filling pressures. Modified from Parmley, 1988.

Little direct information is available on the relation between orthostatic tolerance and cardiac diastolic properties. However, by implication, the normal left ventricle in the normovolemic subject operates on the flat portion of its pressure-volume curve (see Figure 6). This limits the diastolic reserve capacity, defined as the ability to respond to increasing filling pressures with increasing endiastolic volume and stroke volume. In return, the negative effects on stroke volume of a decrease in filling pressure are also limited.

Hypovolemia will cause the ventricle to move to the steep portion of its pressure-volume curve. This may put the patient in double jeopardy. The hypovolemia is likely to amplify the decrease in filling pressure at any level of peripheral pooling. In addition, the change in effective ventricular diastolic characteristics will magnify the decrease in endiastolic ventricular volume and stroke volume caused by any fall in filling pressure.

Neurohumoral regulation.

Short-term regulation of blood pressure is accomplished mainly by neural mechanisms. Carotid, aortic, and cardiopulmonary mechanoreceptors are involved. These receptors all respond to deformation, i.e. to stretch or compression caused by increased intracavitary or transmural pressures. Cardiopulmonary receptor densities are particularly high at the left-sided atrio-venous junctions and in the inferoposterior portion of the left ventricular wall. Afferent impulses travel with the vagus and the glosso-pharyngeal nerves. The nucleus of the tractus solitarius (Speyer, 1988) is the primary site of interaction between impulse traffic in the baroceptor pathways and activity within the central nervous system. Efferent fibers reach the sinus and atrioventricular nodes, the cardiac ventricles, and systemic arterioles and veins by vagal and spinal cord pathways.

A fall in intravascular or intracardiac pressure decreases afferent impulse traffic. This releases central inhibitory activity and alters the efferent impulse flow. Parasympathetic drive decreases but alpha- and beta-adrenergic activities increase. Responses of the target organs include increased heart rate and contractility, and vasoconstriction with reduced blood flow to the skin, to inactive skeletal muscle, and to the renal and splanchnic regions. The majority of the beta-receptors innervated by the sympathetic nerves are of the beta-1 subtype. They regulate heart rate, cardiac contractile state, and the release of renin from juxtaglomerular cells. The beta-2 receptors of the resistance vessels in skeletal muscle have a vasodilator function but are not innervated (Shepherd and Shepherd, 1988).

The existence of a triplicate system for neural control of blood pressure is well established (Mark, 1983; Mark and Mancia, 1983; Mancia and Mark, 1983; Bishop et al., 1983) but the interactions and degree of functional overlap between the three principal baroreflexes are still poorly understood.

Data from experiments in non-human species are not necessarily applicable to human physiology and medicine. Distributions of hydrostatic gradients and blood volumes are markedly different in humans and quadrupeds, but interesting

minimally invasive safe techniques and procedures have recently been developed for human use in the study of specific aspects of short-term reflex regulation of arterial pressure.

Direct microneurographic studies of muscle sympathetic nerve activity (MSNA). A microneurographic technique for direct recording of human sympathetic nerve activity was developed by Hagbarth and Vallbo (1968). It has later been applied extensively to the study of cardiovascular physiology by Wallin and others (Wallin et al., 1973; Wallin, 1981 and 1988; Mark et al., 1985; Aksamit et al., 1987; Victor and Leimbach, 1987; Rea and Eckberg, 1987). The peroneal and median nerve are relatively easily accessible. A thin tungsten electrode is inserted into a nerve fascicle supplying either muscle or skin. The impulse pattern with pulse-synchronous bursts respond in response to changes in blood pressure identifies a muscle nerve (Figure 7). Quantitation of the impulse traffic provides a direct measure of efferent activity. The time resolution is excellent and measurements are highly reproducible in a given subject.

Figure 7.

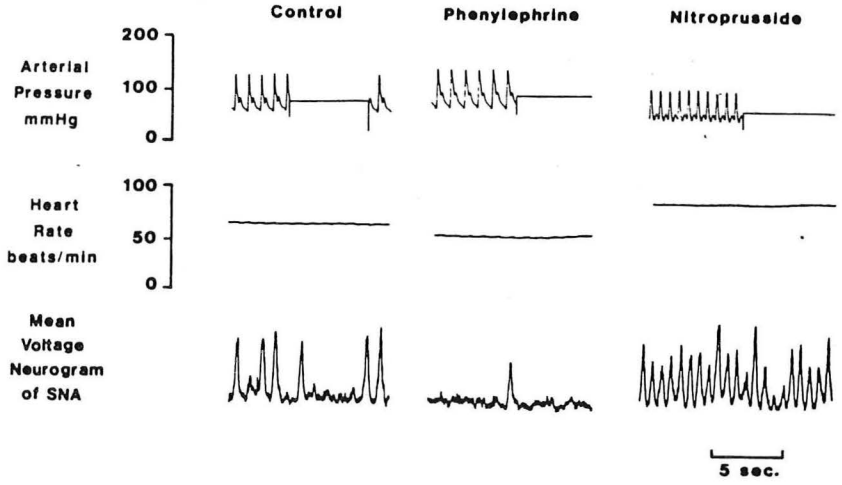

Figure 7. Arterial baroreceptor reflex. Effect of elevating arterial pressure with phenylephrine and lowering arterial pressure with nitroprusside on heart rate and efferent muscle sympathetic nerve activity (SNA) in a normal subject (B). SNA is pulse synchronous. An 8 mm Hg increase in arterial pressure (phenylephrine) caused marked reflex inhibition of SNA and a reflex fall in heart rate. A 15 mm Hg fall in arterial pressure (nitroprusside) caused a reflex increase in SNA and heart rate. From Aksamit et al., 1987.

Carotid and aortic baroceptors. More than thirty years ago, two British flight surgeons (Ernsting and Parry, 1957) described an ingenious noninvasive technique to test carotid baroceptor function. Suction, applied to the neck area by means of an airtight collar, produces an increase in transmural pressure and increased deformation of the mechanoceptors. The stimulus closely simulates an increase in intravascular carotid pressure, but there are no significant direct hemodynamic effects.

The approach has been refined and used extensively by Eckberg and his associates (Eckberg et al., 1975; Eckberg and Eckberg, 1982; Sprenkle et al., 1986) to evaluate the vagally mediated effects on heart rate. A computer-controlled system delivers an ECG-triggered ramp of neck collar pressures. Each pressure level is imposed only during a single cardiac cycle. The reflex response time is very short. The effect of a change in transmural pressure is measured during the next cardiac cycle. The pressure ramp is easily repeated and stimulus-response curves (Figure 8) can be based on multiple measurements. Characteristic abnormalities have been described (Eckberg, 1979) in hypertension. The operating point is reset in mild disease. The sensitivity or slope is reduced in more advanced cases.

Major assets of this approach is the lack of effect on the native hemodynamic state, and the relative ease by which complex quantitative data can be acquired. On the other hand, the procedure generates data only on the heart rate component of the reflex. Activation of the carotid baroceptors by increased transmural pressure of longer duration also affects the sympathetic nerve traffic to the resistance vessels in skeletal muscle (Rea and Eckberg, 1987). At least theoretically, carotid baroceptor function may be normal in the presence of attenuated heart rate responses if the vasomotor effects are enhanced.

