


Postural Hypotension and Anhidrosis

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SUMMARY

Orthostatic hypotension (OH) occurs in 10–20% of patients seen in diabetic practice. Patients can be asymptomatic or manifest symptoms of cerebral hypoperfusion, such as lightheadedness or weakness, or less common symptoms of sympathetic overactivity. Syncope can occur. Symptoms correlate with autonomic deficits. Autonomic laboratory evaluation demonstrates early impairment of cardiovagal and distal postganglionic sudomotor function, eventually leading to generalized autonomic failure. Treatment of OH consists of nonpharmacological and pharmacological therapy. The former involves patient education, management of salt, fluids, sleeping with head of the bed elevated, compression garments, and physical countermaneuvers. Pharmacological therapy with midodrine is efficacious but aggravates supine hypertension. Pyridostigmine will improve OH without aggravating supine hypertension although its effects are the modest. Sudomotor failure is the rule, manifests initially as distal anhidrosis followed by regional, multifocal, and other patterns of sweat loss. Sudomotor symptoms include regional hyperhidrosis and heat intolerance.

Key Words: Adrenergic; anhidrosis; baroreflex; cardiovagal; denervation; gustatory; hypovolemia; midodrine; orthostatic hypotension; vasomotor.

INTRODUCTION

Autonomic failure can occur as part of diabetic and other autonomic neuropathies. Although, cardiovagal impairment is well-recognized, sudomotor impairment occurs just as early if sensitive and quantitative tests are used to detect anhidrosis (1). Manifestations of sympathetic failure include a loss of baroreflex function and loss of sweating. This chapter will focus on orthostatic hypotension (OH) and anhidrosis.

WHAT IS OH?

Consensus criteria for definition of OH is a reduction of systolic blood pressure (BP) of at least 20 mmHg or diastolic BP of at least 10 mmHg within 3 minutes after standing up (2). The use of a tilt table in the head-up position at an angle of at least 60° was accepted as an alternative. The consensus conference recommended that the confounding variables of food ingestion, time of day, state of hydration, ambient temperature, recent recumbency, postural deconditioning, hypertension, medications, sex, and age be considered. OH may be symptomatic or asymptomatic. If the patient has
symptoms suggestive of, but does not have documented OH, BP measurements should be repeated.

The values chosen are reasonable screening values, but are associated with 5% false-positive values. A value of 30-mmHg decrease in systolic BP would reduce the frequency of false-positive values to 1% (3). Preferably, an autonomic laboratory study should be performed to confirm the presence of adrenergic failure. The clinician should further characterize OH in terms of frequency and severity of symptoms, standing time before the onset of symptoms, and presyncope and its influence on activities of daily living. Additionally, it is desirable to document whether OH is associated with supine hypertension and if there is a loss of diurnal variation in BP.

The prevalence of OH is not certainty known. For adults who have diabetes mellitus (combined type 1 and type 2 diabetes) from 1987 to 1997, 10% of patients with OH were evaluated. The mean age of the Rochester Diabetic Cohort over this decade was 60.6 ± 11.7 years.

REGULATION OF BLOOD PRESSURE

The maintenance of postural normotension without an excessive heart rate increment requires an adequate blood volume and the integration of reflex and humoral systems in several key vascular beds. These include striated muscle, splanchnic-mesenteric, and cerebrovascular beds. An adequate blood volume is essential. Hypovolemia regularly causes OH, even if vascular reflexes are intact. Hypovolemia can also be relative. Adrenergic denervation decreases vascular tone and increases vascular capacity, so that these patients are relatively hypovolemic, although plasma volume is normal. A decreased red cell mass or normocytic normochromic anemia of chronic autonomic failure aggravates OH. Correcting anemia with erythropoietin improves orthostatic intolerance (4).

Vasomotor tone is controlled by two sets of baroreflexes, the arterial (or high-pressure) and venous (or low-pressure) baroreflexes. When BP falls, baroreceptors are unloaded in the carotid sinus and aortic arch (5). These are arterial baroreceptors. Afferents through the IX and X cranial nerves synapse in the nucleus of the tractus solitarius. From this nucleus, a polysynaptic cardiovagal pathway travels to the nucleus ambiguus and dorsal motor nucleus of the vagus and hence, through the vagus nerve to the sinoatrial node to control heart rate. Sympathetic function is regulated by the rostroventrolateral nucleus of medulla, which projects to the intermediolateral column of the thoracic spinal cord that in turn provides sympathetic innervation to the heart and periphery (arterioles and venules) (6). In addition to arterial baroreceptors, there are low-pressure baroreceptors, that respond to a decrease in central venous pressure. Cardiopulmonary receptors in the heart and lungs send mainly nonmyelinated vagal fibers to the nucleus of the tractus solitarius. The central pathways and efferents are the same as for arterial baroreceptors. Baroreflexes are often referred to as “buffer” nerves as they maintain BP constant in all positions. Baroreflex failure results in the triad of OH, supine hypertension, and loss of diurnal variation in BP. In normal subjects BP is lower at night than during the day. The converse occurs in baroreflex failure (7).

