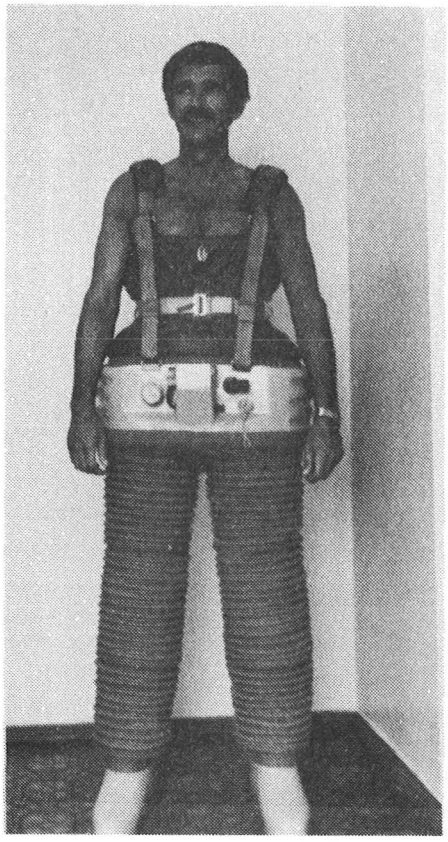
MEDICAL GRAND ROUNDS

November 5, 1981



ORTHOSTATIC HYPOTENSION

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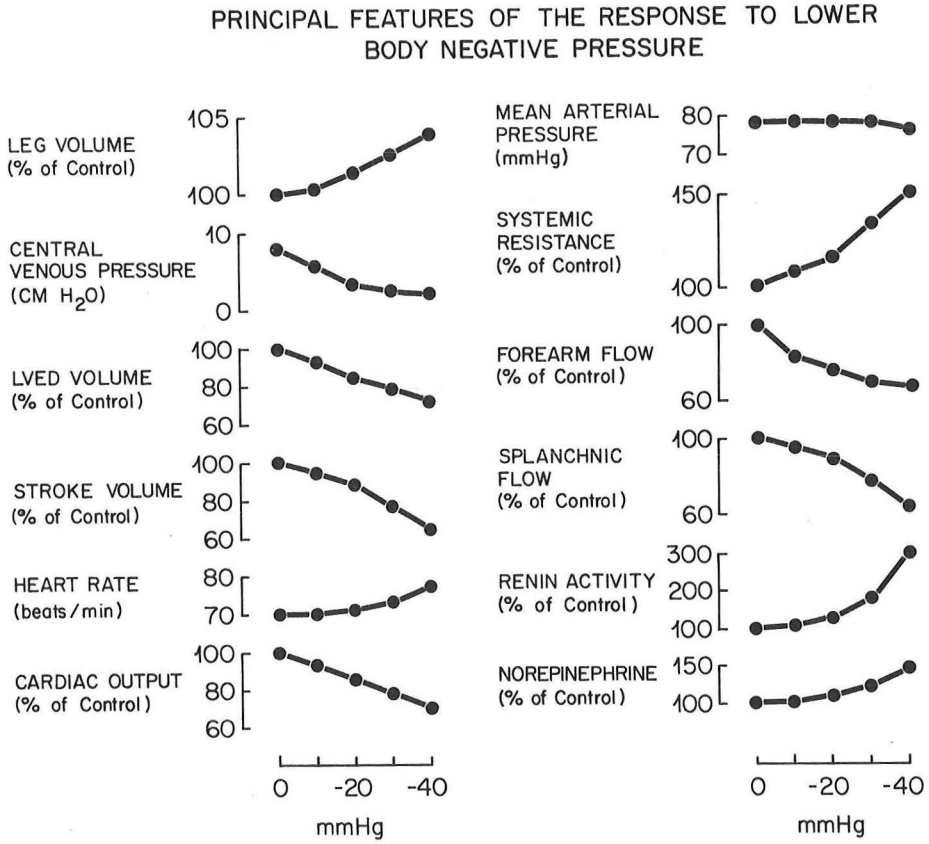
Introduction

Orthostatic hypotension, simply defined, is the inability to maintain an adequate blood pressure in the upright position. There are so many causes of orthostatic hypotension that virtually every specialist, whether medical or surgical, can list several etiologies specific to his or her field of expertise. This etiological variability has produced a rather large body of literature which at times is more confusing than enlightening. The purpose of this Grand Rounds will be to provide the reader with a physiological approach to the understanding, diagnosis, and treatment of orthostatic hypotension. Because baroreceptors (Longhurst, 1980) and autonomic dysfunction (Henrich, 1980) have been discussed recently in Grand Rounds, other aspects of the problem will be given more emphasis.

Normal Response to Upright Posture

When a person stands, gravitational forces produce a pooling of blood in the body below the diaphragm (Figure 1).



In the average size adult, about 500-750 ml will collect in the veins of the legs and buttocks. Some additional volume may be transferred into the splanchnic circulation although this is not well established. This reduces venous return to the right atrium and right ventricle. A decrease in right ventricular stroke volume occurs and within one or two beats reduces left ventricular output proportionately. The decreased systemic output lowers systemic arterial pressure. In a normal individual, compensatory mechanisms quickly act to maintain arterial blood pressure at or above supine levels (Gauer and Thron, 1965).

Probably the first response to diminished venous return occurs at the level of the right atrium (Figure 2).

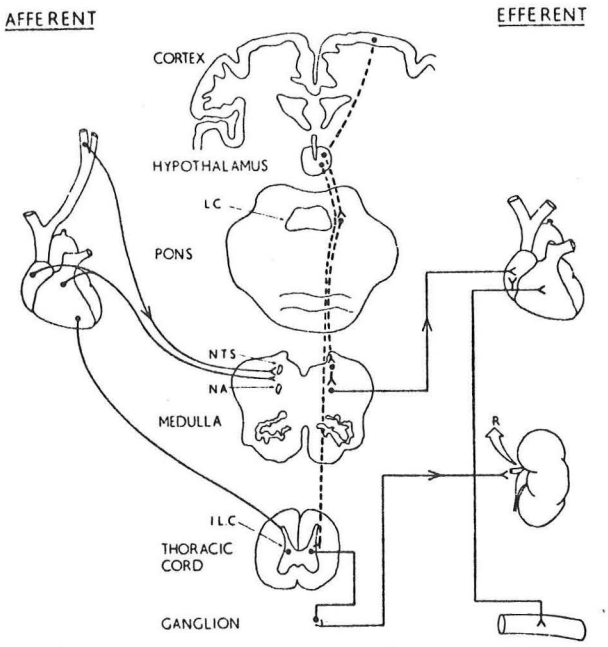


Fig. 2 Diagram of cardiovascular control mechanisms.

L.C.—locus ceruleus; N.T.S.—nucleus tractus solitarius; I.L.C.—intermediolateral column; R.—renin.

Receptors in the region of the junction of the vena cavae and atrium are stimulated. Radiation of these venoatrial fibers to the vasomotor center in the mid brain produces a generalized vasoconstriction, especially in skin and muscle with little effect on splanchnic flow. There also appear to be atriorenal fibers which augment renin release. Fibers in the left atrium serve a similar function. These fibers and responses collectively are referred to as the low pressure baroreceptor system. While these responses are important,

they alone are not adequate to maintain arterial blood pressure (Shepherd and Vanhoutte, 1979).

Carotid and aortic reflexes are the other major component of the overall response. The stretch receptors, located not only in the carotids, but throughout the thoracic aorta, are deformed less by the lower systolic pressure and respond with decreased afferent neural activity. This is processed in the same cardiovascular centers as the atrial afferent traffic, but has a somewhat different efferent activity. Vasoconstriction in skin and muscle beds is augumented. Splanchnic flow is reduced, vagal tone from the heart withdrawn, and sympathetic stimulation increased.

The increased contractility augments stroke volume by reducing end-systolic volume; an increased heart rate also raises cardiac output (CO = SV X HR). Increased resistance to flow in "non-essential" areas raises systemic arterial pressure and diminishes venous volume in those areas by reducing venous inflow pressure. Systemic arterial pressure is thus maintained at or above supine levels (Rowell, 1974). It may seem inefficient to increase pressure above supine levels but in the upright position, an increase of about 20 mmHg is required to maintain cerebral perfusion pressure at supine levels.

It is important to note that active venoconstriction does not seem to play an active role in the normal response to upright posture (Samueloff et al., 1966). Venoconstriction occurs in response to a variety of stimuli including a deep breath, a decrease in ambient temperature, psychological arousal and marked arterial hypotension, but probably is unimportant in the immediate adaptation to upright posture. Recent studies in our laboratory do suggest that slow changes in venous tone do occur in response to alternations in posture, but their time course renders them unimportant as an acute adaptive mechanism.

The above discussion of hemodynamic changes assumes that the individual in an upright position stands quietly. With the first step, muscular contraction in the legs dramatically decreases the hydrostatic gradient which produced leg venous pooling. The increased muscle pressure and venous valves which prevent back flow, constitute the "muscular venous pump" which reduces venous pressure at the level of the ankle from about 80 mmHg when standing still to 20 mmHg while walking (Pollock and Wood, 1948).

Pathophysiology of Orthostatic Hypotension

As one can see, adaptation to the upright posture is a complex response upon which we are critically dependent. A failure to compensate produces diminished venous return and may result in fatigue, confusion, lightheadedness, syncope and seizures. Since the symptoms of orthostatic hypotension are similar, regardless of etiology, they offer few clues for diagnosis and treatment. For that reason, a more systematic approach is required.

One such approach, based on pathophysiology, is to divide the various forms of orthostatic hypotension into two simple categories. Thulesius (1976) termed these "sympathicotonic" and "asympathicotinic." Alternatively, one could refer to these as Hyper- or Hypo- Adrenergic Hypotension (Cryer, 1978). The latter terms will be utilized throughout the rest of this discussion.

Hypoadrenergic Orthostatic Hypotension is the type with which most physicians are familiar. It includes the "Idiopathic Orthostatic Hypotension" described by Bradbury and Eggleston in 1925. Their 3 patients, all men, were 39, 50, and 67 years old. They all complained of weakness, syncope, and anhidrosis. Constipation and impotence were also noted. Their blood pressure fell precipitously whenever they stood. There was a notable absence of tachycardia, despite blood pressures as low as 40/28 mmHg.

The authors correctly noted that these rather diffuse symptoms and signs were a "peculiar disturbance of the autonomic nervous system." Intervention with sympathomimetic drugs and autonomic testing showed there was a loss of peripheral vascular control and a "denervation hypersensitivity." A number of case reports subsequent to theirs confirmed these observations, but added little new clinical information, although neuropathological and endocrine changes are much better understood.

A summary of the literature to that date was published by Wagner in 1959. He reviewed the normal physiology of standing and presented his own cases of various etiological types of orthostatic hypotension. Virtually all fell into the category of "hypoadrenergic hypotension." Less than 6 months after Wagner submitted his extensive review, Shy and Drager (1960) reported two cases of orthostatic hypotension associated with peripheral and central neurological symptoms. These will be discussed in greater detail later, but briefly, their patients had dysautonomia similar to Bradbury's and Eggleston's patients, but also had "Parkinsonian" - like symptoms. Typical neuropathological features were also described and have subsequently been reported under the name Shy-Drager Disease.

A lack of autonomic responsiveness causing orthostatic hypotension has been reported in a number of other clinical states including diabetes mellitus, Parkinson's disease itself, and chronic renal failure. Again, bradycardia and a lack of vasoconstriction associated with widespread autonomic dysfunction are the recurring theme (Thomas et al., 1981). These will be discussed individually in subsequent sections.