The operating characteristics of the carotid and aortic baroreflexes appear to be different in different species. In dogs, the aortic reflex has a higher threshold and lower sensitivity than the carotid baroreflex. Ferguson et al. (1985) and Sanders et al. (1988) used a combination of the direct sympathetic nerve recording technique and the pressurized neck collar to examine the relationship between aortic and carotid reflexes in human subjects. Phenylephrine was infused, with and without external pressure application to the neck to cancel the effects on transmural carotid sinus pressure. This approach left the aortic baroceptors free to respond. The carotid baroceptors were also activated separately by neck suction. The results confirm that both reflexes participate in the control of arterial pressure in human subjects, and suggest that the aortic reflex is more powerful than the carotid. The greater sensitivity applies to the control of both heart rate and adrenergic vasoconstrictor activity.

Figure 8.

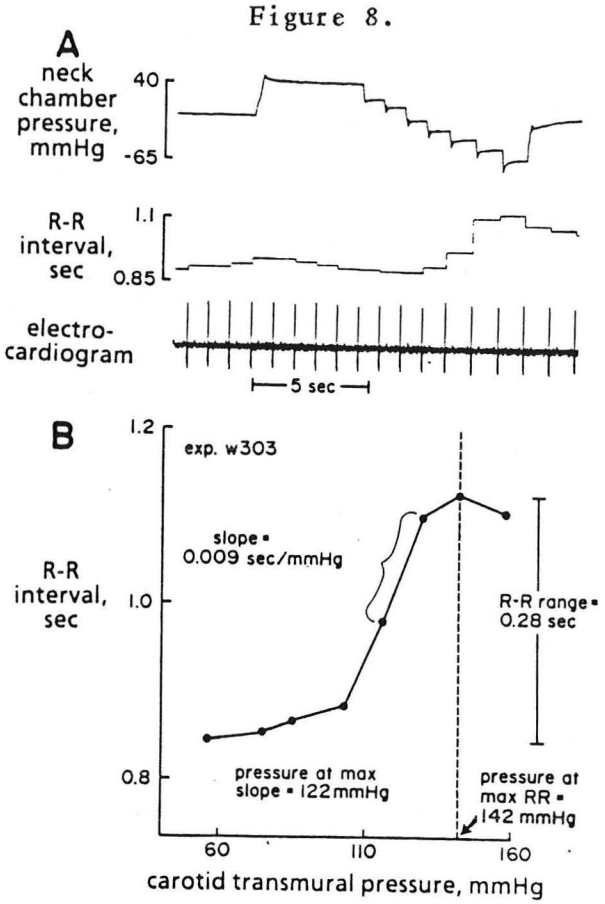

Figure 8. Experimental record (A) and average responses of 1 subject to 7 applications of neck pressure sequence (B). B indicates method used to analyze baroreflex relations. Carotid transmural pressure was considered to be average systolic pressure minus neck chamber pressure. Pressure at maximum slope was taken as carotid transmural pressure halfway between pressures bracketing maximum slope. From Kasting et al., 1987.

Loss of arterial baroceptor function. Aksamit et al. (1987) recently described a patient with loss of carotid and aortic baroceptor function, attributable to a combination of surgery and radiation therapy. Large changes in arterial pressure, induced by infusions of phenylephrine and nitroprusside, failed to affect heart rate or directly measured adrenergic vasomotor nerve activity. The patient had retained cardiopulmonary reflex activity and responded to a LBNP-induced decrease in cardiac filling with a marked increase in sympathetic nerve activity. Arterial pressure was labile, but sustained hypertension was not present. Sinoaortic denervation in experimental animals produces a similar state. Thus, the cardiopulmonary baroceptor are by themselves unable to prevent rapid changes in arterial pressure. The patient was mildly orthostatic.

Cardiopulmonary receptors. The principal components of the cardiopulmonary receptor system are the left atrial and left ventricular receptors. Both sets respond to deformation. The atrial receptor population directly monitors atrial and indirectly ventricular filling. The ventricular receptors discharge primarily during systole but are also greatly influenced by diastolic events. Ventricular wall stress, which is maximal during isovolumic systole, may be the common denominator.

There are numerous and complex interactions between the mechanisms maintaining arterial pressure and body fluid homeostasis. Arterial pressure levels directly affect tissue filtration rates and renal excretion of sodium and water. The arterial and cardiopulmonary baroreflexes also control renal sympathetic activity (alpha-adrenergic vasoconstriction, beta-1-mediated activation of the renin-angiotensin system).

Vasopressin (ADH or antidiuretic hormone) is released from the neurohypophysis in response to increases in plasma osmolarity as detected by receptors in the hypothalamus. Vasopressin is also released when the atrial mechanoreceptors are unloaded by decreasing filling pressures, usually as a consequence of decreased central blood volume. Unloading of ventricular and arterial baroceptors by decreases in transmural pressures also releases vasopressin. The relative importance or these receptor sites is not known in detail but the atrial release mechanism may be less active in primates than in other species. Vasopressin may be physiologically important as a vasoactive substance, inducing vasoconstriction in skeletal muscle and the splanchnic area, and vasodilatation in the coronary and cerebral circulations by a combination of endothelium-dependent (cyclo oxygenase-mediated, indomethacin-inhibited) and direct relaxation of smooth muscle.

Release of atrial natriuretic peptide (ANP) is caused by an increase in atrial transmural pressures. ANP has multiple effects in addition to inducing natriuresis, including vaso- and venodilatation, inhibition of renin and vasopressin release, and perhaps also a direct effect on capillary permeability (Hall, 1986; Rowell, 1986; Shepherd and Shepherd, 1988).

LBNP at non-hypotensive levels has been used as a means of unloading the low-pressure cardiopulmonary receptors without affecting the arterial sensors. LBNP in the range -5 to -10 or -15 mmHg produces significant vasoconstriction, but there is no change in arterial systolic or diastolic pressures. Pulse pressure and aortic pulse contour also remain unchanged. These findings, combined with the absence of any heart rate change (see Figure 4 and Rowell, 1986), have been taken as evidence for selective involvement of the low-pressure receptor pathway and suggesting that the principal response is vasoconstriction. However, cardiac filling pressures and stroke volume decrease. This is likely to cause a decrease in aortic and arterial pulse volume with a significant secondary change in carotid sinus and aortic wall stress. Activation of arterial baroreflexes cannot be ruled out and the ventricular receptors may also respond.

Loss of cardiopulmonary receptor function. Current surgical technique in cardiac transplantation preserves the dorsal portion of the atria, including

the neural pathways to and from the left atrial receptors. The efferent pathways to the right atrium and the sinus node are also intact, but the node is electrically isolated from the transplanted heart. The ventricular baroceptors are, of course, lost.

