Orthostatic hypotension

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Orthostatic hypotension is a fall in blood pressure when assuming an upright posture. In 1995, the Joint Consensus Committee of the American Autonomic Society and the American Academy of Neurology defined orthostatic hypotension as a reduction of systolic or diastolic blood pressure of at least 20 or 10 mm Hg, respectively, within 3 minutes of standing [5]. Although this is now the accepted definition, it does not take into account the possibility that different blood pressure declines may have different clinical significance, depending on the level of the resting supine blood pressure. Moreover, it does not account for blood pressure changes that may occur after 3 minutes of standing [52]. Ultimately, the significance of any orthostatic fall in blood pressure must be judged by the associated symptoms and the likelihood of an adverse outcome if left untreated.

The prevalence of orthostatic hypotension differs according to the population, the subject's position change (i.e., supine to sitting versus supine to standing), and when the measurements are taken. In a study of subjects without diabetes 25 to 74 years of age, 6.6% had a decrease in systolic blood pressure of 20 mm Hg after moving from a supine to a sitting position [13]. Studies of elderly people living in the community, however, have found a prevalence of orthostatic hypotension of approximately 20% among individuals over 65 years of age [48] and of 30% among those over 75 years of age [33]. In a study of frail, elderly, nursing home residents, the prevalence of orthostatic hypotension was more than 50% [42]. Data on blood pressure measured in the supine and sitting positions in over 8000 participants in the National Health and Nutrition Examination Survey (conducted from 1976 to 1980) not only confirm an increased prevalence of orthostatic hypotension with advancing age but also indicate that this is related primarily to an age-associated increase in systolic
blood pressure in the supine position [13]. Disease-related factors, particularly hypertension and its sequela, therefore, may be the major determinants of orthostatic hypotension in old age.

Orthostatic hypotension may be symptomatic or asymptomatic. Symptoms of orthostatic hypotension occur when assuming the erect posture or during head-up tilting and usually are relieved within 1 minute of lying down. The description and severity of symptoms vary among subjects but most commonly include light-headedness, weakness, cognitive impairment, blurred vision, tremulousness, and vertigo. Falling, unsteadiness, syncope, palpitations, angina pectoris, calf claudication, headaches, paracervical pain, and low-back pain also have been reported.

Several recent longitudinal studies have examined outcomes associated with orthostatic hypotension (Table 1). These studies are particularly important in determining whether orthostatic hypotension is merely an epiphenomenon or a serious independent risk factor for morbidity and mortality that requires aggressive evaluation and treatment in its own right. Data from the Hypertension Detection and Follow-up Program indicate that a decline of 20 mm Hg or more in systolic blood pressure within 3 to 4 minutes of a change from a sitting to standing position is associated with an excess 5-year mortality rate in diabetic patients with hypertension [7]. In the Honolulu Heart Study of healthy, ambulatory, elderly men, orthostatic hypotension was a significant independent predictor of all-cause 4-year mortality [35]. Another study of healthy elderly people living in Finland showed that the diastolic, rather than the systolic, blood