Hyperadrenergic Orthostatic Hypotension has been identified much less frequently. Although cases were probably described by DaCosta (1871), Hill (1895), Lewis (1919), and Grant (1925) (see Wooley, 1976), other symptoms of sympathetic nervous system hyperactivity were emphasized, and little attention was paid to the orthostatic hypotension these patients experienced. Unlike the bradycardia of the hypoadrenergic forms, a marked tachycardia is often

present, as are clinical signs of increased vasoconstrictor activity - cold extremities, pale skin, etc. Wagner (1959) suggested that a defect in venoconstriction might be present, but previous (Stead and Ebert, 1941) and subsequent works show this to be incorrect (Samueloff et al., 1966). Cryer et al. (1978) were probably first to use the term "hyperadrenergic" hypotension in their description of four diabetic patients with orthostatic hypotension. Their patients increased plasma catecholamines and heart rates excessively on standing. Alterations in blood volume were suspected. Tomeh et al. (1979) restudied some of these patients, and confirmed that lower plasma and blood volumes were present. An interplay between diabetic autonomic neuropathy and hypovolemia was a suggested cause for their findings. This explanation is somewhat contradictory, however, in that it implies the presence of simultaneous hypo- and hyperactive states of the same sympathetic autonomic components. An alternate explanation will be proposed after additional forms of hyperadrenergic orthostatic hypotension have been presented.

Clinical Descriptions of Orthostatic Hypotension

Shy and Drager (1960) originally reported two cases of a distinct neurological disorder characterized by orthostatic hypotension, relative bradycardia despite profound orthostatic hypotension, iris atrophy, diminished extraocular movements, tremor, slurred speech, anhidrosis, urinary incontinence, constipation, and fecal incontinence. Generalized muscle weakness, atrophy, fasciculations, and dysmetria were present. Sensation and deep tendon reflexes were well preserved. An electroencephalogram was normal with the patient in the recumbent position, but was markedly abnormal when the patient was tilted. (The changes are typical of cerebral hypoperfusion and probably have nothing to do with Shy-Drager disease per se (Hickler et al., 1959; Sharpe et al., 1972)) (vide infra). The patients were hypertensive while supine and had a further rise in pressure with water loading. Aldosterone secretion with normal and low sodium diets was probably normal. Additional laboratory testing including blood and cerebrospinal fluid chemistries as well as muscle biopsies were normal. One of the two patients died six and one-half years after the onset of his illness and was autopsied.

The brain was grossly normal as were the meninges, spinal cord and autonomic ganglia. Microscopically, the chief changes were in the neuronal elements which were pale with decreased Nissl substance. In the brain, the dorsal nucleus of the vagus, inferior olivary nucleus, cerebellum, locus caeruleus, substantia nigra, and caudate nucleus were particularly affected by cell loss. The intermediolateral columns of the spinal cord showed a profound loss of cells.

Shy and Drager noted the similarity of many of these changes to a disorder called olivo-ponto-cerebellar atrophy (OPCA) and Parkinsonism, but felt that the clinical features (especially orthostatic hypotension, anhidrosis, and ocular disturbances) made their cases unique. (See Johnson et al., 1966

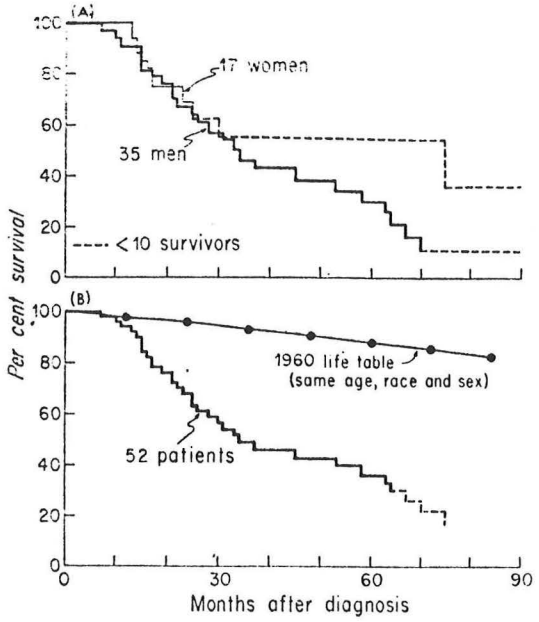
for additional cases and a superb discussion of the overlap of these various disorders.)

Since their report, over 100 more cases of Shy-Drager disease have been reported. Perhaps the largest series is from Thomas and Schirger (1970) at the Mayo Clinic. They found 57 cases from among 532 orthostatic hypotension patients examined at the Clinic from 1963-1968. Of these, two thirds were men, ages were 42-76 with a mean age of 60 years. The average onset of symptoms was at age 55 (37-75 yrs). The prevalence of symptoms and signs is shown in Table I.

Symptom Group	Patients
Postural dysfunction	54
Somatic neurologic dysfunction	48
Urinary dysfunction	37
Bowel dysfunction	17
Impaired potency-libido	29
Decreased sweating	6
Gait disturbance	22
Speech disturbance	18
Generalized weakness	16
Tremor of limbs	15
Clumsiness of limbs	11
Impaired hand writing	10
Numbness of limbs	8
Swallowing disturbance	7

Sign	Patients
Corticobulbar-corticospinal system	
Hyperreflexia	48
Extensor toe signs	29
Dysarthria	17
Sucking reflex	13
Extrapyramidal system	
Masking of face	33
Rigidity with or without cogwheeling of limbs	29
Monotony of voice	18
Rest tremor of limbs	16
Cerebellar system	
Intention tremor of limbs	23
Ataxia of gait	22
Ataxic-dysarthric speech	2
Miscellany	
Horner's syndrome	9
Anisocoria	8
Decreased ankle jerks	6
Intellectual impairment	4
Sensory impairment	1

Pathological findings were typical, i.e., nearly all autopsied patients had involvement as described initially by Shy and Drager. The consistency of neural involvement led them to agree with the original authors that Shy-Drager is a primary degenerative disease of the central nervous system. These patients' prognosis is dismal. Survival curves are shown in Figure 3.



Survival curves for 52 patients with IOH. A indicates for men and women separately; B, for both sexes, combined with comparable survival curve from general population.

Figure 3

Physiological studies have been carried out in Shy-Drager patients by a number of investigators. Bannister et al. (1967) performed lower body negative pressure in four Shy-Drager patients. Arterial blood pressure fell dramatically with no increase in forearm vascular resistance. Changes in calf volume were normal or decreased suggesting normal resting venous tone. Heart rate varied little or none. A marked hypertension occurred on release of the lower body negative pressure.

Mental arithmetic, which normally causes vasoconstriction and elevates arterial pressure, failed to do so. Likewise, the tachycardia and overshoot of arterial pressure with the Valsalva maneuver were absent. Reflex changes in response to heating or cooling could not be elicited. Virtually total anhidrosis was seen in all four patients. From these tests, they concluded that Shy-Drager patients had a profound efferent autonomic defect.

Botticelli et al. (1968) and Chokroverty et al. (1969) performed similar tests and obtained identical results. In addition, they noted a denervation hypersensitivity to exogenously administered norepinephrie and other sympathicomimetics. This has also been reported by Barnett (1968), Kochar and Itskovitz (1978), Niarchos et al. (1978), and Polinsky et al. (1981) (Figure 4).

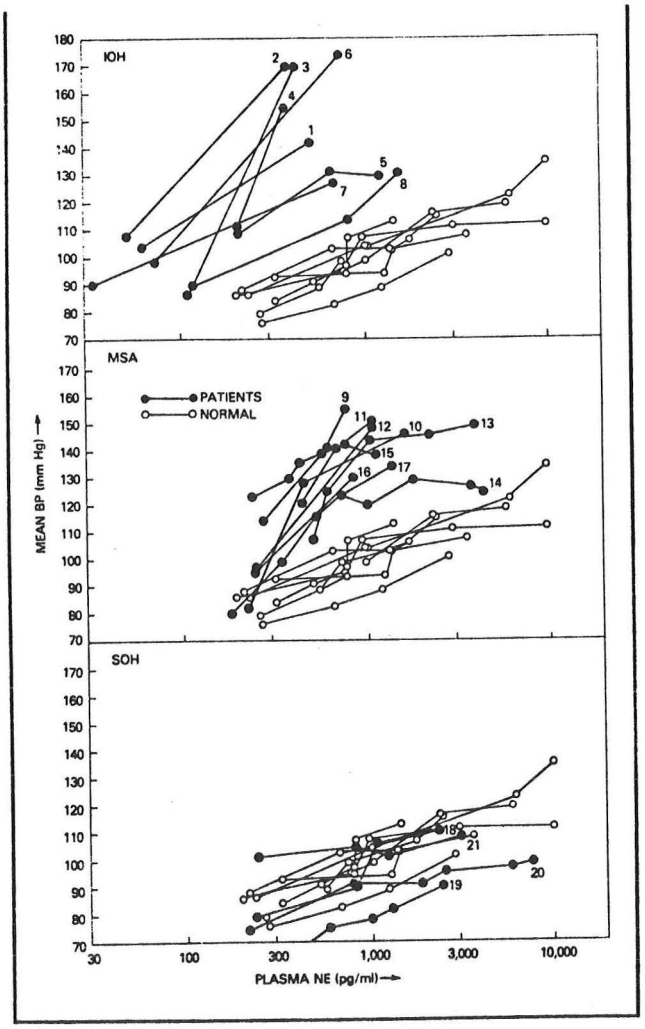


Figure 4 The relationship of plasma norepinephrine levels to mean blood pressure during intravenous infusion of norepinephrine. Control subjects are shown by open circles, and patients (multiple system atrophy = MSA, idiopathic orthostatic hypotension = IOH, sympathotonic orthostatic hypotension = SOH) by closed circles.

In interpreting the pressor response to infused sympathomimetics, it is important to remember that the pressor response is usually attenuated by baroreflexes. Patients with autonomic dysfunction fail to regulate blood pressure properly in either direction, so the altered sensitivity may reflect diminished baroceptor depressor action and not true hypersensitivity. An example of this is seen with normal subjects performing isometric exercise while the carotid baroreflexes are transiently inactivated. An additional 20-40 mmHg rise in pressure is produced (Ludbrook et al., 1978). The only study in which receptor number was actually measured counted β receptors, not α receptors. The latter are the most likely "cause" of the pressor response (Hui and Conolly, 1981). Möhring et al. (1980) infused arginine vasopressin in 2 patients with Shy-Drager. There was almost a thousand-fold increase in pressor response compared with normals, whereas norepinephrine and angiotensin II had 2-8 fold increases in responsiveness (Table II). These investigators postulated a specific effect on baroreflex "gain" to explain their findings.

TABLE II *Doses of angiotensin II and noradrenaline that increase mean arterial blood pressure by 10 or 20 mm Hg in two subjects with idiopathic orthostatic hypotension (E.F. and R.S.) as compared to normal subjects (means and ranges)*

Group	Angiotensin II (μg/kg/min)		Noradrenaline (μg/kg/min)	
	10 mm Hg	20 mm Hg	10 mm Hg	20 mm Hg
Normal subjects (n = 8)	5.9 (4.0–6.5)	9.3 (6.5–12)	32.0 (19.5–46.0)	51.0 (31–73)
Patients				
E.F.	1.5	2.1	18.5	29.5
R.S.	0.6	0.9	15.0	23.0

Catecholamines, renin, and aldosterone were studied in postural hypotension by Hedeland et al. (1969). Although this study is often quoted, it should be noted that only one of their two patients had Shy-Drager disease. The other, a 41 year old woman, had tachycardia, diarrhea, and severe depression, i.e., "hyperadrenergic" orthostatic hypotension (vide infra). There were, however, decreased urinary catecholamines and plasma renin activity in both patients. Numerous other investigators have confirmed these findings, i.e., low renins, but report normal aldosterone excretion (Botticelli et al., 1968; Chokrovety et al., 1969; Bliddal and Nielsen, 1970; Morganti et al., 1970; Love et al., 1971; Wilcox et al., 1974 and 1977; Kállay and Bencsáth, 1976; Mathias et al., 1977; Kochar and Itskovitz, 1978). Only Morganti et al. (1979) speculate on why the urinary aldosterone is normal and appropriate for sodium intake while the plasma renin activity is so low. They believe that activity of the renal baroceptors provides the stimulus for aldosterone release. It would appear that patients with Shy-Drager have low PRA and low or normal aldosterone excretion. All of the studies are difficult to interpret because, in addition to altering sodium intake, arterial and, therefore, renal perfusion pressures vary tremendously (Figure 5).