Mohanty et al. (1987) examined 23 patients after cardiac transplantation. They reported marked attenuation of the normal reflex-induced increases in forearm vascular resistance and plasma norepinephrine levels during LBNP at -10, 20, and 40 mmHg. The impaired responses were not caused by treatment with immunosupressive agents. Renal transplant patients on similar regimens had enhanced vasoconstrictor responses. Furthermore, the vasomotor and norepinephrine responses to a cold pressor test were intact in the cardiac transplant patients. The combined data suggested to the authors that the impaired vasoconstrictor responses were caused by ventricular denervation. However, the patients in this series tended to be hypertensive and their mean forearm vascular resistance at rest was higher than in control subjects during LBNP at -40 mmHg. Mean arterial pressure during LBNP was equally well maintained in patients and controls.

Victor and associates (personal communication) recently studied 12 patients after cardiac transplantation and six normal controls. Left ventricular dimensions during LBNP at -14 mmHg decreased to the same extent in both groups. There was no change in mean arterial pressure or heart rate in the control group. Muscle sympathetic nerve activity (MSNA) during LBNP, measured directly with the microelectrode technique, was twice as high as at rest.

Compared to normal controls, the transplant patients had higher MSNA at rest, but an identical relative change during LBNP. Sinus rate in the atrial remnant increased by 6 bpm in the patients, and mean arterial pressure fell by 3 mmHg. The increases in MSNA and sinus node rate were abolished when mean arterial pressure was kept constant during LBNP by infusion of phenylephrine. These data indicate that arterial baroreflexes can compensate for loss of the ventricular receptor function. Post-transplant patients tend to be hypertensive and rarely have orthostatic hypotension.

Interactions between arterial and cardiopulmonary baroreflexes. Vasovagal or vasodepressor syncope and orthostatic syncope in subjects with intact autonomic nervous system have many common features (Engel, 1978; Weissler and Warden, 1959; Epstein et al., 1968; Mark, 1983).

There is in all these conditions an initial phase with moderate tachycardia and vasoconstriction 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 (Figure 9). The cutaneous circulation is usually vasoconstricted but there is a large decrease in systemic resistance, caused by vasodilatation in skeletal muscle (Goldstein et al., 1982). Paradoxical vasodilatation and bradycardia are also common features of hemorrhagic shock (Mark, 1983; Secher and Bie, 1985). Recent data obtained by direct nerve recording techniques (Wallin, 1981; Wallin, 1988) have documented a strong inhibition of impulse traffic in the alpha-adrenergic vasoconstrictor fibers supplying skeletal muscle.

Figure 9.

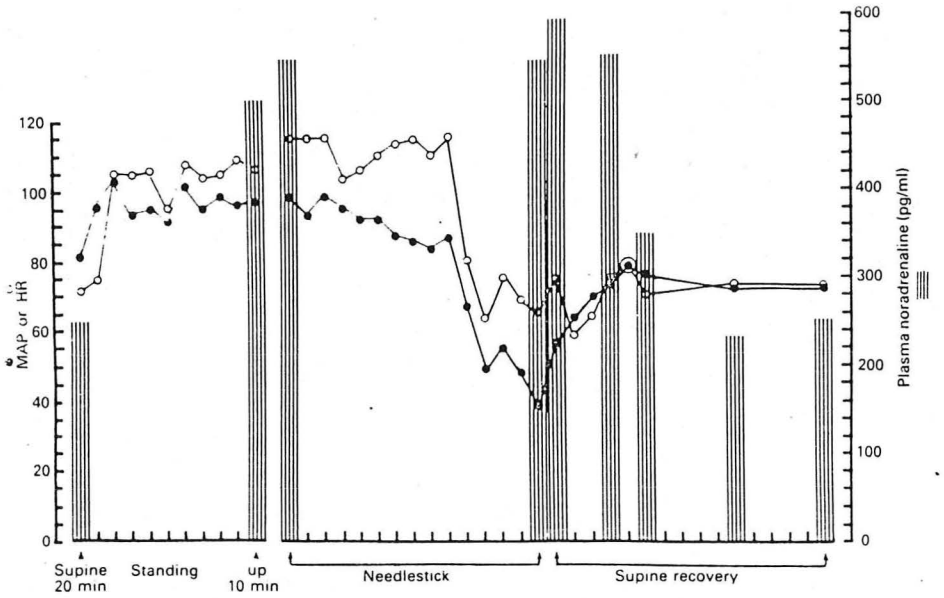

Figure 9. Mean arterial pressure, heart rate and plasma noradrenaline concentrations during syncope, evoked by the emotional response to insertion of an intravenous needle, in a 17-year-old female patient who suffered from recurrent syncopal episodes. Syncope was associated with severe hypotension and bradycardia. There was no noradrenaline response to hypotension during syncope, although the noradrenaline response to standing was intact. From Goldstein et al. (1982).

The most likely cause of this sequence of events is conflicting inputs from arterial and cardiopulmonary baroreflexes. The left ventricular receptors are normally activated by increased intracavitary pressure and/or volume with increased wall stress. A progressive reduction in ventricular volume probably occurs during the pre-syncopal stage. Echocardiographic studies have demonstrated gradually decreasing left ventricular volumes with increasing degrees of peripheral venous pooling (Ahmad et al., 1977). The left ventricular endocardial receptors will eventually be activated by direct compression. The salient stimulus is deformation, but the sensing system cannot differentiate between compression, associated with low volume and pressure, and distension, caused by high ventricular pressure and volume. The normal adjustments to reduced cardiac output and arterial pressure are negated, and bradycardia and vasodilatation are produced.

An unstable autonomic state is sometimes seen during the presyncopal phase with large oscillations in heart rate and arterial pressure (Figure 10, Hyatt, 1971). This 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 signalling high left ventricular pressures at a time when the carotid and aortic receptors sense a low arterial pressure) (Ziegler, 1980).

Figure 10.

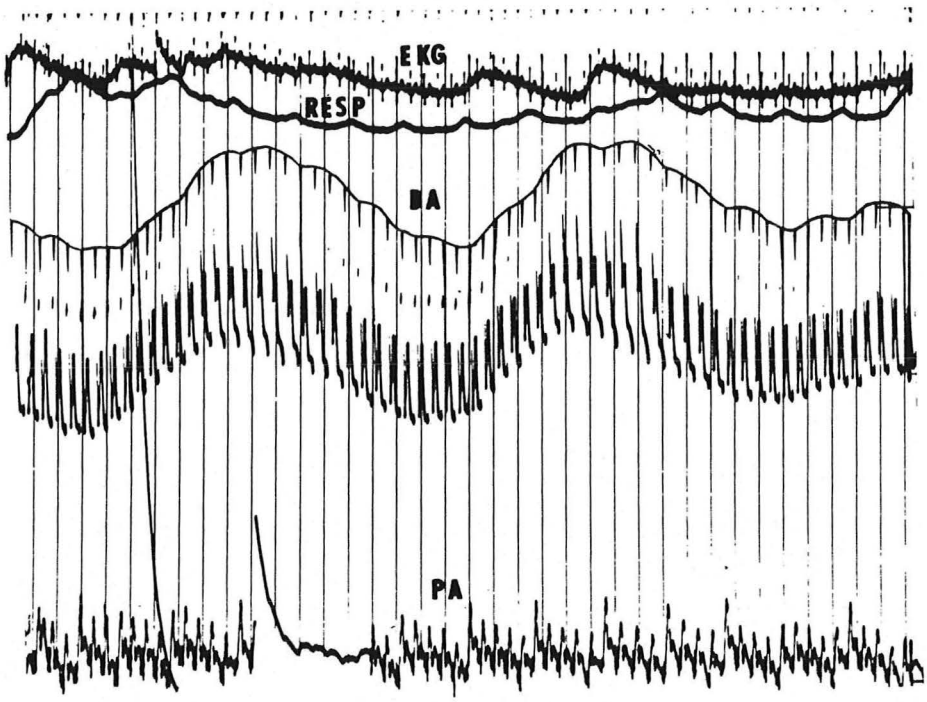

Figure 10. Vasomotor waves are present in the brachial artery pressure tracing (BA), but are not seen in the pulmonary artery pressure tracing (PA). Waves are unrelated to respiration (RESP). Recorded during 70° head-up tilt after a 14-day bed rest period in a subject with reduced orthostatic tolerance. From Hyatt, 1971.