The splanchnic-mesenteric capacitance bed is a large-volume, low-resistance system of great importance in the maintenance of postural normotension in humans. It constitutes 25–30% of the total blood volume (8). Unlike muscle veins, splanchnic veins have an abundance of smooth muscle and a rich sympathetic innervation. The mesenteric capacitance
bed is markedly responsive to both arterial and venous baroreflexes. Venoconstriction is mediated by $\alpha$-adrenergic receptors (9). The nerve supply to the mesenteric bed is mostly from preganglionic axon in the greater splanchnic nerve, with cell bodies in the intermediolateral column (mainly T4–T9) that synapse in the celiac ganglion from where postganglionic adrenergic fibers supply effector cells. Abnormalities in the splanchnic autonomic outflow have been found in human diabetic neuropathy, indicating that preganglionic fibers can be affected (10).

Cerebral vasoregulation is important for ensuring adequate and stable flow to the brain in spite of changing systemic BP. The maintenance of constant blood flow in spite of variations in BP is termed autoregulation (11). Within a mean BP range of approximately 50–150 mmHg, a change in BP produces insignificant change in cerebral perfusion. Previous studies of patients with OH demonstrated an expansion of the autoregulated range at both the upper and lower limits, so that cerebral perfusion remained relatively constant with the patient supine (when supine hypertension might be present) and in response to standing (when OH occurs) (11–14).

**DIABETIC OH**

OH is relatively common in patients with diabetic neuropathy (10,15,16), although the frequency reflects referral bias. OH was found in 43% of 16 patients (10) and 26% of 73 patients (1). Mulder et al. (17) found OH in 18 of 103 unselected patients with diabetes of whom 43 had polyneuropathy. Veglio et al. (16) reported orthostatic intolerance in 34% of 221 patients with NIDDM patients. In some studies clinical failure is very uncommon. For instance, Young et al. (18) in a study of teenagers, did not find any symptoms of autonomic failure. The prevalence of symptomatic OH is less than 1% in population based studies (19), but if asymptomatic OH is considered the prevalence, might be about 10% (ongoing Rochester diabetic study of PJ Dyck).

The mechanism of diabetic OH is multiplex. There is denervation of postganglionic adrenergic nerve fibers that innervate arterioles and venules that occurs as an integral part of diabetic peripheral neuropathy (3). As a result, the adrenergic sympathetic component of the baroreflex arc is defective and arteriolar vasoconstriction fails to occur; and total systemic resistance fails to increment. In the Autonomic laboratory, this is manifested as an exaggerated fall in BP during the Valsalva maneuver with failure of reflex vasoconstriction (loss of late phase II and IV and delayed BP recovery). Reflex changes in heart rate fail to occur because of cardiovagal failure. An important additional mechanism is the consistent and early degeneration of sympathetic pre- and postganglionic fibers supplying the splanchnic mesenteric bed (10,20). The autonomic denervation of the muscle resistance bed is also present, but in humans sustained postural normotension is more dependent on the splanchnic system, whereas innervation of skeletal muscle is important in the regulation of moment to moment adjustments (21). Plasma volume, cardioacceleration, and central blood volume are normal or near-normal in diabetic OH (20). Subcutaneous vasoconstrictor function is impaired (10,20).

Limited information is available on recording of the splanchnic-mesenteric bed in diabetic neuropathy patients. It is possible to measure superior mesenteric artery flow using a duplex scanner (22). Normal subjects undergo a two- to threefold increase in superior mesenteric flow with a meal, and splanchnic capacitance falls with tilt-up.
Patients with neurogenic OH are reported to undergo a normal increase in capacity postprandially, and hypotension develops because of failure of muscle arteriolar vasoconstriction (23). Some workers have reported similar responses to tilt and a meal in diabetic neuropathy patients when compared with controls and conclude that the splanchnic bed may be less important than was assumed (24). One possible explanation is that there is heterogeneity of responses in patients with diabetic neuropathy (22).

CLINICAL MANIFESTATIONS OF OH

OH is manifested as a constellation of symptoms that develop on standing and dissipates on lying back down. Lightheadedness is common, but other symptoms are also very common. These include a sense of weakness, especially of the legs, and difficulty thinking clearly. Pain in the neck and trapezi (coat hanger headache) occurs in about 20% of patients. It was evaluated in a prospective study, 90 patients with symptomatic OH, 60 patients with symptoms but without laboratory confirmation of OH, and 5 patients with asymptomatic OH. Although lightheadedness is common about 50% of patients more than the age of 60 have problems of cognitive impairment on standing that clears on sitting or lying down (25). Cognitive problems are typically more obvious to the companion than the patient, although not infrequently the patient will use terms like “I feel goofy,” at least in Minnesota. Some patients complain of a retrocollic heaviness or headache on continued standing (26). The patient may feel faint only under certain conditions. Many patients complain of weakness, especially in the legs on standing. Some patients develop ataxia when their BP falls. Aggravating symptoms need to be sought. Apart from continued standing other orthostatic stressors include exercise, environmental warming, or food ingestion. Standing time is most commonly less than 1 minute before the onset of symptoms. Indeed, an increase in standing time by 1–2 minutes results in a dramatic increase in activities of daily living. Although it is well known that patients are often worse on first awakening in the morning, the most common time of day when orthostatic intolerance is worse is not particular. It should be emphasized that, although the patients were highly symptomatic about 75% having frequent symptoms, the majority of patients do not have syncope, suggesting that these patients either have sufficient warning to avert syncope or have sufficient compensatory mechanisms to avoid syncope.