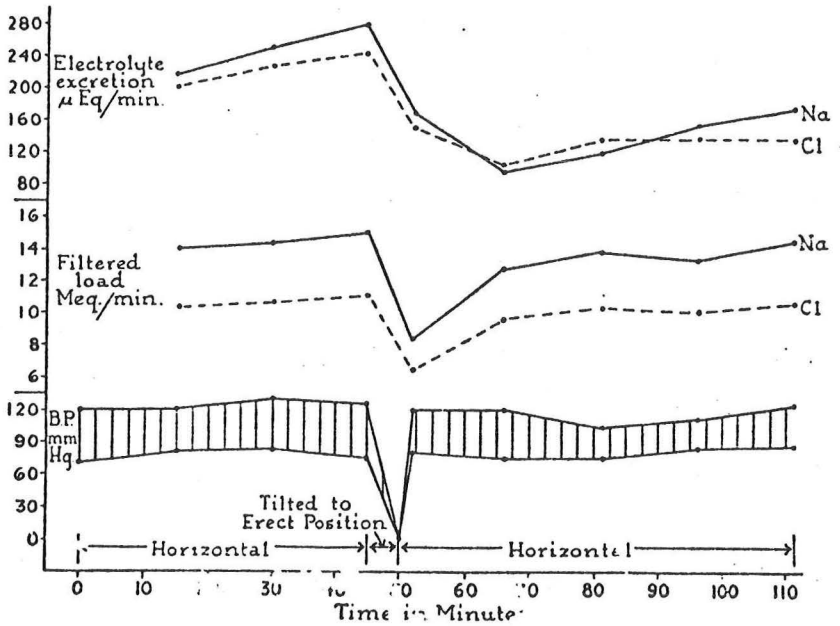


FIG. 5 Comparison of filtered Na and Cl loads with Na and Cl excretion in orthostatic hypotension.

Creatinine clearances during daytime upright posture may be half of the nighttime values. Daytime hypotension is often followed by nighttime hypertension (Scherba, 1954). Although a level of aldosterone appropriate for the level of dietary sodium is found when sodium is withheld, resultant vascular volume changes worsen orthostatic hypotension and provide additional stimulus for aldosterone release. Hence, one cannot say whether the aldosterone release is normal or low if only dietary sodium is considered.

Actual measurements of plasma catecholamines were performed by Hickler et al. (1959) and were shown not to increase normally with tilting. Ziegler et al. (1977) reported similar findings with orthostatic stress, but using the more sensitive radioenzymatic technique showed that resting norepinephrine levels were normal. In contrast, patients with Idiopathic Orthostatic Hypotension (peripheral autonomic neuropathy without the central nervous system manifestations of Shy-Drager) had low supine norepinephrine levels. They too failed to increase their plasma catecholamines on standing (Figure 6).

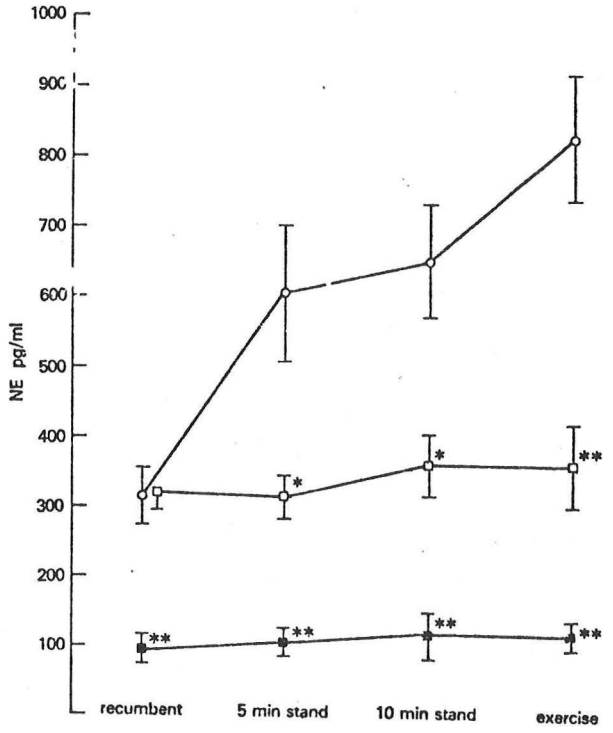


Figure 6 Plasma Norepinephrine (NE) Levels (Mean ±S.E.M.) while Subjects Were Recumbent, Standing for Five and 10 Minutes and while They Were Exercising.

NE concentrations are shown for 10 control subjects (○), six patients with normal plasma norepinephrine while recumbent (□), who also had diffuse neurologic signs (Shy–Drager syndrome), and four patients with low plasma norepinephrine while recumbent (■), who did not have diffuse neurologic signs (idiopathic orthostatic hypotension).

*Different from control subjects ($P<0.01$ by Student's t-test).

**($P<0.001$).

This difference in resting catecholamines has been confirmed and appears to be useful clinically in identifying central versus peripheral forms of hypoadrenergic hypotension (Polinsky et al., 1981). Differential responses to tyramine and norepinephrine have served a similar function (Polinsky et al., 1981).

Petito and Black (1978) examined tissue catecholamine metabolism in Shy-Drager disease. They found depressed tyrosine hydroxylase activity in the central nervous system locus caeruleus, but normal levels in the post-synaptic ganglia (peripheral). Dopamine β hydroxylase was depressed in the neurons of the sympathetic ganglia. Choline acetyltransferase, which catalyzes acetylcholine biosynthesis in presynaptic cholinergic nerve terminals was normal. They concluded that Shy-Drager disease primarily affects noradrenergic neurons, but there is substantial variability among patients. These findings suggest defects in presynaptic norepinephrine synthesis. However metabolism and excretion of norepinephrine appears to be normal (Goodall et al., 1967 and 1968).

Quik et al. (1979) have used [^{3}H] spiperone binding to assess dopaminergic receptor affinity in the substantia nigra and caudate nucleus of patients with Shy-Drager, or Parkinson's disease. Both seem to be associated with decreased binding in the substantia nigra, but decreased affinity in the caudate nucleus was seen only with Shy-Drager. The authors suggest that this may account for different responses to levodopa and that perhaps Shy-Drager patients might require higher doses.

Cerebral blood flow regulation during hypotension may be disturbed in patients with Shy-Drager. Carrona and Plum (1973) measured regional blood flow by the Xenon-133 washout technique and found "breaks" in autoregulation in 4 patients, 3 with Shy-Drager and 1 with Idiopathic Orthostatic Hypotension. They believed that the autonomic nervous system was involved in "autoregulation," but in an unspecified way. Depresseux et al. (1979) noted normal flow with normal perfusion pressure, but regional inequalities between frontal (increased) and occipital (decreased) areas were noted with orthostatic hypotension. The response to changes in pCO_2 during hypotension was subnormal. These hypotension induced changes were self-correcting after several minutes and were associated with significant improvement in cortical function. It is possible that the time course for "autoregulation" may be longer than previously believed. Shinohara (1978) postulated that diminished responsiveness to increases in pCO_2 was due to an inability of a maximally dilated system to dilate further. Calculations of cerebral vascular resistance would have been useful in answering this question, but these were not provided. It appears that regardless of etiology severe postural hypotension affects regulation of cerebral blood flow and distribution, but the studies in 8 patients thus far do not provide sufficient data for definitive conclusions.

In summary, Shy-Drager disease is a progressive, fatal disorder, primarily affecting men over age 40. Central and peripheral manifestations of autonomic dysfunction are combined with a Parkinson's disease like picture. Baroreflexes are generally absent. Profound orthostatic hypotension is combined with supine hypertension. Norepinephrine and renin release in response to upright posture and profound hypotension are abnormally low, but aldosterone secretion appears to be appropriate, at least for the level of

dietary sodium intake. It is probably too low if one considers the level of orthostatic stress present. There is no specific therapy, but general measures may be effective. These will be discussed in a later section.

Diabetes Mellitus

The presence of autonomic neuropathy in diabetics has been well described by several authors (Sharpey-Schafer and Taylor, 1960; Ewing et al. 1976; Hosking, 1978; Henrich, 1980). Sharpey-Schafer examined responses to tilt, cough, hyperventilation, and mental arithmetic in 337 unselected diabetics. Seventeen had absent reflexes, 14 had partial defects, while 3 had postural syncope. Watkins and Mackay (1980) had similar findings in 287 diabetics. They noted apparently progressive degrees of autonomic involvement. About one-half the patients had intact knee and ankle jerks, although many required augmentation for this to be elicited. About one-third had a peripheral sensory neuropathy, but no autonomic neuropathy. Sixty patients had evidence of autonomic involvement including orthostatic hypotension (25 patients), diarrhea (43 patients), gustatory sweating (37 patients), gastric atony (9 patients), and bladder atony (5 patients). More than half the patients in this group had multiple defects. These findings suggest that, in addition to hypoglycemia, postural hypotension should be ruled out when syncope, dizziness, etc. are present in patients with diabetes mellitus.

The various metabolic and anatomic defects possibly responsible for these findings were discussed by Hosking et al. (1978). They note that although segmental demyelination and axonal degeneration have been found in autonomic nerves, there is a general lack of specific clinicopathological findings. While they agree that peripheral sensory and autonomic dysfunction usually coexist, their timing and extent of involvement vary widely. They also report that they have never seen sympathetic involvement in the absence of parasympathetic disease, although the converse is often found. There is often an intact afferent, but defective efferent system, e.g., the diving reflex - facial immersion in ice water - produces some bradycardia, but peripheral vasoconstriction fails to occur. Moorhouse et al. (1966) also described the autonomic defect as an "efferent" deficit. They, like Hosking's group, also demonstrated apparent denervation hypersensitivity to catecholamine infusions. Again, baroreflexes are abnormal in these patients also, so "Hypersensitivity" data should be interpreted with caution.

Local vasoconstrictor "autoregulation" was studied by ^{133}Xe washout in diabetics with varying degress of peripheral sensory and autonomic involvement (Hilsted, 1979). Abnormal autoregulation in the microvasculature at the level of the ankle was found in diabetics with autonomic dysfunction.

Plasma catecholamine release with standing was studied in 100 non-ketotic diabetics by Cryer et al. (1978). Almost three-quarters had a normal rise in norepinephrine and no orthostatic hypotension. Fifteen had orthostatic hypotension but "normal" norepinephrine levels standing. In a functional sense, a

"normal" norepinephrine level with hypotension is not really normal, in that the hypotension should have triggered a greater release. The cause for this was not found.

Tohmeh et al. (1979) restudied the hyperadrenergic patients in Cryer's study. Plasma and blood volume were significantly reduced. Hematocrits in 3 of the 4 patients were above the average for the other 96 patients. Two of the four had large amounts of glycosuria, but two did not. Likewise, these 4 had increased supine and standing plasma norepinephrine levels and orthostatic hypotension. Another 7 patients had similar catecholamines, but no orthostatic hypotension. The authors did not have an explanation, except that a contracted volume state might play an important role. This does not explain why the supine catecholamines were elevated, nor why the patients without glycosuria should be volume contracted. In other words, are the catecholamines elevated because of volume contraction or vice versa?

It would appear that many patients with diabetes have autonomic neuropathy which often produces postural hypotension. In most cases, this is due to a lack of sympathetic (efferent) responsiveness of baroreflexes, but rarely represents a hyperadrenergic, hypovolemic orthostatic hypotension. The presence of these autonomic defects seems to be associated with a significantly higher mortality in diabetes (Ewing et al., 1976), although the deaths in this series, were not, on the whole, directly related to autonomic dysfunction (Ewing, 1980; Figure 7).

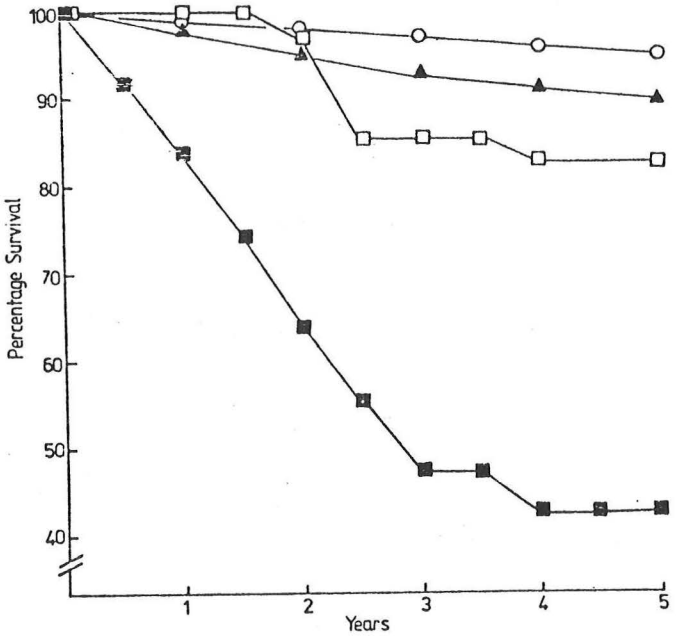


Figure 7 Five-year survival curves for age- and sex-matched general population (○), age- and sex-matched diabetic population (▲), 33 diabetic patients with normal (□) and 40 diabetic patients with abnormal (■) autonomic function tests.