There is strong collateral support for an important role for the ventricular baroceptors. Beta-adrenergic blockade increases left ventricular endiastolic and endsystolic volumes and improves orthostatic tolerance after bed rest (Sandler et al., 1985). Activation of ventricular deformation receptors by high ventricular transmural pressure or direct contact is likely to be the principal cause of syncope in aortic stenosis and in idiopathic hypertrophic subaortic stenosis (Mark, 1983).

Bradycardia and arterial hypotension are also common features during the early stage of an acute inferior or inferoposterior myocardial infarction (Mark, 1983). The activity of ventricular mechanoreceptors is likely to be enhanced

by increased deformation of the ischemic segment of the ventricular wall. Reflex inhibition of renal sympathetic activity may -at least theoretically- limit the ability to conserve intravascular volume and to enhance vasoconstrictor responses (no renal vasoconstriction and no activation of the renin-angiotensin system). The hemodynamic effects at rest are usually transient, but relative bradycardia and hypotension are often present during the standard submaximal exercise test at discharge. The attenuated exercise responses are usually normalized within a few weeks when the healing process is completed (unpublished observations), and there is likely to be less deformation in or at the edge of the infarcted area.

CLINICAL ASPECTS OF ORTHOSTATIC HYPOTENSION.

Effect of Ageing. Orthostatic hypotension from all causes becomes more prevalent with increasing age (Cunha, 1987). Caird et al. (1973) studied a large group of ambulatory men and women 65 and older. Decreases in systolic blood pressure to 20+ mm Hg below supine resting levels after 1 minute of standing occurred in 24% and decreases of 30+ mm Hg in 9% of the study population. A majority of the subjects had two or more conditions likely to be associated either with hypovolemia or maldistribution of the blood volume (anemia, chronic infection, or varicose veins) or with impaired cardiovascular control mechanisms (treatment with pharmacological agents having a known potential to cause orthostatic hypotension, including levodopa, phenothiazines, tricyclic antidepressants, or vasodilators; evidence for structural neuorological lesions).

Cardiovascular control mechanisms tend to have reduced efficiency even in generally healthy older people. Changes in arterial pressure produce a smaller heart rate response than in younger subjects, suggesting a blunting of the arterial baroreflex (Gribbin et al., 1971; Shimada et al., 1986). Ageing also attenuates responses mediated by beta-1 adrenoceptors. There is no conclusive information on the effect of age on alpha-receptor characteristics and responses to exogenous alpha-adrenergic stimulation, or on humoral mechanisms modulating effector responses, i.e. locally released or circulating prostaglandin, kinins, angiotensin, etc. (Davies and Sever, 1988).

Effect of Physical Fitness. Much attention has recently been paid to a possible inverse relationship between physical fitness and orthostatic tolerance (Klein et al., 1969; Stegemann et al., 1975). One important reason is simply that physical fitness usually is perceived as a state with increased ability to withstand stress, particularly stress in the form of environmental extremes (Klein et al., 1969). Decreased orthostatic tolerance is then paradoxical, particularly in a condition associated with expanded blood volume, large heart size, and large functional reserves that may be used to compensate for decreased filling by increased heart rate and peripheral resistance. The paradox has been heightened by the fact that physical deconditioning by bedrest inevitably produces orthostatic intolerance.

An early study indicated increased degree of peripheral venous pooling in fit subjects (Luft et al., 1976), but later work has provided only limited support for increased venous compliance (Pawelczyk et al., 1988). Several cross-sectional and longitudinal studies have examined various aspects of baroceptor function. Fit individuals have shown to have attenuated heart rate (Klein et al., 1969; Luft et al., 1976; Mangseth and Bernauer, 1980; Raven et al., 1984; Smith and Raven, 1986) and vasoconstrictor responses to orthostatic stress (Raven et al., 1984; Smith and Raven, 1986; Mack et al., 1987). Corresponding findings have been made in experimental animals (Bedford and Tipton, 1987).

The combined results are still inconclusive. Significant group differences in orthostatic tolerance have not been uniformly present (Convertino, 1987) but have, on the other hand, been reported in the absence of any difference in baroreflex function (Levine et al., 1988). It is possible that the decreased orthostatic tolerance is a consequence of cardiac rather than neurohumoral regulatory adaptations to training. Physical training alters the effective ventricular pressure-volume relationships. Fit subjects have increased diastolic reserve and are able to respond to increased ventricular filling during exercise with a larger increase in stroke volume than sedentary individuals (Blomqvist and Saltin, 1983). This implies that the ventricle operates on the steep portion of its pressure-volume curve and that the functionally favorable effect of increased filling is balanced by a correspondingly large decrease in endiastolic volume and stroke volume when filling pressure decreases. This hypothesis has not yet been tested.

The relationship between fitness and orthostatic tolerance has important practical implications in aerospace medicine. Modern high-performance military aircraft are able to withstand considerably higher G-force levels than their pilots. A rapid increase in +Gz forces can produce a sudden decrease in cerebral perfusion and sudden loss of consciousness with incapacitation. Full recovery may take as long as 30 seconds with catastrophic consequences (Burton, 1988; Whinnery, 1988). Straining maneuvers and isometric muscle activity during acceleration stress can substantially improve G tolerance and require a high level of fitness, but extreme levels of aerobic fitness may be counter-productive. Optimal exercise training regimens are yet to be defined.

Table 2. Postexercise Hemodynamic Data in Six Normal Subjects.

Variable	Preexercise Control	Postexercise (min) 5	25	50	110
Heart rate (beats/min)	60	105*	89*	79*	74*
Mean arterial pressure (mm Hg)	94	90*	88*	87*	93
Central venous pressure (mm Hg)	6	4*	3*	4*	4*
$[HCO_3]$ (mmol/L)	24	15*	20*	23	24
Plasma volume (%)	100	84*	89*	98	100

*$p<0.05$, compared with control values. All measurements in the supine position. Data reprinted from Bjurstedt et al., 1983.

Heavy exercise also has acute effects on orthostatic tolerance by producing a combination of transiently increased body temperature, metabolic acidosis, and hypovolemia with reduced central venous pressure and mean arterial pressure (Table 2 from Bjurstedt et al., 1983). This phase is followed by increased orthostatic tolerance, probably due to an expansion of the plasma volume (Convertino, 1987).