<table>
<thead>
<tr>
<th>Study</th>
<th>Participant</th>
<th>Number</th>
<th>Predictor</th>
<th>Outcome</th>
<th>Relative risk</th>
</tr>
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<tbody>
<tr>
<td>Davis [7]</td>
<td>Hypertensive persons (30 to 69 yr)</td>
<td>10,940</td>
<td>Systolic OH(^b) with diabetes</td>
<td>5-yr mortality</td>
<td>2.28 (1.27–4.11)</td>
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<td>Syncope patients (16 to 89 yr)</td>
<td>223</td>
<td>Systolic OH(^d)</td>
<td>Syncope recurrence</td>
<td>NS</td>
</tr>
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<td>Raiha [45]</td>
<td>Community-living elderly (&gt;65 yr)</td>
<td>347</td>
<td>Diastolic OH</td>
<td>10-yr mortality</td>
<td>2.70 (1.30–5.61)</td>
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<td>4-yr mortality</td>
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<td>Masaki [35]</td>
<td>Japanese American men 71 to 93 yr</td>
<td>3522</td>
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<td>4-yr mortality</td>
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<td>Systolic OH(^b)</td>
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<td>Luukinen [33]</td>
<td>Home-dwelling persons (&gt;70 yr)</td>
<td>792</td>
<td>Diastolic OH</td>
<td>4-yr vascular death</td>
<td>1.69 (1.02–2.80)</td>
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<td>Viramo [57]</td>
<td>Home-dwelling persons (&gt;70 yr)</td>
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<td>Cognitive decline</td>
<td>2.04 (1.01–4.15)</td>
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<tr>
<td>Ooi [43]</td>
<td>Institutionalized persons (&gt;60 yr)</td>
<td>844</td>
<td>Systolic OH(^c)</td>
<td>Fall recurrence</td>
<td>2.1 (1.4–3.1)</td>
</tr>
</tbody>
</table>

NS: not significant, no relative risk reported.
\(^a\) 1 min standing.
\(^b\) 3 min standing.
\(^c\) 1 or 3 min standing.
\(^d\) Within 10 min standing.
pressure decline was associated with an excess 10-year vascular mortality [45]. In a nursing home population, Ooi et al. [43] reported that orthostatic hypotension is an independent risk factor for recurrent falls. Although currently it seems that orthostatic hypotension is an independent risk factor for morbidity and mortality, further studies are needed to identify the subgroups of elderly people who are at greatest risk.

**Normal orthostatic blood pressure regulation**

In healthy humans, orthostatic pooling of venous blood in the legs and abdomen begins almost immediately after changing from a supine to an erect posture. Depending on the type of orthostatic stress (i.e., active standing, lower-body negative pressure, or head-up tilt), approximately 0.5–1.0 L of thoracic blood is transferred to the region below the diaphragm. Several normal physiologic responses are designed to maintain vital organ perfusion during this orthostatic redistribution of intravascular volume. Decreased venous return to the heart transiently reduces blood pressure and unloads cardiopulmonary, carotid sinus, and aortic arch baroreceptors, resulting in sympathetic activation, parasympathetic inhibition, and associated increases in heart rate and vascular resistance. These compensatory responses restore cardiac output and return blood pressure to normal. Orthostatic hypotension may result from an excessive reduction in blood volume when the patient is upright or from inadequate cardiovascular compensation for the decline in cardiac preload when the patient changes to an upright posture.

**Age-related changes in blood pressure regulation**

Normal human aging is associated with several changes in the autonomic regulation of blood pressure that may predispose elderly people to orthostatic hypotension. Although orthostatic hypotension probably does not result directly from these age-related changes, the superimposition of cardiovascular diseases and the medications used to treat them often leads to further decrements in autonomic function that manifest as hypotension and syncope in elderly patients.

The baroreflex maintains a normal blood pressure by increasing heart rate and vascular resistance in response to transient reductions in the stretch of arterial baroreceptors and by decreasing these parameters in response to an increase in such a stretch. Normal human aging is associated with a reduction in baroreflex sensitivity, which is evident in (1) the blunted cardio-acceleratory response to stimuli such as upright posture [4], nitroprusside infusion [39], and lower-body negative pressure [4] (all of which lower arterial pressure); and (2) the reduced bradycardic response to drugs such as phenylephrine (which elevate arterial pressure) [37]. That plasma norepinephrine levels are heightened and prolonged during hypotensive stress in healthy elderly people [61] suggests that aging
causes an impaired beta-mediated adrenoreceptor response to sympathetic activation. This notion is further supported by the findings that the infusion of beta-adrenergic agonists results in smaller increases in heart rate, left ventricular ejection fraction, cardiac output, and vasodilatation in older men compared with their younger counterparts [25].