Treatment of these patients is non-specific and will be discussed later. An exception is that insulin administration has been reported to worsen postural hypotension (Page and Watkins, 1976; Palmer et al., 1977). Insulin administration produces an increased plasma epinephrine level which reduces plasma volume. Presumably, this decrease in plasma volume produces the orthostatic hypotension (Kaltraider et al., 1942; Miles et al., 1968; Gundersen and Christiansen, 1977). This effect is clinically difficult to detect, in that insulin is usually given in the early morning when orthostatic intolerance is worst. If an insulin-orthostatic hypotension interaction is suspected, alteration of the time of insulin administration may be helpful.

Chronic Renal Failure

End-stage renal disease (ESRD), like diabetes mellitus, is clearly associated with diffuse autonomic dysfunction. Ewing and Winney (1975) found defective vasoconstrictor responses in 26 patients with ESRD, but there was substantial variability. Pickering et al. (1972) clearly demonstrated diminished baroreflex sensitivity, but found strong correlations with age and the level of hypertension, factors known to influence baroreflex sensitivity. Cohn et al. (1966) found similar results.

Although there is agreement that autonomic dysfunction is common in ESRD, there is no agreement on whether this is the cause of hemodialysis-induced hypotension. Kersh et al. (1974) studied 8 patients with ESRD and dialysis hypotension and concluded that dysautonomia was an important factor. Two patients had normal peroneal nerve conduction velocities, tachycardia with hypotension and appropriate vasoconstriction. Six had autonomic neuropathy and did not respond to volume loading or norepinephrine infusion. Nies et al. (1979) reached the opposite conclusions after studying 13 ESRD patients, 8 without and 5 with recurrent dialysis-induced hypotension. Responses to the Valsalva maneuver, cold pressor (hand in ice water), mental arithmetic, hyperventilation, and baroreflex sensitivity were not different for the two groups. Plasma norepinephrine levels were also not different, although both groups had elevated resting levels. Since both groups had dysautonomia to an equal extent, it seemed unlikely this was the cause of dialysis hypotension, but a facilitating role could not be ruled out.

Lilley et al. (1976) did extensive metabolic and hemodynamic studies in 20 ESRD patients, half with dialysis hypotension 90% of the time, and half less than 10% of the time. The hypotensive group had higher standing blood pressures, but otherwise both groups were similar with respect to plasma renin activity, renin response to ultrafiltration, age, duration of dialysis, peripheral nerve conduction velocity, plasma protein concentration, hematocrit, dialysis weight change, resting heart rate, sex, race, and response to the cold pressor test. Although plasma volumes were said to be similar in that both were higher than "normal," there were large differences. The dialysis-hypotension patients' volumes were 107% of predicted, while the non-hypotensive groups' plasma volumes were 142% of predicted. Despite this relative

hypovolemia, supine and standing blood pressures were significantly higher in the dialysis induced hypotension group. Plasma dopamine β hydroxylase levels, which correlate roughly with plasma catecholamines, were also increased in the former group.

Thus, the patients with recurrent dialysis induced hypotension appear to have a relative hypovolemia and are excessively vasoconstricted. This would render them especially sensitive to volume shifts. Autonomic dysfunction, especially decreased baroreflexes, would worsen this even more. Recent work by Henrich et al. (1980) seems consistent with this hypothesis. Ultrafiltration or infusion of hypertonic mannitol with dialysis virtually eliminates the problem of hypotension in these patients. This technique avoids the large changes in plasma osmolality that would otherwise occur and would presumably lead to rapid changes in intravascular volume. Isokalemic dialysis was not successful in preventing hypotension. The patients with hypotension induced by dialysis would seem pathophysiologically very similar to those with other forms of hyperadrenergic orthostatic hypotension, i.e., elevated catecholamines, marked vasoconstriction and relative hypovolemia.

Orthostatic Hypotension in the Elderly

The prevalence of orthostatic hypotension in the elderly was examined by Johnson et al. (1965). They measured blood pressure in 100 patients over 70 years old on a geriatrics ward. Seventeen had orthostatic pressure decreases of 20-60 mmHg. Patients with hypotensive medications, hypovolemia, and other known causes of orthostatic hypotension, e.g., diabetes, tabes dorsalis, etc., were not included. Nine of the 17 hypotensive patients were studied further with 60° head-up tilt, Valsalva maneuver, mental arithmetic, and hyperventilation. All nine had evidence of autonomic dysfunction on one or more tests. Autopsies in four revealed none of the classic neuropathological changes of idiopathic orthostatic hypotension, although 3 did have multiple small cerebral infarcts.

Caird et al. (1973) measured supine and 1 min standing blood pressures in 494 randomly selected general practice patients over age 65 and living at home. They did not exclude patients as Johnson et al. (1965) did, and obtained a significantly higher prevalence of orthostatic hypotension. Their data are shown in Figures 8 a and b.

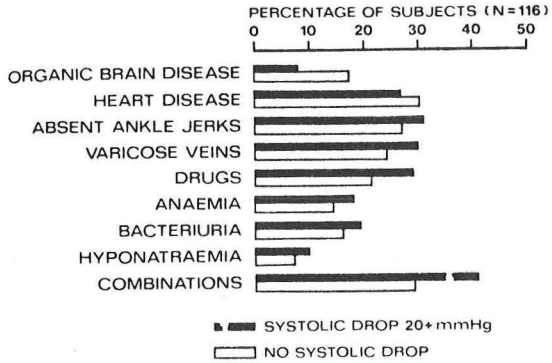


FIG. 8a *Comparison between subjects with postural drop in systolic pressure of 20 mmHg or more and matched group without*

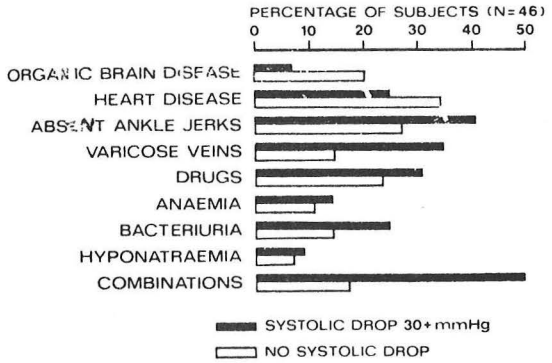


FIG. 8b *Comparison between subjects with postural drop in systolic pressure of 30 mmHg or more and matched group without*

About 38% of this group had a fall in systolic blood pressure greater than 20 mmHg. A greater frequency and severity was seen with increasing age. Factors such as varicose veins, drugs, anemia, and absent ankle jerks tended to be associated with more orthostatic hypotension, but only when taken in combination was there a statistically significant relationship. Heart disease and organic brain syndrome tended to be found less in patients with orthostatic hypotension.

The causes of orthostatic hypotension in the elderly have not been well studied. Interestingly, neither of these studies mentions heart rate, yet its failure to increase with hypotension can be an important contributing factor and a clue to search further for other manifestations of symptomatic bradycardia. White (1980) recently reported the time course of standing heart rates in 16 patients with orthostatic hypotension and 20 controls. Both groups had a mean age of 78 years. A significantly lower rate of rise and peak heart rate were seen in the hypotensive group (Figure 9).

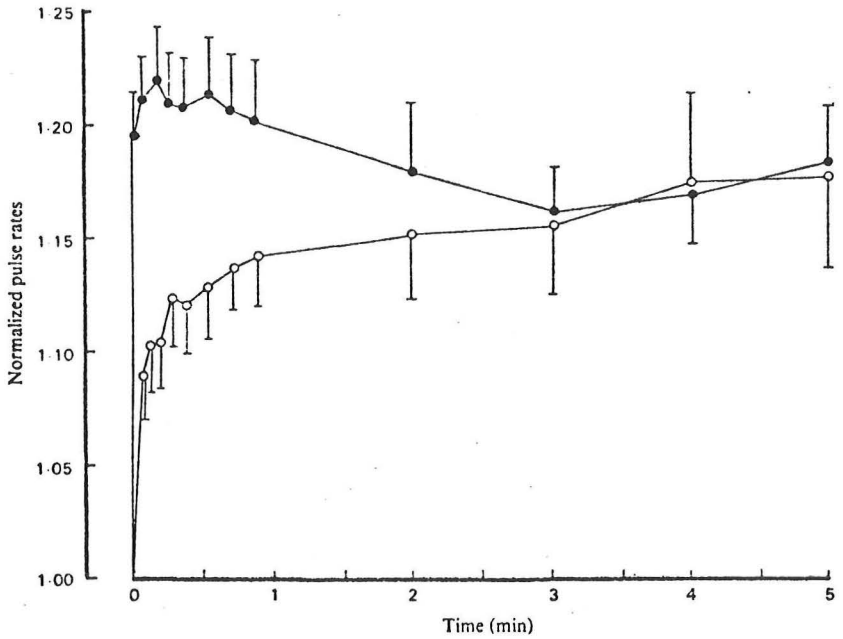


FIG. 9 Changes in normalized heart rate (instantaneous heart rate derived from ECG R–R interval/preceding lying heart rate) on standing upright. Mean ± 1 SEM values are shown: ○, 16 elderly patients with idiopathic orthostatic hypotension; ●, 20 controls. The patients with orthostatic hypotension have a significantly smaller ($P < 0.05$) increment in heart rate until 40 s has elapsed since standing.

Another explanation for orthostatic hypotension in this group is altered vascular compliance producing an immediate, but transient fall in blood pressure on standing (Thulesius, 1976). Hasleton and Heath (1976) found significant atherosclerotic involvement of the carotid sinuses in elderly autopsied patients. Such involvement may be a partial cause of the abnormal

baroreflexes often found in elderly patients.

Because of these defects in cardiac acceleration and baroreflexes, it is recommended that the elderly patient avoid rising suddenly, especially at first in the morning. Sitting a few minutes permits a more effective orthostatic adaptation to occur. Later in the day, orthostatic stress will be better handled (Figure 10).

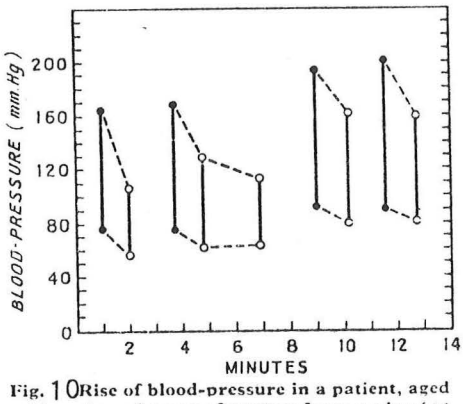


Fig. 10 Rise of blood-pressure in a patient, aged 74, on four changes of posture from supine (●) to 60° feet down (○).

More severe degrees of orthostatic hypotension or other symptoms of autonomic dysfunction, (impotence, anhidrosis, tremor, dyskinesis) would suggest the need for more extensive evaluation and perhaps some of the therapeutic interventions described in the section on Treatment.

Amyloid

There are several reports of patients who initially presented with an "autonomic" neuropathy but later were found to have systemic amyloidosis (Brown, et al., 1968; Burns et al., 1971; Gaan et al., 1972). The patients typically present with the "Bradbury Eggleston" pattern of Idiopathic Orthostatic Hypotension, i.e., impotence, lack of vasoconstriction and heart rate response to hypotension, bowel and bladder dysfunction. However, unlike patients with Idiopathic Orthostatic Hypotension or Shy-Drager disease, patients with amyloid may also have a profound peripheral sensory neuropathy with loss of deep tendon reflexes, although this may not always be true (Kyle et al., 1966). In a retrospective study with incomplete data, these authors found only 2 of 11 patients had a sensory neuropathy. Deep tendon reflexes were not mentioned. Diarrhea occurred in all 11 amyloid patients. Its frequency of occurrence in the entire group of 138 patients with orthostatic hypotension was not stated. Cardiac involvement with cardiomegaly but low voltage on the ECG, if present, is an additional important diagnostic clue. A rectal biopsy may or may not be diagnostic. Brown et al. (1968), Slaton and Biglieri, (1967) report cases in which a negative rectal biopsy mislead

physicians away from the correct diagnosis.