Hyper-Reactive Hypovolemic Orthostatic Hypotension.

Orthostatic intolerance caused by prolonged bed rest and related conditions. Prolonged bed rest is a common cause of orthostatic intolerance and decreased exercise performance (Taylor et al., 1949; Saltin et al., 1968; Chobanian et al., 1974; Blomqvist and Stone, 1983). The hemodynamic syndrome is of the hypovolemic hyperreactive variety. There is generally only a modest loss of blood volume (300 to 500 ml), and the degree of hemodynamic abnormality is greater than predicted from the magnitude of the hypovolemia. The development of cardiovascular dysfunction during bed rest has generally been attributed to the prolonged physical inactivity. A series of studies performed in our laboratory suggest that a rapid response to the redistribution of body fluids is the primary mechanism (Nixon et al., 1979; Blomqvist et al., 1980; Gaffney et al., 1985).

Head-down tilt at moderate degrees was first introduced by the Russians as a means of simulating the redistribution of fluids that occurs at zero gravity (Kakurin et al., 1976). A 20-24 hour period of tilt at -4 to -6° 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 also a significant humoral response with inhibition of vasopressin, renin and aldosterone (Nixon et al., 1979).

A negative fluid balance is established within hours during head-down tilt. Filling pressures, stroke volume, and cardiac dimensions decrease to a level below the supine base line 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 series of adaptations consistent with Gauer's view (see Blomqvist and Stone, 1983) that the upright position defines the normal operating point for the human cardiovascular system. Once adaptation has been achieved and supine hemodynamics approach the normal upright pattern, the subject will have lost the capacity to deal with the fluid shift that occurs during the transition from supine to upright position. Orthostatic intolerance becomes manifest. The degree of cardiovascular dysfunction is similar after a 3-week bed rest period and after 24 hours at head-down tilt (Figure 11).

A similar sequence of events is likely to occur during adaptation to microgravity. Post-flight orthostatic intolerance is to some extent present in virtually all returning astronauts. The degree of orthostatic intolerance

and the loss of exercise capacity following space flight is also significantly greater than would be predicted from the total blood volume loss.

Figure 11.

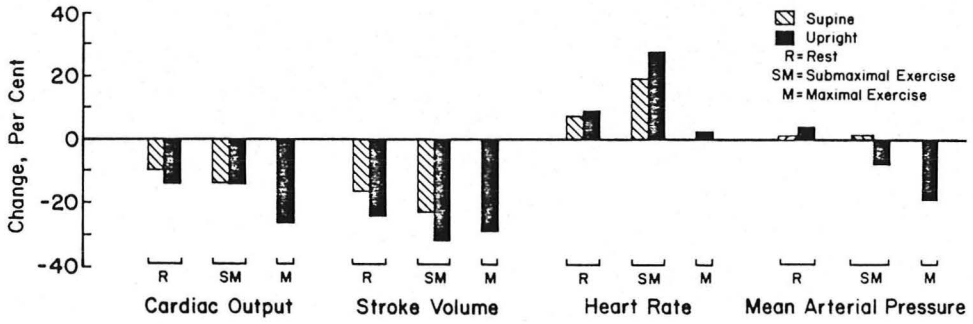

Figure 11. Hemodynamic effects of 3-wk bed rest on cardiac output, stroke volume, heart rate, and mean arterial pressure supine and upright at rest during exercise in 5 normal young men. Control measurements before bed rest = 100%. Data from Saltin et al., 1968.

It has been shown that blood volume loss during bed rest can be prevented by the administration of 9-alpha-fluorohydrocortisone, or corrected by intravenous fluid administration, without completely restoring normal hemodynamics (Blomqvist and Stone, 1983). Exercise in the supine position during bed rest does not prevent the development of orthostatic intolerance, whereas a few hours per day spent in the standing or sitting position are effective countermeasures (Blomqvist and Stone, 1983).

The exact regulatory adaptations that are responsible for the disproportionately large effect of the hypovolemia are still 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 has clinical relevance and provides a rationale for re-emphasis of the arm chair approach to the treatment of acute cardiovascular disorders as described by Levine and Lown (1951).

Mitral valve prolapse and related conditions. Much attention has recently been paid to a fairly large, but poorly defined, group of patients 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 any physical or echocardiographic findings of mitral valve prolapse (MVP), these patients are often given diagnosis of dysautonomia, vasoregulatory

asthenia (Holmgren et al., 1957) or hyperkinetic heart syndrome (Gorlin, 1962), or considered to have cardiovascular symptoms related to anxiety neurosis. Circulatory control mechanisms in these disorders have recently been reviewed by Mitchell (1986). Mitchell quoted Starr (1944) who suggested that the primary defect in neurocirculatory asthenia may be "clumsiness of the circulation," analogous to the ordinary clumsiness of muscular movements. Clumsiness in a sense of lack of precise control is a prominent feature of the mitral valve prolapse syndrome (MVPS, the combination of prolapse and symptomatic autonomic dysfunction) and related disorders. Some patients with MVPS have either markedly attenuated or grossly enhanced vagally mediated cardiovascular responses to standard stimuli, e.g. to the Valsalva maneuver or the diving reflex (Gaffney et al., 1979; Coghlan et al., 1979).

Many aspects of the mitral valve prolapse syndrome have been examined in great detail in a recent volume edited by Boudoulas and Wooley (1988). A series of studies in our laboratory by Gaffney, Schutte, and associates (Gaffney et al., 1979; Gaffney et al., 1981; Schutte et al., 1981; Gaffney et al., 1983) have dealt with the nature of the autonomic dysfunction in mitral valve prolapse, including its links to the degree of valvar abnormality, and its relation to similar functional abnormalities in patients without valvular defects. The combined experience was recently reviewed by Gaffney and Blomqvist (1988).

There is a tenuous relationship between the degree of anatomical abnormality and the severity of any symptoms. The characteristic click-murmur complex is only a marker that reflects an abnormal relationship between valvular and ventricular anatomy. Prolapse can be the consequence of a redundant valve or 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. (1981) described a distinctive habitus in women with MVP. A discriminant function that used only height, arm span, and anteroposterior chest diameter, produced correct classification of 75 to 85% of patients with MVP and controls. The combination of prolapse and these anthropomorphic features is inherited as a dominant trait. On the opposite side of the spectrum are patients who may be symptomatic with chest pain, palpitations, fatigue, exercise intolerance, and marked orthostatic hypotension, and who have prolapse with normal valvar anatomy but a small left ventricle. Furthermore, mitral valve prolapse can be produced in perfectly normal asymptomatic individuals by interventions that decrease the size of the left ventricle. Beattie and coworkers (1985) in our laboratory performed two-dimensional echocardiograms in 20 normal subjects during lower body negative pressure which induced a progresive reduction in left ventricular volume. Almost 1/3 of the subjects developed posterior bowing of the mitral leaflets and fulfilled classical echocardiographic criteria for MVP.

It has been suggested that many patients with prolapse have a primary hyperadrenergic state (Boudoulas et al., 1980; Pasternac et al., 1982; Puddu et al., 1983), expressed primarily as increased beta-adrenergic activity which 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 and normal hemodynamic state during supine rest. The

heart rate response to exogenous beta-adrenergic stimulation by infusion of isoproterenol is within normal limits.