The alpha-1-adrenergic vasoconstrictor response to norepinephrine infusion is reduced in the forearms of healthy elderly subjects [18]. Although muscle sympathetic nerve activity is increased during baroreceptor unloading by lower-body negative pressure, the vasoconstrictor response to increased sympathetic nervous system activity is reduced [9]. This apparent alteration in sympathetic transduction into vascular resistance also may predispose elderly people to orthostatic hypotension.

Age-related alterations in the parasympathetic nervous system are difficult to evaluate because of the lack of established noninvasive methods to measure parasympathetic activity. Currently available clinical evidence derived from studies of heart rate variability suggests there is a decline in parasympathetic function with aging. Recently, the technique of frequency domain analysis has been used to quantify the contribution of the parasympathetic nervous system to heart rate variability. The power spectrum produced by this technique can be divided into low-frequency (0.04–0.15 Hz) and high-frequency (>0.15 Hz) components. Previous pharmacologic blocking studies using atropine and a beta-blocker suggest that the high-frequency component represents cardiac parasympathetic tone [14]. Frequency-domain analysis techniques have shown that healthy elderly people have reductions in the high-frequency parasympathetic modulation of heart rate variability [28].

With aging, there is also an increase in heart and vasculature stiffness. In the large vessels, this rigidity is caused by a reduction in elastic tissue and an increase in the amount of collagen, resulting in elevated systolic blood pressure, increased pulse wave velocity, increased cardiac afterload, and moderately increased thickness of the left ventricular wall [26]. With advancing age, there is also an increase in the cross-linking of myocardial collagen and a prolongation of the isovolumic relaxation period [26]. These changes in the physical properties of the heart restrict cardiac relaxation and impair early left ventricular diastolic filling. Despite the reduction in early diastolic filling, end-diastolic volume and cardiac output are preserved through enhanced atrial contraction during late diastole [2]. Conditions that further impair diastolic filling (e.g., a reduction in intravascular volume [49], reduced venous return to the heart during upright posture, the administration of nitrate venodilators), however, may diminish cardiac output and result in orthostatic hypotension.

**Effect of hypertension on blood pressure regulation**

Partly because of the greater vascular stiffness associated with advanced age, systolic hypertension increases in prevalence with aging. Indeed, more than 30%
of people over 75 years of age have resting systolic blood pressures above 160 mm Hg. Both normal aging and hypertension reduce baroreflex sensitivity independently. Sustained blood pressure elevations also reduce vascular and ventricular compliance [24]. Therefore, the effects of hypertension being superimposed on the effects of aging may further impair blood pressure homeostasis, causing hypertensive elderly individuals to be particularly vulnerable to orthostatic hypotension. This notion raises the possibility that the judicious treatment of hypertension may improve blood pressure regulation.

Hypertension may increase the risk of cerebral ischemia from sudden declines in blood pressure. Both cross-sectional and longitudinal studies of cerebral blood flow, using xenon- and nitrous oxide–inhalation techniques, have demonstrated a progressive decline in cerebral blood flow with advancing age. Cerebral blood flow is reduced further by the presence of hypertension and other risk factors for cerebrovascular disease. Although the autoregulation of cerebral blood flow in response to decreased perfusion pressure is preserved into old age (except in certain persons with symptomatic orthostatic hypotension [60]), chronic hypertension shifts the lower and upper blood pressure limits of cerebral-blood-flow autoregulation toward higher pressures. Elderly patients with hypertension, therefore, have a resting cerebral blood flow that is closer to the threshold for cerebral ischemia. Consequently, relatively small, short-term reductions in blood pressure in these patients may produce cerebral ischemic symptoms.