It is important to obtain an estimate of the severity and its effect on the patient’s activities encountered in daily living. An orthostatic intolerance grade has been generated that grades patients by the severity of symptoms, standing time, and interference with ability to perform activities of daily living (Table 1) (27). This scale was validated against comprehensive autonomic function tests in 145 patients, 97 (67%) of whom had OH. The 5-item scale demonstrated strong internal consistency (coefficient $\alpha = .91$). Patients with OH had significantly higher scores on each questionnaire item and the composite autonomic severity score (CASS) subscores than those without OH. The scale items correlated significantly with each of the CASS subscores, maximally with the CASS adrenergic subscore. Based on this evaluation, the following conclusions were made. OH is not the only cause of reduced orthostatic tolerance, and some patients may have OH, but be asymptomatic. Results of this study indicate that this 5-item questionnaire is a reliable and valid measure of the severity of symptoms of OH and that it can supplement laboratory-based measures.
### Table 1
**Symptom Scale for Evaluation of Autonomic Symptoms**

1. **Frequency of orthostatic symptoms**
   - 0. *Never or rarely* experience orthostatic symptoms when I stand up
   - 1. *Sometimes* experience orthostatic symptoms when I stand up
   - 2. *Often* experience orthostatic symptoms when I stand up
   - 3. *Usually* experience orthostatic symptoms when I stand up
   - 4. *Always* experience orthostatic symptoms when I stand up

2. **Severity of orthostatic symptoms**
   - 0. *Do not* experience orthostatic symptoms when I stand up
   - 1. Experience *mild* orthostatic symptoms when I stand up
   - 2. Experience *moderate* orthostatic symptoms when I stand up and *sometimes* have to sit down for relief
   - 3. Experience *severe* orthostatic symptoms when I stand up and *frequently* have to sit back down for relief
   - 4. Experience *severe* orthostatic symptoms when I stand up and *regularly faint* if I do not sit back down

3. **Conditions under which orthostatic symptoms occur**
   - 0. *Never or rarely* experience orthostatic symptoms under any circumstances
   - 1. *Sometimes* experience orthostatic symptoms under certain conditions, such as prolonged standing, a meal, exertion (e.g., walking), or when exposed to heat (e.g., hot day, hot bath, hot shower)
   - 2. *Often* experience orthostatic symptoms under certain conditions, such as prolonged standing, a meal, exertion (e.g., walking), or when exposed to heat (e.g., hot day, hot bath, hot shower)
   - 3. *Usually* experience orthostatic symptoms under certain conditions, such as prolonged standing, a meal, exertion (e.g., walking), or when exposed to heat (e.g., hot day, hot bath, hot shower)
   - 4. *Always* experience orthostatic symptoms when I stand up; the specific conditions do not matter

4. **Activities of daily living**
   - 0. My orthostatic symptoms *do not interfere* with activities of daily living (e.g., work, chores, dressing, bathing)
   - 1. My orthostatic symptoms *mildly interfere* with activities of daily living (e.g., work, chores, dressing, bathing)
   - 2. My orthostatic symptoms *moderately interfere* with activities of daily living (e.g., work, chores, dressing, bathing)
   - 3. My orthostatic symptoms *severely interfere* with activities of daily living (e.g., work, chores, dressing, bathing)
   - 4. My orthostatic symptoms *severely interfere* with activities of daily living (e.g., work, chores, dressing, bathing). *I am bed or wheelchair bound because of my symptoms.*

5. **Standing time**
   - 0. On most occasions, I can stand as long as necessary without experiencing orthostatic symptoms
   - 1. On most occasions, I can stand *more than 15 minutes* before experiencing orthostatic symptoms
   - 2. On most occasions, I can stand 5–14 minutes before experiencing orthostatic symptoms
   - 3. On most occasions, I can stand 1–4 minutes before experiencing orthostatic symptoms
   - 4. On most occasions, I can stand *less than 1 minute* before experiencing orthostatic symptoms
to provide a rapid, more complete clinical assessment. This questionnaire would also be useful as a brief screening device for orthostatic intolerance to aid physicians in identifying patients who may have OH.

LABORATORY EVALUATION

The patient with OH should be subjected to a full autonomic evaluation in order to determine the severity and distribution of autonomic failure. The recommended panel is shown in Table 2. The autonomic reflex screen evaluates the severity and distribution of postganglionic sudomotor, cardiovagal, and adrenergic failure. The thermoregulatory sweat test is a useful test in diabetic autonomic neuropathy, as the sweat loss has a number of different patterns (10, 28). These can be multifocal, distal, regional, or generalized.

In the evaluation of adrenergic function, the beat-to-beat BP (BP_BB) responses to the Valsalva maneuver and to HUT are the most sensitive and useful tests. There are four main phases in the Valsalva maneuver (29–31). In phase I, there is a transient rise in BP because of increased intrathoracic and intra-abdominal pressure causing mechanical compression of the aorta (32). In early phase II (phase II_E), the reduced preload (venous return) (33) and reduced stroke volume (34) lead to a fall in cardiac output in spite of tachycardia caused by a withdrawal of cardiovagal influence. Total peripheral resistance increases as a result of efferent sympathetic discharge to muscle (35) and within 4 seconds after the increase in sympathetic discharge the fall in BP is arrested. This is late phase II (II_L). In normal subjects phase II_L is so efficient that by the beginning of phase III, MAP is at the resting MAP level or above. Phase III like phase I is mechanical, lasting 1 to 2 seconds during which BP falls. The major mechanism is the sudden fall in intrathoracic pressure. There is a further burst of sympathetic activity during this phase. In phase IV, venous return (36) and cardiac output (34) have returned to normal whereas the arteriolar bed remains vasoconstricted, hence the overshoot of BP above baseline values. In the clinical autonomic laboratory setting, with studies done on the patients lying supine, phase IV may be more dependent on cardiac adrenergic tone than on systemic peripheral resistance. Intravenous phentolamine 10 mg resulted in the expected elimination of late phase II, but augmented rather than blocked phase IV. In contrast, 10 mg intravenous propranolol completely blocked phase IV (30). The use of the phases of the Valsalva maneuver to evaluate adrenergic function has been validated in using pharmacological dissection (30) and by studying its effect on normal subjects and patients with different severities of autonomic failure a CASS has been generated.