The hypotension of amyloid is usually severe. The peripheral neural involvement interferes with normal vasoconstriction. Additionally, alterations in myocardial compliance and contractility prevent normal cardiac compensatory responses. Death due to a low cardiac output and hypotension is common in these patients. Treatment is not well established, but excessive diuresis and hypovolemia should be avoided. The increased sensitivity to digitalis preparations, etc. is well discussed in several standard medical texts.

Vacor Induced Hypotension

An unusual but interesting hypoadrenergic form of orthostatic hypotension is seen in survivors of Vacor rat poisoning (LeWitt, 1980). A new rodenticide unrelated to warfarin was marketed briefly as "Vacor Rat Killer" (Rohm and Haas Co., Philadelphia). The drug is a competitive antagonist of nicotinamide and leads to β-islet cell necrosis and degeneration of paravertebral sympathetic ganglion cells. The dorsal root ganglia are also involved. Peripheral nerves show swelling of nerve fibers and thinning of the myelin sheaths (Papasozomonos, 1980). Clinically, the patients have diabetes mellitus and widespread sympathetic and parasympathetic autonomic dysfunction. Profound orthostatic hypotension is a universal finding and improves minimally if the patient survives. Plasma catecholamines are reduced, and do not rise on standing. Studies performed in our laboratory in a patient with Vacor poisoning demonstrated a normal plasma volume and cardiac output at rest. On sitting, arterial pressure was undetectable with syncope occurring in 10 sec. Lower body negative pressure produced profound hypotension but no vasoconstrictor activity or tachycardia occurred. Pooling of blood in the legs with suction was normal for the level of negative pressure obtained. These results are similar to findings in both Idiopathic and Shy-Drager hypotension. Florinef, up to 1 mg 1/d, did not increase plasma volumes, but was associated with subjective improvement. Head-up tilt was tried, but briefly and without a high enough level to benefit the patient. Profound orthostatic hypotension has persisted for 17 months since ingestion, but surprisingly, systolic pressures of 60-70 mmHg are well tolerated in this patient.

Because of the mode of action of Vacor, immediate therapy with nicotinamide is recommended for acute ingestions. Dosage and duration of therapy are not established. The diabetes and chemical sympathectomy following Vacor ingestion provide a dangerous clinical state requiring careful long term care if the patient survives. Benowitz et al. (1980) have reported good results with dihydroergotamine in one patient. Because our patient is currently asymptomatic, we have not instituted a trial of therapy with this agent.

Drugs

The list of drugs producing orthostatic hypotension is long (see Medical Letter, 2/10/78 for references). Agents which alter heart rate, plasma

volume, central or peripheral neural catecholamine levels have been implicated. Patients with conditions associated with autonomic dysfunction are more likely to be affected. Diabetes mellitus, Parkinson's disease, and old age are examples. Antipsychotic and antidepressant drugs, especially the phenothiazines can be hypotensive. Like the antihypertensives, these side effects are more likely to occur in elderly and/or hypovolemic patients. Central nervous system drugs for Parkinson's disease and narcotics produce a decrease in vasoconstrictor tone and lead to hypotension. Alcohol can potentiate this.

Prazosin and Guanethidine are two of the better known offenders among the antihypertensive drugs. The relationship to drug-induced orthostatic hypotension has been especially well established for the specific α antagonist prazosin. This drug can produce profound orthostatic hypotension, but usually it occurs only with the first dose. Semplicini et al. (1981) studied arterial blood pressure and plasma volumes in 9 patients with moderate to severe hypertension (Figure 11).

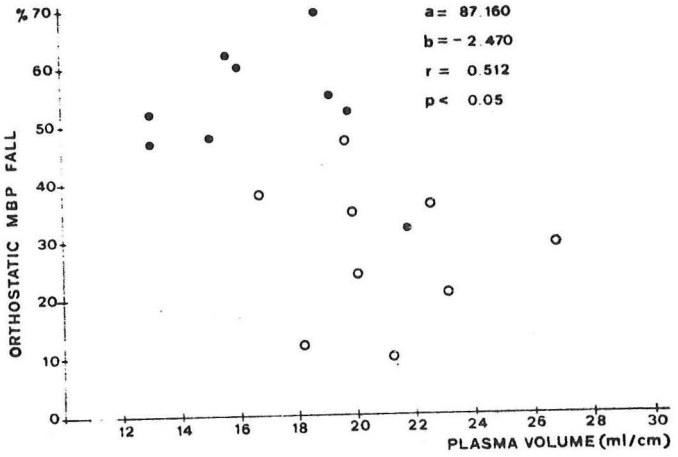


Fig. 11 Correlation between plasma volume and orthostatic mean blood pressure fall (percentage of control values) with 2 mg prazosin p.o. before (filled circles) and after acute plasma volume expansion (unfilled circles).

The degree of orthostatic tilt correlated with the patients' plasma volume but not with the prazosin plasma levels. Because this was an acute administration study only, the reason for the "first dose" effect is not known. Experience with other antihypertensives such as guanethidine show that substantial increases in plasma volume occur chronically (Weil and Chidsey, 1968). These volume adjustments may prevent subsequent hypotension. The desirable and undesirable hypotensive effects of these agents are clearly potentiated by the use of diuretics.

Vincristine therapy produces orthostatic hypotension as part of a peripheral neuropathy. Carmichael et al. (1970) reported a case of profound orthostatic hypotension in a 26-year old man treated with vincristine. Intact baroreflexes are evidenced by the fact that hypotension induced tachycardia and a norepinephrine infusion reflexly lowered the heart rate. The pressor response to norepinephrine was exaggerated. There was also normal sweating. Veno- and vaso- motor tone and responsiveness were very abnormal. Similar defects were reported by Aisner et al. (1974) in 4 patients. Additionally, ileus, impotence, bladder atony, and axonal degeneration were seen. Symptoms resolved with cessation of therapy. Presumably, peripheral nerve damage is repaired in time and vasoconstriction activity restored.

Miscellaneous

A number of neurological disorders including Parkinson's disease, tabes dorsalis, Wernicke's disease, syringomyelia, porphyria, and pernicious anemia can cause postural hypotension. These are covered in several excellent reviews (Wagner, 1959; Thomas and Schirger, 1968; Bannister, 1979; Schirger et al., 1981; Table III).

Table III Classification of Disorders of Postural Blood Pressure Regulation

I. Poor postural adjustment
- Tall, asthenic habitus
- Advanced age
- Physical exhaustion
- Prolonged recumbency
- Pregnancy
- Gastrectomy

II. Orthostatic hypotension
- A. Secondary orthostatic hypotension
  - 1. Endocrinologic-metabolic disorders
    - Diabetes mellitus
    - Primary amyloidosis
    - Primary and secondary adrenal insufficiency
    - Pheochromocytoma
    - Primary aldosteronism with marked hypokalemia
    - Porphyria
  - 2. Central and peripheral nervous system disorders
    - Intracranial tumors (parasellar and posterior fossa)
    - Idiopathic paralysis agitans
    - Wernicke's encephalopathy
    - Multiple cerebral infarcts
    - Brainstem lesions
    - Tabes dorsalis
    - Syringomyelia
    - Traumatic and inflammatory myelopathies
    - Guillain-Barré syndrome
    - Chronic inflammatory polyradiculoneuropathy
    - Peripheral neuropathies
    - Familial dysautonomia (Riley-Day syndrome)
  - 3. Miscellaneous disorders
    - Hypovolemia
    - Hypochromic anemia
    - Electrolyte disturbance
    - Psychotropic and antihypertensive drugs
    - Extensive surgical sympathectomy
    - Chronic hemodialysis
    - Anorexia nervosa
    - Hyperbradykininism
- B. Primary or idiopathic orthostatic hypotension
  - Idiopathic orthostatic hypotension
  - Idiopathic orthostatic hypotension with somatic neurologic deficit (Shy-Drager syndrome)

Malaria has been reported to cause orthostatic hypotension and bradycardia, but the cause of this is unknown (Butler and Weber, 1973). Viral infections also cause orthostatic intolerance by an unknown mechanism. Orthostatic hypotension associated with deconditioning following bed rest or zero gravity were recently discussed in Grand Rounds (Blomqvist, 1981).

Hyperbradykinism was reported in 5 members of a family (Streeten et al., 1972). On standing, the patients had a normal heart rate response, but abnormal vaso- and venodilation which produced ecchymoses and a purple discoloration of the legs. A decreased bradykinin breakdown rate due to a plasma bradykinase-I deficiency was believed to be the cause of this rare syndrome. Good therapeutic responses to either propranolol, cyproheptadine or fludrocortisone were reported.

Carcinoma can cause orthostatic hypotension. Park et al. (1972) presented their own case and 3 others from the literature. Their patient presented with classic Idiopathic Orthostatic Hypotension, but during the work-up was found to have inoperable oat cell carcinoma of the lung. Recovery from the dysautonomia occurred with radiotherapy induced remission of the tumor. Although the authors thought this was likely to be a "paraneoplastic" process, direct involvement of cardiopulmonary receptors is also possible. Boasberg et al. (1977) reported orthostatic hypotension in 4 patients with thoracic tumors. Tilting in 2 patients showed a normal heart rate response to hypotension suggesting a normal "high pressure" baroreflex system. During immersion, an inappropriately high ADH was found. They concluded that direct tumor involvement of the low pressure cardiopulmonary baroreceptors in the chest prevented the normal suppression of ADH produced by immersion. It is possible that these receptors were mechanically prevented from stretching. Riedel et al. (1974) reviewed 4 additional cases, including 2 of their own with posterior fossa tumors and idiopathic orthostatic hypotension with dysautonomia. They implied that the location of the tumors adjacent to circulatory control centers produced the symptoms.

Depression is not usually included in lists of causes of orthostatic hypotension, but a number of factors suggest that it may belong there. Although no single series has been published, a surprising number of patients with depression as the only concomitant to orthostatic hypotension have been reported (Witton, 1966; Gilbert, 1968; Frewin et al., 1973; Ibrahim et al., 1974; Kontos et al., 1976; Lübke, 1976). In addition, there is a substantial body of literature detailing the marked hypotensive effects of tricyclic antidepressants when administered to depressed patients.

Hayes et al. (1977) reported the results of tricyclic drug therapy in 20 adults with depression. All had significant orthostatic hypotension at some point during their therapy. Most commonly, this appeared during the first few weeks of therapy. Tacycardia was not commonly seen despite systolic blood pressure decreases of more than 30 mmHg. A larger, combined retrospective and prospective study was carried out by Glassman et al. (1979). They found a 20%

incidence of significant complications related to orthostatic hypotension among 148 patients with depression. Another 50 patients studied prospectively had a similar frequency of orthostatic complications. The plasma level of desmethylimipramine did not correlate with the frequency or severity of orthostatic intolerance. Pre-treatment orthostatic pressure drops were strongly correlated with post-treatment orthostatic changes ($r = 0.69$). This reflects the expected intra-individual consistency of pressures over time, but also provides a clinically useful marker for the patient who is likely to develop orthostatic hypotension on tricyclic drug therapy.

Unfortunately, comparable studies in age and sex matched non-depressed controls to determine whether depressed persons are especially sensitive to those agents are not available. Hypotension does not seem to be a problem in children taking these drugs for enuresis, although one such case report has been published (Koehl and Wenzel, 1971). Whether depressed patients actually have an increased incidence of orthostatic hypotension and/or an increased sensitivity to neurally active drugs like the tricyclics is unknown. Plasma volumes and vasoconstrictor state would have to be determined if such studies were carried out.