Not only does hypertension interact with aging to impair the physiologic mechanisms that maintain organ perfusion, but blood pressure elevations also influence the measurement of blood pressure changes during the assumption of an upright posture. A previous study of daily blood pressure responses to a posture change in nonmedicated, institutionalized, elderly people found marked day-to-day variability in blood pressures in the supine and upright positions and a strong relationship between the postural blood pressure change and the basal supine blood pressure on any given day [31]. Another study showed that both supine systolic blood pressure and baroreflex sensitivity are related independently to the maximum change in systolic blood pressure during head-up tilting [20].

The acute treatment of hypertension can result in orthostatic hypotension via several mechanisms, including reduced systemic vascular resistance, contraction of plasma volume, inhibition of cardiac inotropy, limitation of cardiac chronotropy, and decreased renin and aldosterone secretion [3]. Chronic therapy, however, rarely is associated with orthostatic hypotension [6, 50]. Antihypertensive treatment may improve cerebral and systemic vascular response to hypotensive stress, and many drugs (e.g., beta-adrenergic blockers [12], angiotensin-converting–enzyme inhibitors [40], calcium-channel blockers [11]) have been shown to improve baroreflex sensitivity in hypertensive subjects. Chronic suppression of heightened sympathetic nervous system activity with guanadrel in elderly people improves arterial alpha-adrenergic responsiveness to norepinephrine [17]. Furthermore, recent data from our laboratory suggest that previously treated elderly hypertensive subjects retain
<table>
<thead>
<tr>
<th>Age</th>
<th>Young (N = 10)</th>
<th>Normal old (N = 10)</th>
<th>Hypertensive Old (N = 10)</th>
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<tr>
<td></td>
<td>24 ± 1</td>
<td>72 ± 3</td>
<td>72 ± 2</td>
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<tr>
<td>Sit-to-standing</td>
<td></td>
<td></td>
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<tr>
<td>MBP change (mm Hg)</td>
<td>−24 ± 2</td>
<td>−21 ± 2</td>
<td>−26 ± 2</td>
</tr>
<tr>
<td>CBFV change (cm/s)</td>
<td>−10 ± 1</td>
<td>−5 ± 1*</td>
<td>−5 ± 1*</td>
</tr>
<tr>
<td>% change CVR</td>
<td>−15 ± 3</td>
<td>−15 ± 3</td>
<td>−27 ± 3*</td>
</tr>
</tbody>
</table>

Values are mean ± SE. MBP, mean blood pressure; CBFV, cerebral blood flow velocity; CVR, cerebrovascular resistance.

* P < 0.05 vs. Young.

Cerebral-blood-flow autoregulatory capacity in response to acute orthostatic hypotension (Table 2) [29].

**Etiology of orthostatic hypotension**

Common causes of orthostatic hypotension are:

**Systemic disorders:**
- Dehydration
- Deconditioning
- Prolonged immobility
- Adrenocortical insufficiency

**Medication**
- Antipsychotics
- Monoamine-oxidase inhibitors
- Tricyclic antidepressants
- Antihypertensives and diuretics
- Vasodilators (nitrates)
- Levodopa
- Beta-blockers
- Calcium-channel blockers
- Angiotensin-converting–enzyme inhibitors

**Central nervous system (CNS) disorders:**
- Multiple systems atrophy (MSA)
- Parkinson’s disease
- Multiple cerebral infarctions
- Myelopathy
- Brain-stem lesions

**Peripheral autonomic neuropathy**
- Pure autonomic failure
- Diabetes mellitus
Amyloidosis
Tabes dorsalis
Paraneoplastic
Alcoholic and nutritional

These can be divided into systemic and medication-related causes and disorders of the central and peripheral nervous systems. Acute orthostatic hypotension most commonly results from dehydration during an acute illness. In young subjects, excessive cardio-acceleration when standing suggests hypovolemia rather than autonomic dysfunction as the cause of orthostatic hypotension. In normal elderly subjects, however, cardio-acceleration often is blunted, so it may not occur in patients whose orthostatic hypotension results from hypovolemia. Total blood volume decreases with age in healthy men of similar body size and chronic physical activity level [8]. Moreover, as elderly men develop hyperosmolarity during water deprivation they do not experience the same degree of thirst as do their younger counterparts [44].