Table 2
Studies for the Patient With Suspected OH

<table>
<thead>
<tr>
<th>1. Autonomic reflex screen</th>
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<td>• Quantitative sudomotor axon reflex test</td>
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<td>• Tests of cardiovagal function</td>
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<td>• Beat-to-beat BP responses to the Valsalva maneuver</td>
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<tr>
<td>• BP and heart rate response to HUT</td>
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<tr>
<td>2. Thermoregulatory sweat test</td>
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<td>3. Plasma catecholamines—supine/standing</td>
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<td>4. 24-hour urinary sodium excretion</td>
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that corrects the confounding effects of age and gender (37). The most reliable phases of the maneuver are late phase II and IV. More recently, it has been demonstrated that BP recovery time defined as the duration from phase III to baseline may be a better index (38). It is free of the limitations of late phase II that is lost with even moderate autonomic failure.

Orthostatic BP recordings to tilt are recorded using BP_BB and with a sphygmomanometer cuff with the patient supine and following tilt to 70° using an automated tilt-table. Cuff recordings are obtained at 1 and 5 minutes after tilt up. It is important to perform the upright tilt procedure at a standard time after lying down because the orthostatic reduction in BP is higher following 20 minutes of preceding rest as compared with 1 minute. During upright tilt, normal individuals undergo a transient reduction in systolic, mean, and diastolic BP followed by recovery within 1 minute. The decrement is modest (<10 mmHg, mean BP). Normative data, based on 270 normal subjects aged 10–83 years have been obtained (3). Patients with adrenergic failure have a marked and progressive reduction in BP and pulse pressure. The heart rate response is typically attenuated, but in patients whose cardiac adrenergic innervation is spared, heart rate response is intact and may be increased.

TREATMENT OF OH

The goal of treatment is to improve standing BP, minimize symptoms, and improve orthostatic quality of life without causing excessive supine hypertension. In this chapter, nonpharmacological and pharmacological approaches to therapy will be covered. OH and supine hypertension that occurs under specific conditions will also be addressed.

NONPHARMACOLOGICAL TREATMENT OF OH

Nonpharmacological approaches are extremely important (Table 3).

Patient Education

Patient education is extremely important. The patient should understand in simple terms the maintenance of postural normotension. They need to understand the orthostatic stressors and their mechanisms. Important items of education include the following.

1. Advice on handling early morning and postprandial worsening of OH.
2. Instructions on how to keep a BP log. The patient or caregiver should learn to use an automated sphygmomanometer to measure BP with the patient supine and after standing for 1 minute. It is helpful to the physician if, for 2 or 3 days before a visit, recordings have been
taken and recorded on awakening, after a meal, during a time of maximal orthostatic tolerance, during a time of poor orthostatic tolerance, and before and 1 hour after medication.

3. Salt and volume expansion. All patients with neurogenic OH require generous fluid intake of five to eight 8-ounce glasses of fluid each day. Salt supplementation is essential. Most patients manage with added salt with their meals. Occasionally, patients prefer to use salt tablets (available as 0.5 g tablets). Adequate salt and fluid intake can be verified by checking the 24-hour urinary volume and concentration of sodium. Patients who have a value less than 170 mmol/24 hours can be given supplemental sodium, 1–2 g three times daily. Their weight, symptoms, and urinary concentration of sodium should be checked 1 or 2 weeks later.

4. Oral water bolus. The imbibing of a moderate volume of water results in a reduction in OH that lasts for about 2 hours. In a recent study, rapid water drinking (480 mL) increased BP by a mean of over 30 mmHg in patients with multiple system atrophy and pure autonomic failure. The pressor response was evident within 5 minutes after drinking started, reached a maximum after 30–35 minutes, and was sustained for 1–2 hours. The practical application of this observation is that the patient who needs to be subjected to sustained orthostatic stress should drink two 8-ounce glasses of water 10–20 minutes before such activity.

5. Raise head of bed. The head of the bed is elevated four inches for two reasons. First, it reduces nocturia, probably by stimulating renin release. Second, it reduces supine hypertension. During the day, it is important to maintain adequate orthostatic stress. If patients are tilted up repeatedly, OH gradually attenuates. This likely result from the release of renin and arginine vasopressin, which requires more sustained or repetitive orthostatic stress. Another mechanism that has been suggested is extravasated plasma around veins providing a vascular cuff, increasing venomotor tone.