Some patients show large postural increases in plasma norepinephrine levels, but these patients also tend to have a large postural decreases in ventricular endiastolic volume and stroke volume. Massive sympathetic activation with tachycardia and vasoconstriction is necessary to maintain normal blood pressure and cerebral perfusion in the upright position. However, some patients have an exaggerated vasoconstriction and produce blood pressures above control values even in the presence of an abnormally low cardiac output, suggesting true alpha-adrenergic hyper-reactivity. Maintaining a normal activity pattern and spending the day in the upright position, sitting, standing and walking then produces a chronic hyperadrenergic state.

Hypovolemia is also a common feature of the prolapse syndrome. The combination of increased alpha-adrenergic activity and hypovolemia in MVPS is reminiscent of the findings in patients with pheochromocytoma, in whom excessive cathecholamines cause a volume-contracted state. Other studies in normo- and hypertensive subjects have also documented a strong, general, inverse relationship between blood volume and the levels of sympathetic stimulation. Increased vascular tone in both arterial and venous systems reliably produces a rapid and marked decrease in total blood volume. The hypovolemia will become chronic if the increase in sympathetic drive persists. Mechanisms by which chronic vasoconstriction, hypovolemia, and MVP and MVPS might interact are presented in Figure 12.

Figure 12.

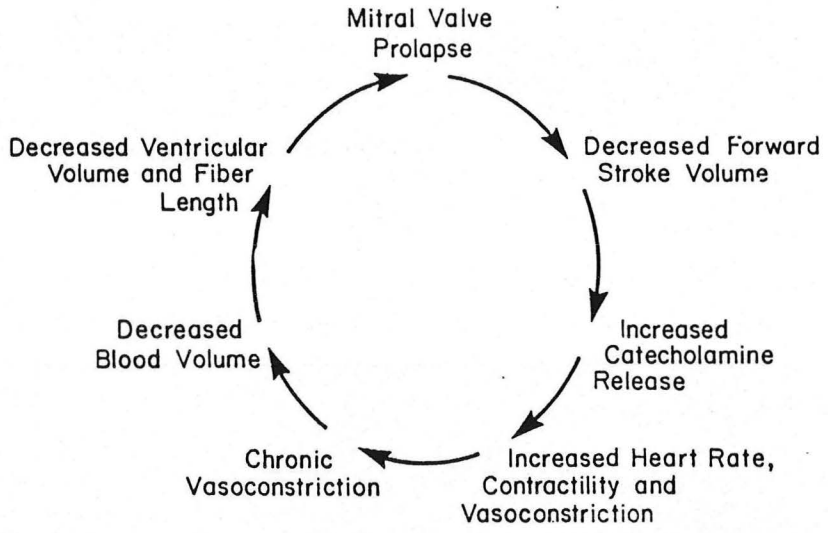

Figure 12. A proposed set of pathophysiological mechanisms linking mitral valve prolapse and autonomic nervous system dysfunction in a vicious cycle. A hemodynamically significant prolapse is not a requirement. From Gaffney and Blomqvist, 1988.

The hypovolemia and MVP combine to magnify the reduction in forward stroke volume that normally occurs during orthostatic stress. A vicious cycle is established when marked vasoconstriction is required to maintain arterial blood pressure and cerebral perfusion in the upright position. Substantial mitral regurgitation is not a pre-requisite for an exaggerated postural stroke volume reduction. The increasing volume contained by the ballooning mitral leaflets with decreasing ventricular size may produce, for any given reduction in left ventricular filling pressure, an exaggerated decrease in diastolic sarcomere length, fiber shortening, and forward stroke volume. These effects are likely to be further amplified by effects of hypovolemia on effective ventricular pressure-volume relationships (Figure 6). Measurements based on radionuclide ventriculography have shown marked reduction in left ventricular end-diastolic volume in MVP patients during upright rest and exercise. This supports the concept that decreased ventricular filling and forward stroke volume in the upright position are critical features in the pathophysiology of this syndrome (Gaffney et al., 1979, Gaffney and Blomqvist, 1988).

This relationship between MVP, reduced blood volume, and chronic vasoconstriction may well provide an explanation for the complex overlap of features in MVP and in a variety of functional and psychiatric syndromes (Wooley, 1976). Excessive vasoconstriction caused by chronic anxiety with elevated catecholamines, high resting heart rates, and diminished plasma and ventricular volumes may produce functional MVP defined as abnormal motion of a structurally normal mitral valve. Similarly, autonomic dysfunction with orthostatic intolerance in patients with myxomatous MVP could be expected to increase the frequency of symptoms such as palpitations, easy fatigability, near syncope and resting tachycardia which often are interpreted as signs of psychoneurosis.

Although studies specifically linking anxiety, vasoconstriction, and diminished blood volume are not available, a number of psychophysiological studies document a strong relationship between acute and chronic stress, anxiety, and vasoconstriction. This relationship forms the rationale for the use of skin temperature as an indicator of the levels of stress and anxiety when training subjects in relaxation techniques and biofeedback. There is also evidence that hypovolemia can be found in patients with severe, chronic stress and anxiety, directly related to serious somatic disease. The **"Missing Blood Syndrome"** refers to a profound hypovolemia in wounded Vietnam war casualties undergoing long-term reconstructive treatment. This "anemia" is actually a severe hypovolemia, characterized by a near-normal or even slightly elevated hematocrit. It is resistant to transfusion and iron therapy and associated with significant hypotension during surgery. It eventually disappears spontaneously when the patient's underlying condition has improved to a point when he otherwise is ready for discharge home.

Fouad et al. (1986) recently described a previously unknown variety of hypovolemia. They studied a group of 11 patients with orthostatic intolerance and a marked reduction (average -27%) in blood volume. Extensive diagnostic studies excluded pheochromocytoma and hypoaldosteronism. The hemodynamic pattern at rest supine was characterized by subnormal cardiac output and high peripheral resistance. The blood pressure tended to be labile, but

catecholamine responses to head-up tilt and cardiovascular responses to the Valsalva maneuver, to the cold pressor test, and to exogenous beta-adrenergic stimulation were all appropriate. The hemodynamic state at rest was temporarily normalized by blood volume expansion by intravenous human albumin. The syndrome was termed **idiopathic hypovolemia** in the absence of any identifiable cause of the abnormal cardiovascular state.

NORMOVOLEMIC HYPOREACTIVE ORTHOSTATIC HYPOTENSION

There is a wide spectrum of neurogenic causes of orthostatic hypotension. Bannister's (1988) classification (Table 3) of autonomic failure includes: **(1) Primary defects,** in which the disease process is well-defined and involves only a limited number of structural elements, **(2) Secondary defects,** in which the involvement of the autonomic nervous system is part of a more general process, and, **(3) Drug-induced autonomic failure.**

Orthostatic hypotension is often the first symptom of autonomic failure. Bannister (1988) suggested that the need for precise postural adjustments of the circulation arose during a late evolutionary stage, and that the mechanisms preventing orthostatic cerebral ischemia therefore are less robust than other more basic control systems. However, many patients with autonomic failure present with apparent Parkinson's disease or with bladder symptoms and impotence. Most of the different conditions listed in Table 3 are discussed in great detail in a recent monograph by Schatz (1986) and in Bannister's textbook (1988).