Any disease that impairs mobility or results in prolonged inactivity also may produce orthostatic hypotension. For example, prolonged bed rest after myocardial infarction commonly results in orthostatic hypotension [10]. A much less common cause of acute orthostatic hypotension is adrenocortical insufficiency accompanied by hyponatremia and hyperkalemia.

Orthostatic hypotension caused by autonomic insufficiency is usually chronic and often is associated with symptoms of autonomic nervous system dysfunction (e.g., fixed heart rate, visual difficulty, incontinence, constipation, inability to sweat, heat intolerance, impotence, and fatigability). The CNS disorders that cause orthostatic hypotension include multiple cerebral infarctions and MSA. Previously known as Shy–Drager syndrome, MSA is associated with neuronal degeneration in several areas of the CNS, including the corticobulbar, corticospinal, extrapyramidal, and cerebellar system of the brain and the intermediolateral columns of the spinal cord. It has three clinical presentations:

1. A parkinsonian syndrome with orthostatic hypotension and extrapyramidal features, usually without tremor, that is unresponsive to dopamine
2. A cerebellar syndrome with prominent cerebellar ataxia and, frequently, pyramidal features
3. A mixed form with parkinsonian, cerebellar, and pyramidal abnormalities

Parkinson’s disease itself may be associated with autonomic insufficiency and orthostatic hypotension and is often difficult to distinguish clinically from MSA. The stimulation of growth-hormone release by clonidine infusion may be a useful test for distinguishing these conditions. Clonidine raises circulating concentrations of growth hormone in Parkinson’s disease but not in MSA [23].

Disorders of the peripheral autonomic nervous system that cause orthostatic hypotension include insulin-dependent diabetes mellitus, in which severe
peripheral neuropathy and other end-organ damage is evident, and less common entities such as amyloidosis, tabes dorsalis, vitamin deficiencies, and the neuropathies associated with cancer (particularly that of the lung or pancreas). (See the list at the beginning of this section.) If no cause is evident, orthostatic hypotension may be primary or idiopathic. Pure autonomic failure (previously called idiopathic orthostatic hypotension, progressive autonomic failure, and Bradbury-Eggleston syndrome) is characterized by (1) low basal plasma norepinephrine levels while the patient is supine, (2) little or no increase in the norepinephrine level when he or she stands up, (3) a low threshold for the pressor response to infused norepinephrine, and (4) low plasma norepinephrine levels in response to tyramine despite a greater pressor response to the drug. These findings are consistent with a depletion of norepinephrine from sympathetic nerve endings, with resultant postsynaptic denervation supersensitivity.

The adverse effects of medications are among the most commonly encountered causes of orthostatic hypotension. Culprit medications include antipsychotics, tricyclic antidepressants, diuretics, and antihypertensive medications, particularly when these are first administered.

**Evaluation**

Clinicians should not assume that an elderly person who complains of postural dizziness and lightheadedness is suffering from orthostatic hypotension. Instead, blood pressure and pulse rate should be measured after the patient has been recumbent for at least 5 minutes, after standing quietly for 1 minute, and again after standing for 3 minutes. A hypotensive response may be immediate or delayed. Prolonged standing or a tilt test may be needed to detect a delayed hypotensive response. If the patient is unable to stand, sitting will suffice; however, postural blood pressure changes may be missed with this method. The detection of orthostatic hypotension may require numerous blood pressure measurements on different occasions. The time of day is important; postural hypotension is often worse in the morning when rising from bed [42]. Food and alcohol can exacerbate orthostatic hypotension, as can activities that raise intrathoracic pressure (e.g., micturition, defecation, coughing).