6. Compression garments. For some patients, wearing a tightly fitting body stocking ameliorates OH and associated symptoms. These stockings have to be well-fitted and put on before arising. They work by reducing the venous capacitance bed. Their disadvantages are the cumbersome application and discomfort in hot weather. Calf compression alone confers minimal benefit, but a reasonable substitute to Jobst compression is the use of a tightly fitting abdominal binder, which confers about two-thirds of the benefit.

7. Physical countermaneuvers. Physical counter-maneuvers that involve the contraction of certain muscle groups of the lower extremities decrease venous capacitance and increase venous return. These maneuvers, which once learned can substantially prolong standing time, include crossing of the legs and contracting the leg muscles of one leg against the other, slow stepping or marching on the spot, propping the leg up on a chair, or contraction of the thigh muscles.

PHARMACOLOGICAL MANAGEMENT

Drug treatment is an important part of the overall therapeutic regimen and, if used well, greatly enhances BP control. The main drugs are midodrine, pyridostigmine, and possibly fludrocortisone.

Midodrine

The optimal approach, with the availability of midodrine, is to expand plasma volume modestly with increased salt and fluid intake without aggravating supine hypertension and to add midodrine during the waking period to reduce OH. The safest approach to volume expansion is oral salt supplementation. The best guide to adequate salt intake is the 24-hour urinary sodium. The patient has a normal plasma volume and adequate salt
intake if the 24-hour urine sodium is at or slightly exceeds 170 mequivalents per 24 hours. Patients who achieve this excretion have normal measured plasma volumes. To ensure adequate fluid intake, it is optimal to aim for a volume of 1500–2500 mL in 24 hours.

Midodrine is a directly acting α-agonist. The minimal effective dose of midodrine is 5 mg. Most patients respond best to 10 mg. The duration of action is between 2 and 4 hours, corresponding to the blood levels of midodrine and its active metabolite desglymidodrine. The onset of action is between 30 minutes and 1 hour. In some patients, the duration of action of midodrine is short, less than 4 hours. Because one of the mechanisms of hypertensive swings is severe hypotension, it is best to increase the frequency of dosing to every 3 hours during the period of maximal orthostatic stress. Patients should generally avoid midodrine after 6 PM so as not to aggravate supine nocturnal hypertension. The main limiting factor is the worsening of supine BP. The drug dose-dependently increases both supine and standing BP.

Pyridostigmine

As baroreflex activity is modest with the patient supine and increases proportional to orthostatic stress, a novel approach in treatment is to enhance ganglionic transmission (through autonomic ganglia) by acetylcholinesterase inhibition. Pyridostigmine has minimal effect on supine BP, but improves standing BP (by enhancing standing baroreflex-mediated vasoconstriction). It functions as a smart drug, improving OH without aggravating supine hypertension (Fig. 1). The preferred dose is 180 mg per day as the time span. To minimize cholinergic side effect, the drug can be started as 30 mg morning and noon and slowly increased.

Fludrocortisone

For patients who cannot take enough salt or who do not have an adequate response to midodrine, fludrocortisone, 0.1 mg once or twice daily, can be added to provide volume expansion and to sensitize vascular smooth muscle. This approach of reducing dependence on fludrocortisone and avoiding nocturnal midodrine substantially reduces supine hypertension. Uncommonly, the dose of fludrocortisone may be increased to 0.4 or 0.6 mg daily for patients with refractory OH. Because the regulatory reflexes are greatly impaired, it is necessary to overexpand the plasma volume slightly in these patients. A reasonable clue for adequate volume expansion is a weight gain of 3–5 pounds. Mild dependent edema is to be expected. The potential risks are congestive heart failure and excessive supine hypertension. Two weeks after starting treatment with fludrocortisone, patients should have their BP checked while supine and standing.

TREATMENT FOR PERIODS OF ORTHOSTATIC DECOMPENSATION

Patients who have restricted autonomic neuropathy and associated postural tachycardia have periods of orthostatic decompensation. Patients with generalized autonomic failure also have episodes of apparent decompensation when they have greater OH or less response to pressor agents. These patients need to be evaluated for a cause of decompensation. The causes include fluid deficit, hypokalemia, anemia, deconditioning related to a recent period of recumbency, and another illness (including pump [cardiac]
failure). Often, however, no cause is found. The patient appears to respond to management with volume expansion. The first approach is the “bouillon treatment.” The patient makes one of these extremely salty soups and drinks about five 8-ounce servings in half a day. An alternative is supplemental sodium chloride, 2 g three times daily, and a minimum of eight 8-ounce servings of fluids daily for 2 days. If the patient does not have improvement with this regimen or reports that fluid is not being retained, desmopressin, one puff each nostril at bedtime, is taken for 1 week. The dose of vasoconstrictor can be adjusted upward. This is when a tight-fitting body stocking (e.g., Jobst) can be beneficial. Fludrocortisone, 0.2 mg three times daily, can be taken for 1 week. The drug is traditionally considered to be slowly cumulative in its action; however, recent studies have suggested that it also has a rapid mode of action. If all these measures are unsuccessful, the treatment is isotonic saline, 1–2 L, given intravenously.