Orthostatic Dysregulation is a term used by the Japanese and Europeans to describe a group of patients with dizziness, orthostatic intolerance, palpitations, syncope or near-syncope, pallor, anorexia, fatigability, headache, and a history of motion sickness (Abe et al., 1965; Schneider and Schulz, 1969; Tanaka et al., 1976; Lübke, 1976). One can immediately recognize the similarities between these patients and those with "effort syndrome," "soldier's heart," "neuroregulatory asthenia," or "poor postural adjustment." A less well known but perhaps more descriptive name would be that of "orthostatic tachycardia" since many of these patients do not actually have hypotension, but maintain their pressure with marked degrees of tachycardia (MacLean and Allen, 1940; Nanda and Johnson, 1975 (Case I)). The cause of these patients' symptoms is not known, but evidence supporting a genetic basis for their autonomic dysfunction has been described.

Tanaka et al. (1976) studied 427 family members from 133 probands with "autonomic dysregulation" as defined by the Japanese Task Force established to study it. These authors measured patients' heart rate and blood pressure responses to head-up tilt in comparison with 1,359 unselected normal controls. An inventory of orthostasis related symptoms was also obtained from each subject. A significantly higher number of symptoms was found among the relatives of the patients. Likewise, relatives were significantly more often hyper-responsive to tilting than the normal controls.

The physiological basis for these patients symptoms is not at all understood, but in one study, plasma volumes and blood volumes were abnormally low in a group of children with orthostatic dysregulation (Lübke, 1976). This is consistent with the findings of Ibrahim et al., 1974 who found decreased plasma volumes in some of their patients with orthostatic hypotension, tachy-

cardia, and "psychiatric" symptoms - mainly depression.

Mitral Valve Prolapse Syndrome (MVPS) patients often complain of palpitations, diminished exercise capacity, easy fatigability, and syncope or near-syncope associated with upright posture (Devereaux et al., 1974; Gaffney et al., 1981). The cause for these findings is not known, but several investigators have suggested autonomic dysfunction as a possible etiology (Coghlan et al., 1979; Gaffney et al., 1979). Studies of orthostatic tolerance were performed in 19 women with MVPS. Lower body negative pressure was utilized instead of a tilt table to produce footward shifts in venous blood. The MVPS patients with the high resting heart rates surprisingly were actually more vasoconstricted at rest and during LBNP. As a result, they pooled less blood in their legs, and despite a 25% fall in cardiac output, actually raised their mean arterial pressure (Figure 12).

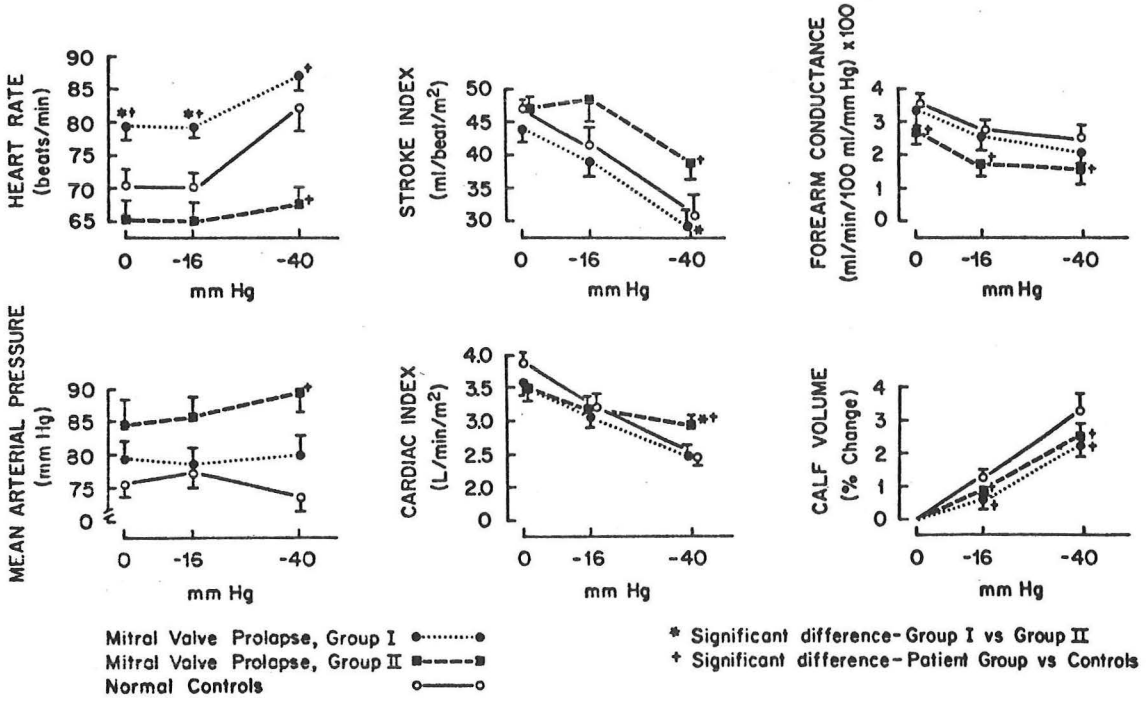
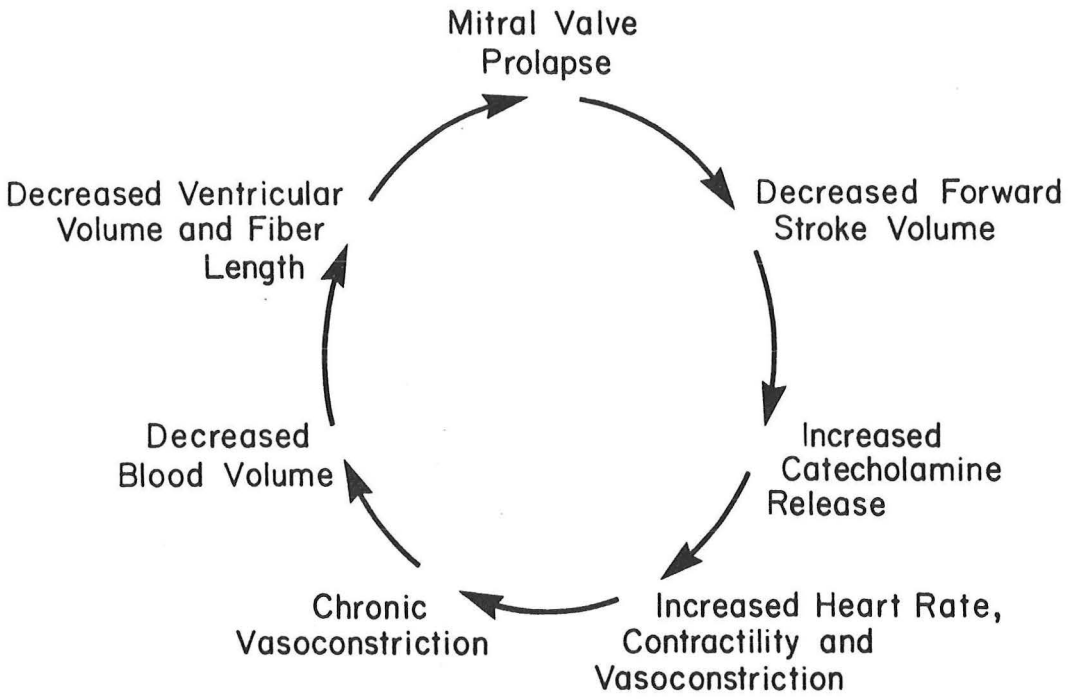


FIGURE 12 *Hemodynamic data from lower body negative pressure studies. Values are mean ± SEM.*

Their response to standing was examined in a subsequent study (Gaffney et al., 1980). Plasma catecholamines were markedly elevated in those patients who also had dramatic decreases in upright stroke volume. Cardiac output was maintained by a high heart rate. Again orthostatic stress tended to produce a paradoxical increase in arterial pressure, but pulse pressure was significantly reduced. Although hematocrits were slightly higher among the patients when compared with healthy controls, plasma volumes were significantly (≈ 12%)

lower. While this may seem to be a small difference, it is approximately the same reduction in plasma volume that Bergenwald et al. (1977) found in normal young men to be associated with a marked decrease in orthostatic tolerance and a tendency to fainting. DeCarvalho et al. (1979) reported similar plasma volume reductions in a group of women with MVPS, high heart rates on standing, and labile hypertension.

A proposed pathophysiological explanation for these findings is shown in Figure 13.



The patients have excessive α-adrenergic activity evidenced by increased supine and standing plasma norepinephrines, and the tendency to increase arterial pressure abnormally in response to orthostatic stress. The anticipated effect of hypovolemia would be an arterial pressure slightly lower than normal. "Overcompensation" implies a primary defect in the α-adrenergic nervous system. Chronic vasoconstriction leads to a reduced plasma volume (Finnerty et al., 1958; Weil and Chidsey, 1968). The low blood volume renders the patient intolerant to orthostatic stress. Because there is no efferent defect in the sympathetic system, hypovolemia and hypotension stimulate tachycardia and intense vasoconstriction, thus completing the cycle.

Subsequent studies in these patients have confirmed that there is a marked reduction in ventricular filling in the upright position (Gaffney et al., 1981). Significant mitral regurgitation was not found, although one may have expected it on the basis of the effects of decreased ventricular volume on the degree of prolapse. In addition, unlike normal subjects with acute

hypovolemia, these patients fail to increase venous return normally during exercise. The expected increases in end-diastolic volume are not seen. This means that cardiac output is increased only by increasing heart rate. A substantial decrease in upright exercise capacity is produced. Substantially lower heart rates occur at the same workloads when these patients exercise in the supine position.

Miscellaneous Hypovolemic States

Although the above studies were performed in symptomatic women with mitral valve prolapse, there is no reason to believe that the pathophysiology described for them is specific for MVPS. Cryer's (1980) "hyperadrenergic" patients with orthostatic hypotension, high plasma norepinephrines, and low plasma volumes are virtually identical to those orthostatic MVPS patients hemodynamically. (One wonders whether any of those four were examined for the typical click and murmur of mitral valve prolapse.)

Cohn (1966) described 3 patients with malignant hypertension, marked volume contraction, and extreme sensitivity to antihypertensive drugs. Such patients are probably not rare, although they are often not recognized.

Valeri and Altschule (1981) have recently published a monograph Hypovolemic Anemia of Trauma: The Missing Blood Syndrome. They studied a group of Vietnam War casualities sent home for chronic rehabilitation after major trauma. These patients had low normal hematocrits with 12-45% reductions in red cell mass and plasma volumes. Extensive investigation failed to identify a cause for the reduced blood volume. Clinically, however, these patients were vasoconstricted with extremity wounds that healed poorly. They demonstrated abnormal sensitivity to anesthetic agents, and often became profoundly hypotensive during anesthetic induction. They were all psychologically depressed, and recovered only over a long period of hospitalization. A centrally mediated hyper α-adrenergic state similar to that found in the MVPS patients would appear to explain all of their findings.

Hemodynamic Summary

All orthostatic hypotension is characterized by a decrease in venous return which leads to decreased cardiac output and hypotension. The nature of the responses of the various cardiovascular regulatory systems to this insult is determined by the underlying disease process which produces the orthostatic hypotension. Nonetheless, in many cases they are relatively consistent, regardless of the cause. A brief summary will be provided to review what has been presented and provide a rational basis for therapy. References have already been provided and will not be repeated.

Venous Pooling is important in the pathogenesis of orthostatic hypotension but only because other compensatory mechanisms are inoperative or blood volume is diminished. Excessive venous pooling is rare and probably

occurs only with varicose veins (Bevegård and Lodin, 1962; Grimby et al., 1964) or in the congenital absence of the deep venous valves (Zsoter and Cronin, 1966).

Myocardial Dysfunction is not usually a cause of orthostatic intolerance. In fact, the opposite is usually true (Abelman and Fareeduddin, 1969). Congestive heart failure is associated with increased vascular volume, vasoconstriction, and large ventricular volumes.

Chronotropic Failure or the inability to increase heart rate appropriately is occasionally a problem, especially among elderly patients. Exercise testing and ambulatory monitoring may be used to detect this. Other cardiac arrhythmias are often present, but sustained, symptomatic bradycardia would be the critical diagnostic feature.