The heart rate response to posture change can provide important information about the cause of orthostatic hypotension. Minimal cardio-acceleration (<10 bpm) in the face of hypotension suggests baroreflex impairment, whereas tachycardia (>100 bpm) indicates volume depletion or sympathicotonic orthostatic hypotension (orthostatic intolerance). Because of the age-related reduction in baroreflex sensitivity, the absence of cardio-acceleration does not rule out volume depletion in an elderly patient. Occasionally, posture change results in bradycardia and hypotension (a vasovagal response), possibly because the cardiac vagal afferents are stimulated by vigorous ventricular contraction around a relatively hypovolemic chamber [34]. This effect is seen often in
young military personnel who must stand at attention for prolonged periods of time.

The remainder of the evaluation requires taking a detailed history that focuses on autonomic symptoms, diseases that are likely to cause orthostatic hypotension, and medications. The physical examination should investigate the size and responsiveness of the pupils, abnormal sweating, cardiovascular disease, peripheral neuropathy, and CNS abnormalities.

Useful bedside tests of autonomic function include (1) the heart rate response to deep breathing (respiratory sinus arrhythmia) and the Valsalva maneuver, and (2) the blood pressure response to hand immersion in cold water (the cold pressor test). The respiratory sinus arrhythmia is measured with electrocardiography during 1 minute of slow, deep breathing (5 seconds of inspiration and 7 seconds of expiration). The maximal R-R interval during expiration divided by the minimal R-R interval during inspiration is greater than 1.15 for most healthy elderly persons [51]. The mechanism of respiratory sinus arrhythmia is not understood completely, but the efferent path is the vagal supply to the heart. To perform a Valsalva maneuver, after a deep inspiration, the subject exhales forcibly through a tube connected to a mercury manometer and maintains a pressure of at least 30 mm Hg for 10 to 15 seconds. The ratio of the longest R-R interval after the maneuver to the shortest R-R interval during the maneuver should exceed 1.20 [58]. The cold pressor test is used as a non-baroreflex-mediated sympathoexcitatory stimulus. One hand is immersed up to the wrist in ice water for 1 minute. A normal pressor reaction is a systolic blood pressure rise that exceeds 15 mm Hg and a diastolic rise of at least 10 mm Hg. Subjects are instructed to avoid isometric contraction, performance of the Valsalva maneuver, or holding one’s breath during the test.

The measurement of plasma norepinephrine levels while supine and after standing for 5 to 10 minutes is occasionally useful in determining the site of an autonomic defect. Normal subjects experience a two- to threefold increase in their plasma norepinephrine levels when in an upright position, whereas those with autonomic insufficiency have a blunted response (<50% increase). Generally, patients with CNS causes of autonomic insufficiency (e.g., Shy-Drager syndrome) have normal supine norepinephrine levels, whereas those with a peripheral cause have low supine levels. However, in practice, these levels are quite variable and often misleading.

Recently, the measurement of circulating vasopressin levels during upright tilting has been used to distinguish patients with pure autonomic failure from those with MSA. Patients with pure autonomic failure have marked increases in plasma vasopressin, whereas patients with MSA have virtually no change during 10–30 minutes of tilting [22]. Additionally, clonidine infusion stimulates growth-hormone release in patients with pure autonomic failure but not in those with MSA [55]. These tests may serve as neuroendocrine markers to distinguish patients with central from peripheral autonomic nervous system defects.
Treatment

When orthostatic hypotension is an asymptomatic finding that is confirmed on repeat examination, it should be considered a risk factor for falls or syncope and treated by performing the following nonpharmacologic interventions:

- Withdrawing drugs (either discontinuation, substitution or dose change)
- Avoiding warm environment
- Avoiding of straining activity
- Squatting, stooping forward
- Crossing one's leg
- Increasing salt intake
- Wearing waist-high compression stockings
- Sleeping in the head-up position

If, however, the orthostatic hypotension is symptomatic or associated with a new illness or medication, the goal of treatment is the improvement of the patient's functional capacity, rather than a specific target blood pressure. Chronic, symptomatic orthostatic hypotension caused by true autonomic insufficiency is less common but extremely disabling, often requiring the use of the following pharmacologic agents:

- Fludrocortisone
- Midodrine
- Nonsteroidal anti-inflammatory drugs
- Octreotide
- Caffeine
- Erythropoietin
- Clonidine
- Yohimbine
- Beta-blockers

Nonpharmacologic interventions

Initial therapy should include the discontinuation of any prescribed or over-the-counter medications that could be responsible for the orthostatic hypotension. In one study of institutionalized elderly patients with syncope, nitrate medications and antidepressants were found to be the major causes of orthostatic hypotension [30]. Additionally, patients should be taught to rise slowly from beds and chairs after a prolonged period of lying down or sitting. A warm environment, such as summer weather, central heating, or a hot bath also can provoke hypotension. Patients should avoid activities that involve straining, such as lifting heavy objects, because increased abdominal or intrathoracic pressure at these times compromises venous return and can precipitate hypotension. Coughing and straining while urinating or defecating may result in hypotension.
Exercises that involve dorsiflexion of the feet before standing may be helpful in promoting venous return to the heart, accelerating the pulse, and increasing blood pressure. Sitting down usually raises blood pressure in a patient who has been standing. Squatting, stooping forward while maintaining an upright posture, and resting one leg in an elevated position all have been shown to restore blood pressure in some patients [46]. Crossing one's legs, which involves the contraction of agonist and antagonist muscles, has been shown to be a simple and effective countermaneuver to increase cardiac output and blood pressure while standing [59].

In the absence of a history of congestive heart failure, a high salt diet aimed at producing a modest weight gain may blunt the symptoms of orthostatic hypotension in many patients. Waist-high support garments that cover the calf and thigh or abdominal binders may be effective. The head of the patient's bed should be elevated 5°–20° to prevent the nocturnal diuresis and supine hypertension that results from nocturnal shifts of interstitial fluid from the legs to the systemic circulation [53,56].

**Pharmacologic interventions**

A large number of drugs have been used to raise blood pressure in patients with orthostatic hypotension. One of the most useful pharmacologic agents is fludrocortisone acetate (a synthetic mineralocorticoid), which expands circulatory volume. Although this drug is not licensed specifically for the treatment of orthostatic hypotension, fludrocortisone has been used for this purpose for over 40 years [15]. Its pressor effects are caused by increases in extracellular and plasma volumes, which develop over 1 to 2 weeks. The initial dose is 0.1 mg at night, titrated upward in 0.1-mg increments at weekly or biweekly intervals until mild peripheral edema develops or a maximal dose of 1.0 mg is achieved. Adverse effects include supine hypertension, hypokalemia, and congestive heart failure. The drug should be used cautiously in elderly patients, with careful monitoring of cardiac status and serum potassium levels. Occasionally, potassium supplementation is required.

In peripheral autonomic dysfunction, midodrine (an alpha-agonist with selective vasoconstrictor properties) is often effective [21,32,38]. Midodrine is usually most effective when used in combination with fludrocortisone and achieves the greatest benefit when administered early in the day. Side effects of midodrine include piloerection (gooseflesh), paresthesia of the scalp, and pruritus, probably all of which are caused by the effects of muscle contractions on integumentary hairs. Midodrine cannot be recommended for use in patients with coronary or peripheral arterial disease.

Drugs that inhibit the vasodilating actions of prostaglandins (e.g., indomethacin [19], other nonsteroidal anti-inflammatory drugs) have been helpful in some patients with orthostatic hypotension by raising systemic vascular resistance. Side effects of gastrointestinal intolerance and hemorrhage, however, cause these drugs to be contraindicated in many elderly patients.
The somatostatin analog octreotide, which causes splanchnic vasoconstriction, is a useful adjunct for the short-term treatment of orthostatic hypotension [27], particularly when associated with postprandial hypotension. Unfortunately, octreotide must be given as an injection with meals and has a short duration of action.