HOSPITAL MANAGEMENT OF SEVERE OH

Some patients with severe OH need acute hospital management. In addition to a search for the cause of OH and specific treatment, management is aimed at improving orthostatic tolerance to the degree that subsequent management can be continued on an outpatient basis. A regimen of treatment extending for approximately 3 days is suggested. These patients are volume-depleted, either absolutely or relatively (because of increased capacity as a result of denervation). Intravenous infusion of 1–2 L of isotonic saline is needed to expand plasma volume. Early volume expansion is critically important because hypovolemia greatly reduces the effectiveness of vasoconstrictors in increasing BP, markedly affecting the sensitivity of cardiopulmonary, but not carotid-cardiac baroreflex responses to α-agonists (48). In elderly patients, care needs to be exercised to avoid heart failure. Postural training is needed. The head of the bed is elevated 4 inches or at an angle of 10–30°. The patient spends an increasing period of time seated and standing. Treatment with fludrocortisone, 0.2 mg per day, is commenced, as is sodium chloride, 1 g three times daily, and high fluid intake. During this time, the patient is educated about dietary salt content, maintenance of postural normotension, physical countermaneuvers, management of periods of increased orthostatic stress, and supine
hypertension. Blood pressure is measured with the patient supine and standing 1 minute before and 1 hour after 10 mg of midodrine, and the supine and standing values are recorded hourly to establish the optimal dose and duration of action.

**TREATMENT OF EARLY MORNING OH**

The most common time of day that OH is worse is on awakening. In some patients, this occurs because of excessive nocturia. For many patients, the situation is improved by sleeping with the head of the bed elevated (reducing nocturia). A common routine is to drink two cups of strong coffee (250 mg caffeine), to take vasoconstrictors, and to read the newspaper before getting up.

**TREATMENT OF POSTPRANDIAL OH**

Patients often have postprandial accentuation of OH. This can occur with any type of neurogenic OH, but is particularly common with diabetic autonomic neuropathy. It often occurs on the background of gastrointestinal autonomic neuropathy, highlighting the great importance of the splanchnic-mesenteric bed in orthostatic BP control. This is a large-volume (20–30% of total blood volume) capacitance bed that, unlike other venous beds, is exquisitely baroreflex responsive. Some patients with mild postprandial OH discover that the worsening can be reduced by frequent small meals, and some find that certain foods are most troublesome and should be avoided. Some patients report that hot drinks or hot food need to be avoided. Carbohydrates are especially troublesome. Ibuprofen, 400–800 mg, or indomethacin, 25–50 mg, with the meal is well-tolerated and should be tried. The next step is the administration of a vasoconstrictor such as midodrine, 10 mg. A problem with vasoconstrictors is the aggravation of gastroparesis. Rarely, symptoms suggestive of gut ischemia may occur. If all the approaches are inadequate, the somatostatin analog octreotide can be administered with the meal. The dose is 25 µg by subcutaneous injection. The dose can be increased if necessary to 100–200 µg. This is the most efficacious agent but requires parenteral administration.

**TREATMENT OF NOCTURNAL HYPERTENSION**

Normal subjects have a diurnal variation in BP, with lower nocturnal BP. Patients with neurogenic OH have nocturnal hypertension. To minimize the problems of nocturnal hypertension, pressor medications should not be taken after 6 PM. The head of the bed should be elevated, resulting in lower intracranial BP. A nighttime snack with a glass of fluids (not coffee or tea) results in some postprandial hypotension, and can be used to increase fluid intake and decrease nocturnal hypertension. Patients who enjoy a glass of wine should drink it at this time for its vasodilator effect. Occasionally, it is not possible to control OH without marked nocturnal hypertension. For these patients, hydralazine (Apresoline), 25 mg, can be given at night. Because this drug has sodium-retaining properties, it is especially suitable. Alternatives include the angiotensin-converting enzyme inhibitor nifedipine (Procardia), 10 mg, or a nitroglycerin patch.

**ERYTHROPOIETIN**

Mild-to-moderate normocytic, normochromic anemia is not uncommon. After it has been determined that iron stores are adequate, the patient can be given erythropoietin. The anemia may be because of renal denervation, resulting in a decrease in renin. A typical
dose of erythropoietin, administered subcutaneously three times weekly, is 50 U/kg until reticulocytosis and an increase in the hematocrit occur (4,49). The duration of treatment is 3–10 weeks.

DIABETIC SUDOMOTOR DISORDERS

Sudomotor Symptoms

Sudomotor symptoms are common, but do not usually command much attention. Initially, there may be hyperhidrosis of the feet associated with coldness (I can’t keep my feet warm). This is followed by anhidrosis and vasomotor alterations, which can be variable, with venous congestion and a purple discoloration being common. Some patients will have alternating warming and cooling. Infrequently, widespread anhidrosis results in heat intolerance. In these patients, a high ambient temperature and sustained physical exertion results in overheating. In most patients, the diabetic state results in a significant impairment in exercise capacity, and heat intolerance does not develop.

Gustatory sweating commonly occurs in diabetics with cervical sympathetic denervation. The patient has excessive facial sweating in response to food, especially spicy food. The suggested mechanism is denervation of postganglionic sudomotor fibers with faulty reinnervation, although some evidence suggests a more dynamic metabolic mechanism and an association with nephropathy.

Sudomotor Failure

Sudomotor deficits are very common if quantitative approaches are used to detect autonomic sudomotor impairment. It is important to detect the severity and distribution of sudomotor deficit. The most commonly used tests to evaluate sudomotor function are as follows:

1. Quantitative Sudomotor Axon Reflex Test (QSART).
2. Thermoregulatory sweat test.
4. Skin biopsy.

QSART

QSART evaluates postganglionic sudomotor function. It probably evaluates the distal ends of the postganglionic axon (50). The test is quantitative, reproducible, and noninvasive with a coefficient of variation of 8% (51). QSWEAT is the commercial counterpart, modeled after the Mayo Clinic system.