Schatz (1986) classified the neurogenic causes with respect to the anatomic site of the principal defect. Involvement of **afferent pathways** is relatively rare but occurs in diabetes mellitus, alcoholic neuropathy, and the Holmes-Adie syndrome. **Central lesions** with autonomic failure include familial dysautonomia (Riley-Day syndrome. Multiple cerebral infarcts and Wernicke's encephalopathy may induce autonomic dysfunction with orthostatic hypotension. Mild orthostatic hypotension is also often present in idiopathic parkinsonism.

The majority of the causes of neurogenic orthostatic hypotension involve primarily the **efferent pathways** of the autonomic nervous system. Pure autonomic failure (formerly idiopathic orthostatic hypotension) is characterized by denervation-type hypersensitivity to direct-acting catecholamines but decreased response to tyramine, and low peripheral catecholamine stores but increased alpha-adrenergic receptor density, all of which are features consistent with a post-synaptic lesion. Multiple System Atrophy (Shy-Drager Syndrome) is a more diffuse degenerative process. Abnormalities have been documented in several areas, including the solitary nucleus and preganglionic vagal neurons. Norepinephrine levels at rest are normal, and the peripheral sympathetic system is probably intact. Spinal cord trauma may affect the function of the intermediolateral column and produce orthostatic hypotension.

Table 3. **General Classification of Autonomic Failure.**
Modified from Bannister (1988).

1. Primary
   a. **Pure autonomic failure**
      (Bradbury-Eggleston syndrome, formerly idiopathic orthostatic hypotension)
   b. **Autonomic failure with multiple system atrophy**
      (Shy-Drager syndrome)
   c. **Autonomic failure with Parkinson's disease**

2. Secondary
   a. **General medical disorders**
      (diabetes, amyloid, carcinoma, alcoholism)
   b. **Autoimmune diseases**
      (acute and subacute dysautonomia, Guillaine-Barre, connective tissue diseases)
   c. **Metabolic diseases**
      (porphyria, B-12 deficiency, Tangier disease, Fabry's disease)
   d. **Hereditary disorders**
      (dominant or recessive sensory neuropathies, familial dysautonomia, familial hyperbradykinism)
   e. **CNS infections**
      (syphilis, Chaga's disease, herpes zoster, HIV)
   f. **CNS lesions**
      (vascular lesions or tumors involving hypothalamus or midbrain, multiple sclerosis, Wernicke's encephalopathy, Adie's syndrome)
   g. **Neurotransmitter defects**
      (Dopamine beta-hydroxylase deficiency)
   h. **Ageing**

3. Drugs
   a. **Tranquilizers**
      (phenothiazines, barbiturates)
   b. **Antidepressants**
      (tricyclics, monoamine oxidase inhibitors)
   c. **Vasodilators**
      (nitrates, hydralazine, calcium antagonists)
   d. **Adrenergic blocking agents**
      (central or peripheral action)
   e. **Angiotensin-converting enzyme inhibitors**

Autonomic failure is often generalized in diabetes. Orthostatic hypotension may be a relatively late manifestation. Its emergence is usually caused by sympathetic vasoconstrictor nerve damage. As mentioned, diabetic neuropathy may also involve afferent pathways. Any peripheral neuropathy may damage the adrenergic vasoconstrictor nerves. Chronic alcoholism may affect both the afferent and efferent limbs of the autonomic nervous system, but orthostatic hypotension usually occurs late.

TREATMENT OF CHRONIC ORTHOSTATIC HYPOTENSION.

1. Therapy for hypovolemic hyper-reactive orthostatic hypotension.

The following sequence of stepped care is intended primarily for patients with hypovolemic hypereactive orthostatic hypertension, e.g. patients with the mitral valve prolapse syndrome (Gaffney and Blomqvist, 1988), and related conditions.

1. Many patients with orthostatic hypotension are anxious and should be given a liberal amount of attention with detailed explanations and **reassurance.**

2A. A progressive **physical fitness program** is often helpful. Physical training causes a balanced increase in plasma volume and red cell mass, and also enhances the capacity for vasodilatation. Adrenergic activity at rest and during submaximal exercise is reduced (Blomqvist and Saltin, 1983). However, there are occasional patients with markedly impaired cardiac filling also during exercise (Gaffney et al., 1981). They often have very low exercise capacity and derive little benefit from physical training when it is used as the initial intervention. However, these patients may respond favorably if exercise is reintroduced at a later stage of treatment. Swimming has been recommended as an ideal form of exercise. The external hydrostatic pressure effectively prevents any activity-induced orthostatic symptoms, but water immersion, particularly upright immersion, is a powerful diuretic agent and rapidly induces acute hypovolemia (Blomqvist and Stone, 1983).

2B. **Generous salt and fluid intake** (to complement 2A). Many people have been impressed with the potential dangers of excess sodium chloride. Patients with MVPS, including symptoms of chest pain and palpitations, are particularly prone to self-imposed salt restriction which certainly is not needed in the presence of hypovolemia and low blood pressure.

3. **Low-dose clonidine treatment.** Clonidine is an alpha-2 adrenergic agonist. It also has central effects that usually produce adrenergic inhibition. The onset of the action is gentle, and side effects are mostly limited to sedation and dryness of the mouth. The alpha-antagonistic effects usually dominate in subjects with a grossly intact autonomic nervous system, and clonidine has the capacity to break the vicious circle of vasconstriction, hypovolemia, and orthostatic intolerance in patients with MVPS.

Clonidine treatment for at least a month resulted in reduced postural catecholamine responses and relative vasodilatation in the upright position but markedly improved orthostatic tolerance in a series of 8 patients (Figure 13) studied by Gaffney et al. (1983). The treatment also caused a 12% expansion of the plasma volume. Significant improvement was evident measured both by symptoms and by quantitative analysis of the postural hemodynamic responses. Clonidine treatment progressed at two-day intervals from 0.05 mg orally at bed time to 0.4 mg/day, or to side effects.

Figure 13.