Caffeine (250 mg or two cups of coffee each morning) also may attenuate orthostatic hypotension, but tolerance rapidly develops if given more than once a day.

Erythropoietin has been shown to be effective in some patients with autonomic failure and mild to moderate anemia [16]. It probably acts by increasing red cell mass, but its exact mechanism and its long-term effects are not known. The greatest disadvantage of erythropoietin is that it must be administered parenterally. Furthermore, an increase in red cell mass may make patients vulnerable to stroke and myocardial infarction.

Other medications that are useful in some patients include the peripheral alpha-2-adrenergic agonist clonidine. In patients with CNS causes of autonomic insufficiency and reduced central sympathetic outflow, clonidine may promote peripheral vasoconstriction and may increase venous return to the heart [47]. The central alpha-2-adrenergic antagonist yohimbine, which increases central sympathetic outflow in some patients, also may be useful [41]. Beta-blockers, which block beta-2 vasodilatory receptors or have intrinsic sympathomimetic activity (e.g., pindolol), and ergot alkaloids (e.g., oral ergotamine tartrate, subcutaneous dihydroergotamine) are occasionally helpful.

In patients with severe autonomic insufficiency, orthostatic hypotension may be quite disabling, and combinations of pharmacologic agents may be required to permit even brief periods of upright posture. One difficult complication of many medications requires special consideration: severe supine hypertension. To avert this problem, patients should be encouraged to avoid the supine position and to raise the head of their bed or sleep in a recliner at night. Short-acting vasodilators, such as nitroglycerine paste, or a calcium-channel blocker may be given overnight, but a commode should be placed near the bed to minimize the risk of syncope and falls when patients need to void during the night.

In elderly patients who have hypertension and associated asymptomatic orthostatic declines in blood pressure, judicious antihypertensive therapy actually may improve blood pressure regulation. If there is no evidence of autonomic failure, low-dose thiazide diuretics, angiotensin-converting-enzyme inhibitors, calcium-channel blockers, or beta-blockers that are titrated slowly upward (as tolerated) over several weeks may lower baseline blood pressure and ameliorate orthostatic hypotension [36]. During the initial titration of antihypertensive medications, patients should be monitored carefully with a home blood pressure measuring device in the supine and standing positions at different times of day and after meals to be sure their hypotension is not worsened.
Summary

A common problem among elderly people, orthostatic hypotension is associated with significant morbidity and mortality, which may be caused by medications, the cumulative effects of age- and hypertension-related alterations in blood pressure regulation, or age-associated diseases that impair autonomic function. Evaluation requires multiple blood pressure measurements taken at different times of the day and after meals or medications. Central and peripheral nervous system disorders should be sought, and the laboratory evaluation should concentrate on ruling out diabetes mellitus, amyloidosis, occult malignancy, and vitamin deficiencies. If orthostatic hypotension is detected, it should be considered a risk factor for adverse outcomes and treated first with nonpharmacologic interventions, including the withdrawal of potentially hypotensive medications. In patients with hypertension and orthostatic hypotension, the judicious treatment of hypertension may be helpful. For persistent, symptomatic orthostatic hypotension caused by autonomic failure, pharmacologic interventions include fluudrocortisone, midodrine, and a variety of other agents. The careful evaluation and management of orthostatic hypotension will hopefully result in a significant reduction in falls, syncope, and fractures, and an attenuation of functional decline in elderly patients.

Acknowledgment

This work was supported by the Hebrew Rehabilitation Center for Aged and by a Teaching Nursing Home Award (AG04390) from the National Institute on Aging in Bethesda, Maryland. Dr. Mukai is a Visiting Research Fellow from Nagoya City University, Nagoya, Japan. Dr. Lipsitz holds the Irving and Edyth S. Usen and Family Chair in Geriatric Medicine at the Hebrew Rehabilitation Center for Aged in Boston, Massachusetts.

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