The neural pathway consists of an axon “reflex” mediated by the postganglionic sympathetic sudomotor axon. The axon terminal is activated by acetylcholine. The impulse travels antidromically, reaches a branch-point, then orthodromically to release acetylcholine from nerve terminal. Acetylcholine traverses the neuroglandular junction and binds to M3 muscarinic receptors on eccrine sweat glands to evoke the sweat response (52). Acetylcholinesterase in subcutaneous tissue cleaves acetylcholine to acetate and choline, resulting in its inactivation and cessation of the sweat response. The test is usually done on one arm and three lead sites (37).

QSART recordings have been performed in many neuropathies including diabetic neuropathy (1). Distal sympathetic and vagal function were measured in 73 consecutive
patients with diabetic neuropathy seen at the Mayo Autonomic Reflex Laboratory. Postganglionic sympathetic failure measured proximally within the foot occurred as commonly as vagal failure (58 and 55%, respectively) and occurred much more frequently than did OH (26%). This study found that distal sympathetic sudomotor failure and vagal failure occur with equal frequency when sensitive and quantitative recording methods are used. This pattern of distal sudomotor loss is the most common pattern seen in diabetes. It is often associated with the burning feet syndrome in diabetes and idiopathic neuropathies (53). There is a progressive loss of sweating with increasing duration and severity of neuropathy. Early on, there can be an exaggerated forearm (proximal) volume response (54).

QSART sweating is cholinergic. Of interest is that, during development sweating is under adrenergic control, with an adrenergic to cholinergic switch occurring, so that, in postnatal humans only 20% of sweating is under adrenergic control. There is some evidence that in neuropathic pain states, there may be a reversion back to predominantly adrenergic sweating (55). Whether that occurs in diabetic distal small fiber neuropathy is not known.

Thermoregulatory Sweat Test

The thermoregulatory sweat test (TST) is a sensitive qualitative test of sudomotor function that provides important information on the pattern and distribution of sweat loss. The presence of sweating causes a change in the indicator from brown to a violet color. The subject is heated in a sweat cabinet (10,28). The value of the test can be enhanced and rendered semiquantitative by measuring the percent of anterior body surface anhidrosis (56). Certain sweat patterns are recognizable in human diabetic neuropathy (28). Of 51 patients suspected of having neuropathy on the basis of a clinical examination, 48 (94%) had unequivocal abnormalities on the TST. Pathological loss of sweating occurred distally in 65%, segmentally in 25%, and only in isolated dermatomes in 25%; 78% of patients had a combination of two or more patterns. Global anhidrosis was noted in eight patients (16%), all of whom had profound autonomic neuropathy, and in the entire group, the percentage of body surface anhidrosis correlated with the degree of clinical dysautonomia (rank correlation coefficient = 0.77; p < 0.01). Major advantages of the method are its simplicity, sensitivity, the ability to recognize patterns of anhidrosis, including mixed patterns, and its semiquantitative nature. The disadvantages are its inability to distinguish between postganglionic, preganglionic, and central lesions, the discomfort, the qualitative nature of the information obtained, and the staining of clothing.

SSR

Skin potential recordings can be used to detect sympathetic sudomotor deficit in the peripheral neuropathies and central autonomic disorders (57,58). The recording electrodes are commonly electrode pairs 1 cm in diameter applied to the dorsal and ventral surfaces of the foot, the hand, or thigh. The stimulus might be an inspiratory gasp, a cough, a loud noise, or an electric shock. The sources of the skin potential are the sweat gland and the epidermis (59). A reasonable interpretation of studies in mammals, including humans, is that a component of the skin potential (early fast changes) is related to sweating, but that the later changes are because of skin potential changes. The latter can
occur in patients who have congenital absence of sweat glands (60–63). The major advantage of the method is its simplicity so that it can be used in any electromyography (EMG) lab. The disadvantages are its enormous variability and the tendency of the responses to habituate, although claims for low coefficient of variation have appeared, and attempts have been made to reduce variability by using magnetic stimulation (64). The responses vary with the recording system, composition of the electrolyte paste, stimulus frequency, age, temperature, stress, status of central structures, and the effects of hormones and drugs (65). Following peripheral nerve section, skin potentials are no longer obtainable in the affected dermatome on direct and reflex stimulations. There was usually associated hypothermia and anhidrosis. Following sympathectomy, skin potentials are also lost, but only temporarily, returning in 4–6 months (66).

Skin potential recordings to detect sympathetic sudomotor deficit in the peripheral neuropathies and central autonomic deficits have been popularized (58). There is general agreement that a loss of SSR is abnormal. There is some controversy concerning whether a reduction of skin potential and a change in latency are reliable abnormalities (67). There is some evidence that unmyelinated fibers conduct without slowing or not at all (68). The test has been reported to correlate well with QSART (69), but in our experience is often present when QSART is clearly impaired. Potentials are reported to become reduced with aging (70).