Renin Angiotensin System in orthostatic hypotension has been studied by at least twenty different investigators (Scherba, 1954; Botticelli et al., 1964; Chokroverty et al., 1969; Bliddal and Nielsen, 1970; Johnson and Park, 1973; Wilcox et al., 1974; Morganti et al., 1979; etc.). In virtually all of the studies, renin failed to increase appropriately in response to tilt and hypotension. Aldosterone seems to increase appropriately to salt deprivation or tilting, although the response to the latter may be slow and inadequate if the degree of hypotension is considered.

Supine creatinine clearances are normal in patients with all types of orthostatic hypotension (vide supra). Upright clearances are often in the range of 20-60 ml/min when associated with systolic blood pressures of 50-70 mmHg. There is no evidence of a primary renal defect in the various types of postural hypotension, only the expected responses to diminished renal perfusion.

Salt and water conservation and excretion have been similarly studied. A great deal of attention was paid to the abnormal diurnal variation seen in patients with orthostatic hypotension. The major period of water and salt loss is at night, when the patients are supine and their pressures are elevated. During the day, hypotension promotes salt and water conservation.

Supine Hypertension is extremely common in patients with orthostatic hypotension, regardless of cause, although it tends to be worse in the Shy-Drager or Idiopathic varieties (MacLean and Allen, 1940; Wagner, 1959; Shy and Drager, 1960; Bevegård et al., 1962; Bannister et al., 1967; Botticelli et al., 1968; etc.). Patients often have increased peripheral resistance. When supine, these patients have a normal venous return and cardiac output with a high peripheral resistance which produces arterial hypertension. Arterial baroreflexes do not keep pressure regulated downward any better than upward. It is a simple relationship of gravity determining central blood volume which then determines cardiac output.

Denervation Hypersensitivity is found in the Shy-Drager and Idiopathic forms of orthostatic intolerance. The dose of norepinephrine or angiotensin necessary to produce a given level of hypertension is significantly reduced (Goodall et al., 1967 and 1968; Caronna and Plum, 1973; Kontos et al., 1975; Bannister, 1979; Chobanian et al., 1979). Patients with abnormally low resting or standing norepinephrine levels would be expected to show the hypersensitivity (Ziegler et al., 1977). An increased number of β receptors has been found in two patients with "efferent" orthostatic hypotension and decreased plasma catecholamines (Hui and Conolly, 1981). Alpha receptor number has not been measured. The absence of baroreflexes to modulate the pressor response confuses this issue somewhat.

Clinical Approach to Orthostatic Hypotension

As with any disease, the history is extremely important in assessing the patient with orthostatic hypotension. The patient who complains of near-syncope on standing presents no diagnostic challenge. The elderly patient with fatigue, clouded mentation, or near-syncope may have these symptoms on the basis of diminished cerebral perfusion. In order to determine whether orthostatic hypotension is present, one should measure blood pressure and heart rate in the supine and standing position. A failure to increase pulse rate despite significant hypotension is an important clue to both the etiology and the pathophysiology of the hypotension. Sitting blood pressure may be taken if there is some question of the patient's ability to stand, but hydrostatic gradients produced by sitting are not adequate to rule-out orthostatic hypotension. Elderly patients may have a very transient decrease in arterial pressure related to altered vascular compliance more than blunted reflexes, so if the history suggests it, pressure and heart rate should be measured immediately after standing. Otherwise, they should be measured after one and five minutes of quiet standing. This is usually sufficient, but if there is a history of symptoms after prolonged standing, heart rates and pressures should be measured accordingly.

Definitions of orthostatic hypotension vary, but most authorities agree that a decrease of systolic or diastolic pressure by 20 mmHg or more or an increase in pulse of 20 beats/min represent an abnormal response to standing. If the patient has suggestive symptoms and these characteristic rate and pressure changes, further work-up is indicated.

Again, the most fruitful approach is an historical one. Drugs are one of the more common causes of orthostatic hypotension. A list of potentially hypotensive agents has been provided. Any drug which alters blood volume, vascular tone, or myocardial function should be suspected, even if not usually thought to cause hypotension. A concomitant history of anhidrosis, impotence, bowel or bladder dysfunction, tremor, abnormal gait or dysarthria would suggest the presence of some form of hypoadrenergic hypotension. Patients with hyperadrenergic forms often complain of palpitations, near-syncope, cold extremities, diminished sweating, low exercise tolerance, and other anxiety

related symptoms. Diarrhea may be a sign of dysautonomia, although amyloid and Addison's disease are considerations.

A thorough physical examination with special attention to the cardiovascular and neurological systems should be performed. Many of the patients with hyperadrenergic hypotension will have mitral valve prolapse with a mid-systolic click and/or an apical systolic murmur of mitral regurgitation. Neurological findings have been described in the sections on "Idiopathic" and Shy-Drager types of orthostatic hypotension. Significant sensory neuropathies and loss of deep tendon reflexes are not usually part of Idiopathic Orthostatic Hypotension or Shy-Drager and may suggest diabetes mellitus or amyloid.

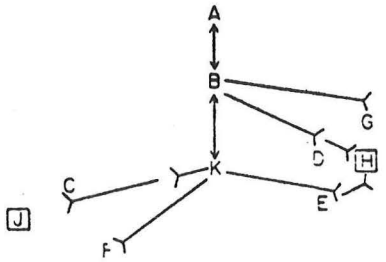
Laboratory testing should include a complete blood count, VDRL, and a routine biochemistry profile. Specific tests such as cortisol levels, a glucose tolerance test, etc. should be performed if the history or physical examination suggest Addison's disease or diabetes. Ambulatory ECG monitoring or an exercise test can be performed to assess heart rate response. If exercise is performed, frequent post exercise blood pressures and heart rates should be measured to rule out chronotropic and vasoregulatory abnormalities. Some patients have particularly severe hypotension following exercise (Calne, 1966). This may occur even when exercise is performed in the supine position (Marshall et al., 1961).

Supine and standing plasma norepinephrine measurements are extremely useful. As noted, the peripheral ganglionic defect in Idiopathic Orthostatic Hypotension produces low supine and standing values. Shy-Drager patients with CNS and cordal involvement will have normal supine levels which fail to rise appropriately. Hyperadrenergic orthostatic hypotension is associated with normal or high resting and very high standing levels (Polinsky et al., 1981).

A number of tests can be performed to determine the precise nature of the cardiovascular defect (Dobkin and Rosenthal, 1975; Table IV). Among the more commonly used are the Valsalva maneuver, mental arithmetic, cold pressor, handgrip, hyperventilation, tilt table, regional body heating, and local cold stimulation. While they are of interest intellectually, and may confirm the presence of efferent neural defects, a thorough history, physical examination with measurements of supine and standing heart rates, and a Valsalva maneuver with measurement of heart rate provide virtually the same clinically relevant information.

With this information, one should be able to determine whether a hypo- or hyper-adrenergic form of hypotension is present and if hypoadrenergic whether it is "Idiopathic," Shy-Drager, or some secondary hypotension. From this, a rational approach to therapy is possible.

A CEREBRUM
B THALAMUS, HYPOTHALAMUS, BRAIN STEM
C SYMPATHETIC EFFERENT
D CRANIAL PARASYMPATHETIC EFFERENT
E SACRAL PARASYMPATHETIC EFFERENT
F AFFERENT SENSORY
G AFFERENT BARORECEPTOR
H PARASYMPATHETIC END ORGAN
J SYMPATHETIC END ORGAN
K SPINAL CORD



A representation of sympathetic and parasympathetic pathways

TABLE IV

Tests for autonomic nervous system function.

Test	Pathway	Normal Response
Pupillary		
1. Ciliospinal reflex	F→B→C	Dilates with neck pinching
2. Light reflex	B→D	Constricts to light
3. Instillation of:*		
1:1000 epinephrine	J	No change in size
5% cocaine	J	Dilation
2.5% methacholine	H	No change
2% pilocarpine	H	Constriction
Vasomotor		
1. Valsalva's (1, 18) maneuver	Strain→G→B→C→J	Mild ↓ BP HR ↑ ~25%
	Release→G→B→D→H	Mild systolic overshoot HR ↓ ~20%
2. Cold pressor (2)	F→A, B→C→J	Syst BP ↑ ~15-20 after hand in ice water for 60 sec.
3. Bloodless phlebotomy (2)	G→B→C→J	Syst BP ↓ <10 after cuffs inflated on thighs just below diast BP for 10 min.
4. Mental stress	A→B→C→J	Variable slight BP ↑, HR ↑
5. Peripheral venous renin (3)	G→B→C→J	↑ 2-4 times upon standing
6. Urinary catecholamines (3)	G→B→C→J	↑ upon standing
7. Norepinephrine infusion .05 mcg/kg/min (4)	J	Syst BP ↑ <23, average ~8 HR same or ↓
8. Epinephrine infusion .15-.3 mcg/kg/min (4)	J	Syst BP ↑ 18-60 HR ↑ 0-16
9. Phenylephrine infusion 0.5-1 mcg/kg/min (1)	J	Mean arterial BP ↑ 14% HR ↓ 25%
10. Amyl nitrate inhalation (1)	G→B→C→J	Mean arterial BP ↓ ~35% HR ↑ ~60%
11. Sublingual nitroglycerin (5)	G→B→C→J	Syst BP ↓ <15
12. Tyramine bolus (7)	C→J	250 mcg—no response 1000 mcg—syst BP ↑ <20 6000 mcg—syst BP ↑
13. Deep breath (38)	F→K→C→J	Immediate ↓ hand blood flow, ↑ vascular resistance (Plethysmography)
Sudomotor, Thermoregulatory		
1. Artificially raise body temperature 1°C (6)	F, B→C→J	Diffuse sweating ↑ skin electric resistance
2. Intradermal 1% pilocarpine	J	Local sweating
3. Heat hand (18)	F, B→C→J	↑ skin blood flow
Visceral		
1. Penile erection	A, F→E→H	
2. Ejaculation	A, F→C→J	
3. Schirmer test	H	Moisten test paper >10 mm. in 5 min.
4. Intravenous atropine 2 mg. (1, 8)	D→H	HR ↑ 30-80%
5. Carotid massage	G→B→D→H	Bradycardia
6. Insulin induced hypoglycemia	B→D→H	↑ gastric acidity
7. Barium enema	E→H	GI motility active

* Ocular installation of 1% hydroxyamphetamine causes mydriasis only if the postganglionic neuron is intact. This test is a very reliable means to distinguish a pre-ganglionic from post-ganglionic lesion of the sympathetic pathway to the iris.

Treatment

There are no large clinical trials for treatment of orthostatic hypotension. In fact, the larger studies often include 4-6 patients. When more are included, there is usually a mix of several types of orthostatic hypotension making accurate assessment of therapeutic efficacy an impossibility. Nonetheless, some therapies seem to enjoy persistent, albeit anecdotal popularity, hopefully because of their intrinsic worth. Those and other more esoteric interventions will be discussed.

Measures to Increase Blood Volume

A high salt diet has been recommended by a number of investigators (Thomas et al., 1981). Blood volumes in the hypoadrenergic patients are virtually always normal or slightly decreased. If supine hypertension is present, it may become worse until the salt and water are excreted.

9-α-Fluorohydrocortisone is a mineralocorticoid virtually devoid of glucocorticoid activity but which promotes salt and water retention. However, there is a high peripheral resistance supine, so plasma volume quickly adjusts to normovolemic levels (Schirger et al., 1962; Figure 14).

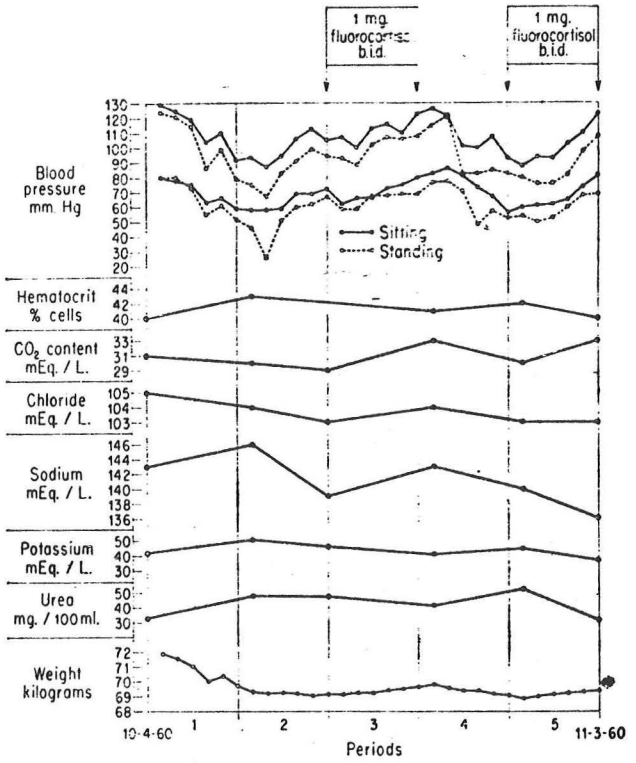


Fig. 14 Effect of 9-alpha-fluorohydrocortisone on blood pressure, hematocrit reading, serum electrolytes, blood urea, and body weight.