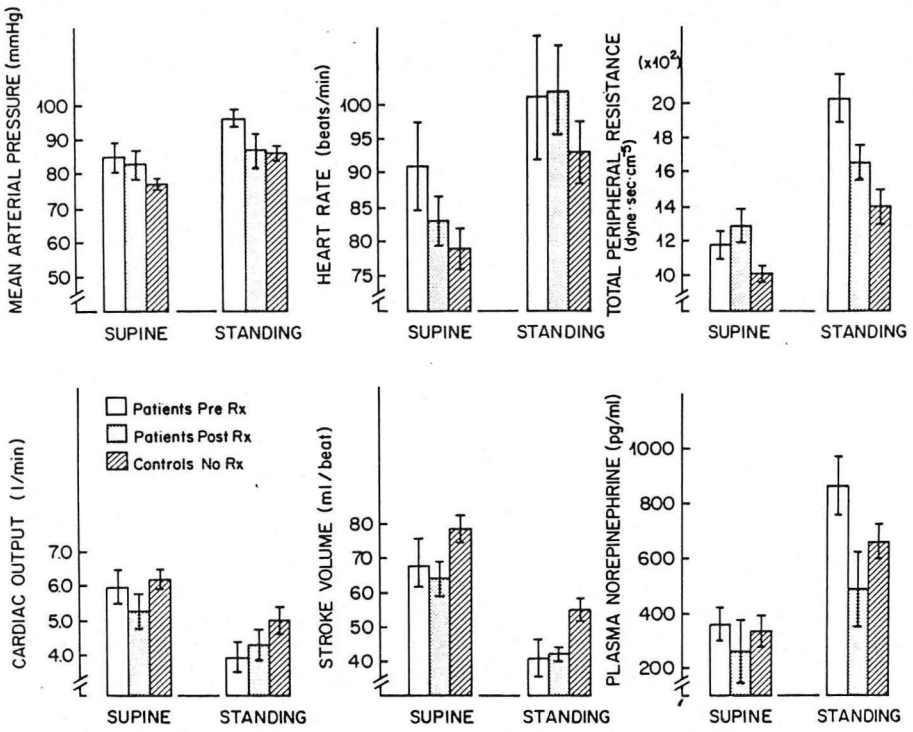

Figure 13. Hemodynamic and neuroendocrine measurements in controls and in patients before and after long-term oral clonidine administration (values are means ± SE). From Gaffney et al., 1983.

Coghlan has successfully used a similar regimen at the University of Alabama, Birmingham (personal communication to Dr. Gaffney). The patients with idiopathic hypovolemia studied by Fouad et al. (1986) received clonidine in low doses (0.1 to 0.2 mg/day) as an effective adjunct to plasma expansion therapy with hydroflourocortisone (0.1 mg b.i.d.) and a high-sodium diet.

Thus, the central adrenergic inhibitory action of clonidine that makes it effective in essential arterial hypertension produces equally beneficial effects in hypovolemic hyper-reactive orthostatic hypotension. Clonidine has also proved to be a useful agent in patients with severe idiopathic hypotension and complete loss of peripheral neural sympathetic and parasympathetic control. In these patients,the alpha-2 agonist properties totally dominate and produce vaso- and venoconstriction with a substantial increase in blood pressure (Robertson et al., 1983).

4. Progression to the treatment usually reserved for patients with normovolemic hyporeactive orthostatic hypotension is indicated if measures 1 through 3 prove ineffective.

2. Therapy for normovolemic hyporeactive orthostatic hypotension.

The approach to therapy is generally more complex in the hyporeactive group. It is often very difficult to determine the exact nature, localization, and extent of the underlying disease process. As a consequence, the therapy will often have an empirical component.

Bannister and Mathias (1988) have reviewed general principles for management and made several important points. Patients with chronic hyporeactive orthostatic hypotension tend to adjust their autoregulatory range for adequate cerebral blood flow. They are often able to maintain adequate cerebral perfusion at subnormal arterial pressures, e.g. at systolic levels of about 60 mmHg compared to 80 in most normal subjects. Therapy should therefore be guided by symptoms and signs of cerebral ischemia rather than by the blood pressure. Furthermore, consistently normal pressures in the upright position can often only be maintained at the cost of inducing hypertension in the supine position. Comprehensive approaches to treatment have been formulated by Schatz (1986) and by Bannister and Mathias (1988).

General Considerations and Recommendations. Trivial stresses can produce symptomatic hypotension in patients lacking essential elements of the blood pressure control system; straining during micturation or defecation, exposure to a warm environment, or having an ordinary meal. Carbohydrates are more likely to induce hypotension than fats or proteins, perhaps via release of insulin and gastrointestinal hormones with vasodilator properties. Alcohol is prone to cause further vasodilatation. On the other hand, **caffeine** has been found to minimize post-prandial hypotension in a placebo-controlled study (Onrot et al., 1985). **Vasoactive drugs** should be avoided. The response to vasodilators is amplified for lack of defense mechanisms and the effects of vaso- and venoconstrictors may be greatly magnified by denervation hypersensitivity.

Most patients with chronic orthostatic hypotension have a definite circadian rhythm with minimal pressures during the morning hours. **Head-up tilt** at night, first proposed by Maclean and Allen (1940), minimizes the redistribution of body fluids that otherwise occurs at night. Normally, the central fluid shift during supine bed rest increases cardiac filling and causes a diuresis with a loss of intravascular and interstitial fluid. These losses -which tend to be abnormally large in patients with autonomic failure- are contained by the use of the head-up tilt. There is often a significant improvement of the blood pressure levels during the day and nocturnal hypertension is avoided. External support, in the form of a custom-fitted **counterpressure garment**, is quite effective in many patients. The garment is constructed of an elastic mesh of graded firmness to match the postural

hydrostatic gradients. The disadvantages of the approach become obvious in a hot climate.

Pharmacological approaches.

A summary of current pharmacological approaches is given in Table 4, modified from Bannister and Mathias (1988).

Table 4. Drugs used in the treatment of postural hypotension. From Bannister and Mathias, 1988.

Site of action	Drugs	Predominant action
Vessels: vasoconstriction		
Adrenoceptor mediated:		
Resistance vessels	Ephedrine	Indirectly acting sympathomimetic
	Midodrine, phenylephrine, methylphenidate	Directly acting sympathomimetics
	Tyramine	Release of noradrenalin
	Clonidine	Postsynaptic α-adrenoceptor agonist
	Yohimbine	Presynaptic α_2-adrenoceptor antagonist
Capacitance vessels	Dihydroergotamine	Direct action on α-adrenoceptors
Vessels: prevention of vasodilatation		
	Propanolol	Blockade of β_2-receptors
	Indomethacin	Blockade of prostaglandins
	Metoclopramide	Blockade of dopamine
Vessels: prevention of postprandial hypotension		
	Caffeine	Blockade of adenosine receptors
	SMS 201–995	Blockade of vasodilator peptides
Heart: stimulation		
	Pindolol	Intrinsic sympathetic action (I.S.A.)
	Xamoterol	
Plasma volume expansion	Fludrocortisone	1. Mineralocorticoid effects 2. Increased plasma volume 3. Sensitization of α-receptors to noradrenalin
Kidney: reducing diuresis	Desmopressin	Action: V_2-receptors of renal tubules

By the nature of these diseases, most agents have been used only in very small groups of patients, and it is difficult to provide adequate evaluation of any single specific approach. The use of **clonidine** has been discussed in an earlier section. **Dihydroergotamine** is a direct-acting alpha-adrenergic agonist that may preferentially cause venoconstriction. The principal disadvantage is poor bioavailability. **Indomethacin** has been used to negate

the vasodilator effects of prostaglandin, but may be effective primarily by increasing smooth muscle sensitivity to norepinephrine. **Fluorohydrocortisone (fludrocortisone)** is the most widely used of all pharmacological agents applied to the treatment of orthostatic hypotension. Its multiple actions include plasma volume expansion and sensitization of vascular receptors to pressor amines, perhaps by increasing the number of adrenergic receptors. The initial dose in autonomic failure is 0.1 mg daily.

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