SSR has been utilized in the evaluation of the peripheral neuropathies, especially diabetic neuropathy (71,72). The SSR deficit in amplitude and volume is reported to worsen with increasing duration of diabetes and correlates with sweatspot values (64) and clinical neuropathy (73). Both amplitude reduction and latency prolongation were seen and abnormalities may precede clinical neuropathy (73). In patients with well-established neuropathy, SSR in the foot is abnormal or absent in the majority of patients (72,74). For instance, in a study of 72 patients with diabetes with electrophysiologically confirmed sensorimotor peripheral neuropathy, SSR was absent in 83%. Statistically significant correlation was found between the Valsalva test abnormality, the degree of peripheral neuropathy, and the SSR (74). Its sensitivity and specificity to detect early abnormalities or improvement in clinical trials have not been established.

**GUSTATORY SWEATING**

Gustatory sweating was first linked to diabetes mellitus by Watkins (75), and is now known to occur quite commonly in patients with either diabetic nephropathy or neuropathy (76). The syndrome consists of localized hyperhidrosis of the face during meals. The mechanism of gustatory sweating is not proven, but is considered to be because of sympathetic postganglionic denervation followed by aberrant reinnervation by parasympathetic fibers. It is suggested that sympathetic cholinergic fibers to eccrine sweat gland are lesioned. These denervated sweat glands are thought to become reinnervated by misdirected cholinergic parasympathetic fibers. Evidence cited usually emanate from surgical lesions (77). In diabetic autonomic neuropathy, the sympathetic denervation that occurs in sweat glands might be compensated by reinnervation of aberrant parasympathetic fibers stemming from the minor petrous nerve, and normally innervating the parotid gland through the auriculotemporal and facial nerve, after being relayed in the otic ganglion (78). Thus, sweating occurs in the reinnervated area when salivation is induced on cholinergic stimulation (food ingestion).
The symptom can be troublesome and embarrassing. Occasionally it affects food intake to the degree that it could make glycemic control difficult. As sweating is controlled by sympathetic cholinergic pathways, treatment has traditionally involved oral anticholinergic drugs, but the acceptability of these to patients is low because of systemic side effects. Topical antimuscarinic agents, such as glycopyrrolate, have been demonstrated to be effective in controlling gustatory sweating caused by parotid surgery and in diabetic gustatory sweating (79,80). Gustatory sweating and flushing within and surrounding the cutaneous distribution of the auriculotemporal nerve (Frey’s syndrome), can develop after surgery or trauma to parotid gland. Surgery as resection of the glossopharyngeal nerve (which supplies the otic ganglion and hence the auriculotemporal and buccal nerves with parasympathetic fibers) abolishes the syndrome (81,82). A better approach is the injection of botulinum toxin into the symptomatic skin to treat pathological gustatory sweating (83,84). This obviously is a major advance in treatment because it is far simpler and less invasive than sectioning parasympathetic nerves intracranially (85). Botulinum toxin enters cholinergic neuron terminals and prevents the exocytotic release of acetylcholine. As parasympathetic secretomotor fibers use acetylcholine as a neurotransmitter, and sweat glands have cholinergic muscarinic receptors, botulinum toxin abolishes the cholinergic activation of sympathetically-denervated sweat glands during salivation.

**PATTERNS OF ANHIDROSIS IN DIABETIC NEUROPATHY**

There are a number of patterns of anhidrosis in diabetic neuropathy. A full appreciation of these patterns requires the administration of the thermoregulatory sweat test, a method that is not under widespread clinical use. Several well characterized patterns are described.

**Distal Small Fiber Neuropathy**

Perhaps, the most common pattern of anhidrosis is distal anhidrosis. The “burning feet” syndrome is perhaps the most common presentation of diabetic neuropathy. These patients have distal involvement with burning, prickling, and some stabbing discomfort with variable allodynia, and most have normal motor function. There is a subset of patients with completely normal motor function, intact tendon reflexes, and nerve conduction studies that are normal or near-normal. For this pattern of neuropathy, the underlying neuropathy has been assumed to be a length-dependent distal small fiber neuropathy demonstrable on skin biopsy (86). Autonomic fibers are presumed to be involved as well because these patients will usually have vasomotor symptoms, manifest as excessive coldness, discoloration, or sometimes erythromelalgia (53,87). Hyper- and hypohidrosis can also be a feature. When sudomotor testing is used, approximately 80% of patients have abnormal QSART responses (53,88). There is good agreement between loss of intraepidermal fibers (somatic C fiber involvement) and QSART loss (autonomic C fiber involvement) (89).

**Multifocal Sweating Loss**

A common and characteristic pattern of anhidrosis in diabetic neuropathy is that of multifocal regions of sweat loss (10,28), which differs in distribution to other neuropathies (10). These patients have anhidrosis that affects parts of the body in the distribution of specific nerve trunks, plexus, or regions in the distribution of autonomic
ganglia. The value of this test is that this pattern of loss reduces the number of likely causes. Apart from diabetes, this pattern is seen with autoimmune autonomic neuropathy and angiopathic neuropathy (although regional anhidrosis is usually not seen in this group of neuropathies).

**Generalized Anhidrosis**

An unusual pattern of anhidrosis is that of generalized anhidrosis, where there is total or subtotal anhidrosis (>70%). This pattern is seen in diabetic neuropathy, autoimmune autonomic neuropathy, chronic idiopathic anhidrosis, pure autonomic failure, and multiple system atrophy. In diabetes, percent anhidrosis provides one index of autonomic failure.

**REFERENCES**