Despite this, its hypertensive effects seem to persist. Several investigators (Schmid et al., 1966) have shown that its mode of action is to increase vascular reactivity to compounds such as norepinephrine and angiotensin. The number of favorable case reports suggests that it is a useful drug in the hypoadrenergic types including Idiopathic, Diabetic, and Shy-Drager orthostatic hypotensions (see Bannister et al., 1969 for references). Starting doses of 0.1-0.2 mg/d are gradually increased until a desired upright pressure is achieved. Doses to 1-1.4 mg have been used. Supine hypertension, hypokalemia, volume overload and congestive heart failure have occurred. Head-up tilt can be combined with administration of this drug to produce the desired pressures.

Pressure Garments are intended to increase central blood volume by decreasing venous pooling. As noted above, excessive pooling is not a common problem in orthostatic hypotension (Stead and Ebert, 1941). Likewise, the gradient produced by the commercially available woven garment is not sufficient to overcome hydrostatic forces in an upright adult. Good clinical studies with these garments are not available. They have been reported to be effective, but the literature seems evenly divided (Schwarz, 1967; McCluer, 1968; Sheps, 1976 (includes review and references)). A specially fitted "pantyhose" garment is the only acceptable type with potential utility. The individual (single leg) stockings have an inadequate gradient and do not apply pressure to the buttocks or upper thighs. Commercially available or military type anti-G suits provide much better support, but also restrict movement so severely that they are generally not acceptable to the patient (Bevegård et al., 1962; Levin et al., 1964; Rosenhamer and Thorstrand, 1973). The tight-fitting rubberized garments also pose a hazard to the patient with orthostatic hypotension and associated peripheral sensory neuropathy.

Atrial Pacing was recommended by Moss et al. (1980) as a method of increasing heart rate in patients with orthostatic hypotension. Unfortunately, an empty heart beating rapidly does not increase cardiac output. Subsequent letters to the editor pointed out this fact (Goldberg et al., 1980). If symptomatic bradycardia is the problem, a pacemaker might help. Otherwise it could do more harm than good.

Head-up tilt at night was originally recommended by MacLean and Allen (1944). This would appear to be a paradox, but the head-up tilt prevents the supine hypertension and nocturnal diuresis which otherwise occurs because of large increases in central blood volume. These authors recommend raising the head of the bed up to 18". This would correspond to approximately a 15-20° head-up tilt. The hydrostatic effects of that can be seen in Figure 15. The authors report great success with this method, but is does not appear to have been used widely. Bannister et al. (1979) recommend its use as do Davidson et al. (1976) and Irvine (1973). It is by far the simplest therapy and is very sound from a physiological point of view. It should probably be the first intervention in treating orthostatic hypotension. The angle is adjusted to give normal pressures supine.

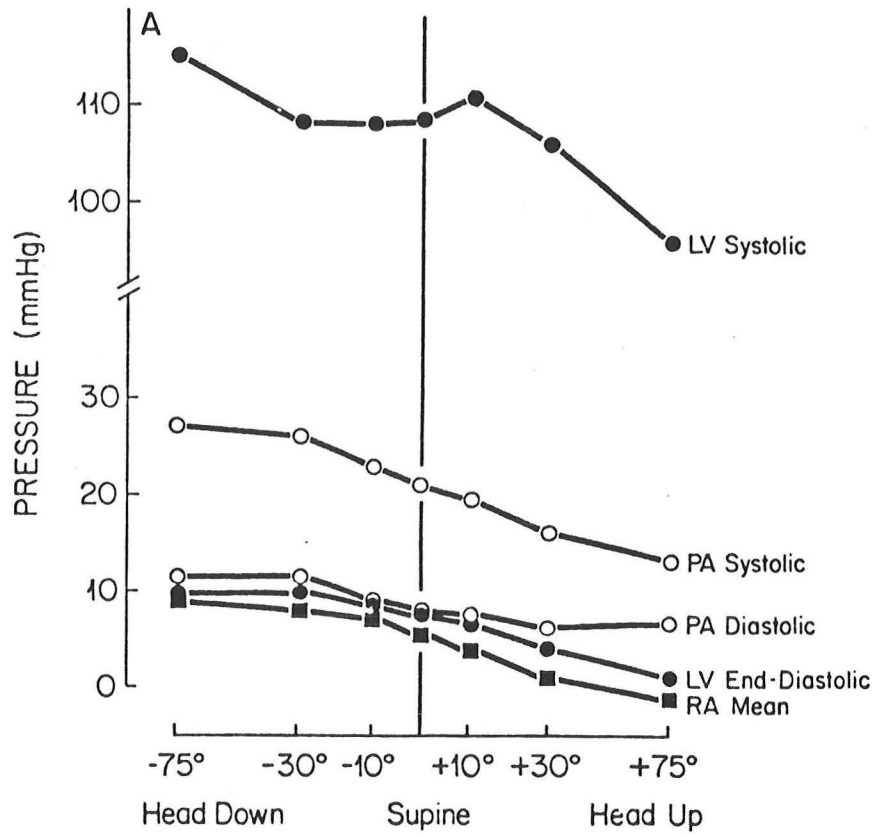


Figure 15

Monoamine Oxidase Inhibitors have been utilized alone and in combination with Tyramine or tyramine containing foods (sharp cheeses, red wines) to produce an elevated blood pressure (Diamond et al., 1978; Sharpe et al., 1972; Lewis et al., 1972; Frewin et al., 1973; Mahar et al., 1975; Nanda et al., 1976; Davies et al., 1978; Jones and Reid, 1980). Nineteen patient's histories were found in the literature. This regimen interferes with norepinephrine reuptake while simultaneously stimulating its release in patients with presumed denervation hypersensitivity. The MAO inhibitor may also interfere with tyrosine metabolism and prolong the hypertension even longer. Blood pressure is virtually always elevated when the patient is supine. The problem has been to avoid severe hypertension. One forthright investigator noted the production of retinal hemorrhages in a patient treated with the MAO inhibitor tyramine combination. Some writers have had success with this drug combination, head-up tilt, Jobst stockings, and fludrocortisone on a short term basis, but long term follow-up is lacking. The consensus is that this is a dangerous therapy, difficult to control, but available as a last resort. Attempts to provide tyramine through dietary sources were usually not successful. Blood levels were too erratic and a pharmacological source of tyramine should be provided.

Dihydroergotamine and its derivatives have been used to treat hypoadrenergic orthostatic hypotension and autonomic dysregulation (McNay, 1976; Nordenfelt and Mellander, 1976). The ergot alkaloids are potent α-adrenergic agonists, but *in vivo* seem to have a higher affinity for the capacitance vascular bed with little or no effect on resistance beds (Stürmer, 1976). A number of investigators have provided experimental and clinical proof of efficacy in selected patient groups. Bevegård et al. (1974) demonstrated increased orthostatic tolerance in 3 of 4 patients with Idiopathic Orthostatic Hypotension during lower body negative pressure. With DHE therapy, stroke volume decreased only 12% compared with 38% pre-treatment. A 50% rise in CVP with no change in total peripheral resistance was also noted. Lübke (1976) obtained good results in 19 patients with various types of orthostatic hypotension.

β-Blockers including propranolol and pindolol (Nanda and Johnson, 1975; Chobanian et al., 1977; Brevetti et al., 1979; Frewin et al., 1980) have been used although the rationale for employing them is unclear. They supposedly prevent β-adrenergic vasodilation, which in a sense augments α-adrenergic vasoconstriction. Heart rate and blood pressure data on their use in hyperadrenergic orthostatic hypotension has been presented and there appears to be some efficacy. The use of β-blockers in the hypoadrenergic forms of orthostatic hypotension seems to be less useful, although 3 of 5 of Chobanian's Idiopathic Hypotension patients had a favorable response.

Metoclopromide is a dopaminergic antagonist recently market in the U.S. Kuchel et al. (1980) suggested that excessive dopamine may produce hypotension in some patients. He presented results from one such patient, a 64 year old woman, who had undergone a sympathectomy for Raynaud's disease 30 years ago. Her urinary dopamine/norepinephrine ratio was increased and plasma aldosterone and renins were also elevated. These improved as did her symptoms of orthostatic hypotension on metoclopromide 10 mg TID. No follow-up is available.

Indomethacin has been suggested for therapy of orthostatic hypotension, but there is serious doubt that it is effective in the hypoadrenergic forms. Kochar and Itskovitz (1978) reported favorable results in four patients with Shy-Drager disease. However, this paper was criticized by Bannister (1978) who suggested that Kochar's patients did not meet the diagnostic criteria of Shy-Drager disease. He added that his experience with indomethacin had been disappointing. Similar unsatisfactory results were reported in 1 patient by Crook et al. (1981). A successful treatment in an 18 year old girl was reported by Perkins and Lee (1978). Their patient had an ill-defined form of hypotension, developed a headache on indomethacin and was successfully switched to flurbiprofen. A possible mechanism of action was suggested by Davies et al. (1980). They noted that indomethacin increases vascular sensitivity to angiotensin and norepinephrine. Four patients treated with indomethacin improved. These 10 patients do not provide adequate data with which to judge the effects of this drug. A trial would seem worthwhile if 9-α-fluorohydrocortisone fails.

Summary

The normal response to upright posture includes an increase in heart rate and cardiac contractility with peripheral vasoconstriction. Venoconstriction plays no role. Orthostatic hypotension is the inability to maintain a normal blood pressure in the upright position. Inadequate venous return results in a diminished cardiac output. Although several distinct forms of orthostatic hypotension exist, these can all be categorized as either hypo-adrenergic or hyper-adrenergic. Examples of the former include "Idiopathic Orthostatic Hypotension" (IOH) and Shy-Drager (S-D) disease. In IOH, the defect resides in sympathetic ganglia, supine and upright plasma norepinephrine levels are reduced, central nervous system disease is usually not present and long term survival is possible. Shy-Drager disease involves cell loss in the intermediolateral columns and olivo-cerebello-pontine atrophy. Supine norepinephrine levels are normal, but standing levels are decreased. Prognosis is poor with death in 6-8 years after onset of symptoms. In both, vasoconstriction is virtually absent. Venous pooling and blood volumes are normal. Other signs of autonomic dysfunction including, anhidrosis, impotence, and bowel and bladder dysfunction are common in both. Treatment is directed toward maintaining blood volume and vascular reactivity to catecholamines. Head-up tilt at night, 9-α-fluorohydrocortisone and pressure garments are useful therapies. There is no known cure.

Hyperadrenergic orthostatic hypotension is a more common but less often diagnosed disorder. Other names include "poor postural adjustment," "vasoregulatory asthenia" and "orthostatic tachycardia." Blood pressure may be maintained in the upright position, but with marked tachycardia and intense vasoconstriction, the opposite of hypoadrenergic hypotension. Supine plasma norepinephrines are normal or elevated, while upright levels are increased substantially. Blood volumes are decreased 10-40%. The cause of this disorder is not known, but an inherited central defect in α-adrenergic autonomic control is postulated. Treatment is directed toward increasing plasma volumes and decreasing tachycardia. Improving fitness levels and α- or β- adrenergic blocking agents have been useful.

Some disorders include patients with either hypo- or hyperadrenergic hypotension. Autonomic neuropathy is common in diabetes mellitus and end stage renal disease. Some patients with peripheral neuropathies have diminished heart rates, vasoconstriction and catecholamines in response to orthostatic stress. Others have high catecholamines, tachycardias, low blood volumes, and increased vasoconstrictor activity. Correct identification of the pathophysiological mechanisms of postural hypotension in these patients is important for selecting the proper therapy.

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