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Update on Management of Neurogenic Orthostatic Hypotension

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Abstract

Orthostatic hypotension (OH) is common in the elderly and in disorders like diabetes and Parkinson's disease. It is important to grade its severity and its impact on the person's quality of life. It is also possible to quantitate the severity of OH. Symptoms of OH vary with orthostatic stress, and it is important to recognize subtle symptoms such as tiredness and cognitive impairment. Standard drug treatment is efficacious in improving OH and its symptoms but will worsen supine hypertension. Pyridostigmine will modestly but significantly improve OH without worsening supine hypertension. Since orthostatic stress varies from moment to moment and drug treatment is suboptimal, it is necessary to combine drug treatment of OH with non-pharmacological approaches, such as compression of venous capacitance bed, use of physical counter-maneuvers, and intermittent water bolus treatment.

Search Strategy: The manuscript is based on a focused review. To achieve this, references for this review were identified by searches of PubMed between 1995 and January 2008 using the search term “orthostatic hypotension”. Articles were also identified through searches of the authors own files. Only papers published in English were selected. The final reference list was generated on the basis of originality and relevance to the topic covered in this review, with a particular focus on data supported by clinical trials.

Introduction

Orthostatic hypotension (OH) is a common problem among the elderly and occurs in patients with many disorders that increase with age, such as Parkinson's disease and diabetes. This update will focus on the three areas. We address recent advances in pharmacologic management of OH, with emphasis on drugs with clinical trial proof of effectiveness. OH varies with varying orthostatic stress, so that it is necessary to couple pharmacologic with non-pharmacologic methods to improve orthostatic BP. Finally, we shift the focus to patient oriented management of OH. The review process is a focused selective review.

A Consensus definition of OH is a reduction of systolic blood pressure (SBP) of at least 20 mm Hg or diastolic blood pressure (DBP) of at least 10 mm Hg within 3 minutes of standing up.[1] The use of a tilt table in the head-up position, at an angle of at least 60 degrees, was accepted as an alternative. OH may be symptomatic or asymptomatic. If the patient has symptoms suggestive of, but does not have documented OH, repeated measurements of BP should be performed. The values chosen are reasonable screening values but are associated with a 5% false positive. A value of 30 mm Hg fall in systolic blood pressure would reduce the frequency of false positives to 1%.[2]

With therapeutic advances, it is important to have a more quantitative approach to grade and quantify orthostatic intolerance. It is possible to generate a formal grading scale (Table 1)[3] based on the frequency and severity of symptoms, standing time before onset of symptoms, influence on activities of daily living, and BP. The patient with grade I OH may not need medications, whereas those with grades III or IV will need aggressive therapy. For monitoring the course and severity of OH or response to therapy, it is helpful to grade these individual components numerically using a self-report orthostatic grading score (Table 2).[4] This scoring scheme was derived from the autonomic symptom profile[5,6] and correlates well with severity

and distribution of autonomic failure. This validated instrument scores symptoms of orthostatic intolerance based on frequency, severity, response to orthostatic stressors, interference with activities of daily living, and subject's standing time.[4] This instrument generates a score from 0 (no symptoms) to 20 (maximal symptoms/dysfunction) (Table 2). This scale provides a practical tool to monitor the status of OH and response to therapy. While these scales are clearly optional, it is important to document the severity of symptoms, their relationship to orthostatic stressors, influence of OH on activities of daily living and the patient's standing time.

The prevalence of OH is high and related to aging. Most estimates of OH in the aged are between 5-30% and the differences in estimates vary, depending in part on the definition of OH, the segment of the population (age range; institutions), the composition of the population (healthy population versus select groups), role of medications, and level of orthostatic stress. Cross-sectional prevalence of OH in unselected elders aged 65 years or older has generally been reported to be between 5 - 30%.[7-10] The “prevalence” of OH is even higher in autonomic disorders such as Parkinson's disease, multiple system atrophy, and the autonomic neuropathies.[11-15]

Clinical Manifestations

OH is relatively common but usually asymptomatic. In fact, most patients with “asymptomatic OH” will have symptoms, albeit subtle, under conditions of increased orthostatic stress, such as postprandial state, raised ambient temperature, or following exertion. Lightheadedness is common, as expected. However, difficulty in concentrating and thinking is present in about half the patients.[16] In patients over the age of 70 years, this may be the most common symptom, and while subtle, seriously impairs quality of life. Symptoms of palpitations, tremulousness, anxiety, and nausea are symptoms of autonomic hyperactivity, and occur in patients who have only partial autonomic failure, typically seen in the autonomic neuropathies and in younger patients.[16]

Symptoms are typically worse in the early AM, after meals, with a rise in core temperature, prolonged standing, and with activity. The early AM severity of OH relates to the nocturnal diuresis that many of these patients have.[17] Postprandial worsening is very common, occurring within 30 minutes and lasting about an hour. Paradoxically, postprandial worsening of OH may disappear in very advanced autonomic failure, when the splanchnic-mesenteric bed is no longer able to vasodilate postprandially.[18] Patients will commonly recognize that they have more orthostatic symptoms following a hot bath, hot tub, or on a hot day. Indeed any stress that results in vasodilatation of skin vessels will worsen symptoms. Patients who get up in the middle of the night out of a warm bed are vasodilated and have worse OH. Similarly, symptoms may be worse after ingestion of alcohol, because of vasodilatation. With physical activity, sufficient to cause muscle vasodilatation, OH is also worse. These symptoms are due to cerebral hypoperfusion. When OH is severe and sustained, syncope will occur. Syncope after diagnosis tends to be less common, as patients learn to recognize the symptoms of OH and take corrective steps.

Pathophysiology and Pathogenesis

The maintenance of postural normotension without an excessive heart rate increment depends on an adequate blood volume, and the integration of many reflex and humoral systems and several key vascular beds, including the striated muscle, splanchnic-mesenteric, and cerebrovascular beds.

An adequate **blood volume** is essential. Hypovolemia will regularly cause OH, even if vascular reflexes are intact. Hypovolemia can also be relative. Denervation decreases vascular tone and increases vascular capacity. The patient with adrenergic failure will be relatively hypovolemic,

although their plasma volume is normal. These patients can improve orthostatic intolerance if their plasma volume is expanded, hence the importance of volume expansion in the treatment of OH. Reduced red cell mass, or the normocytic, normochromic anemia of chronic autonomic failure, will also aggravate OH. Correcting anemia with erythropoietin will improve orthostatic intolerance.[19,20]

Two sets of **baroreflexes**, the arterial (or high-pressure) and venous (or low-pressure) baroreflexes, are mainly responsible for the reflex control of blood pressure and the circulation. When systemic pulse pressure or mean arterial pressure falls, baroreceptors are unloaded in the carotid sinus and aortic arch.[21] These are arterial baroreceptors. Afferent traffic from the carotid sinus travel via the glossopharyngeal and that from the carotid arch via the vagus nerves to synapse in the nucleus of tractus solitarius. From this structure, cardiovagal fibers travel via polysynaptic fibers to the nucleus ambiguus and dorsal motor nucleus of vagus and thence as the vagus nerve to the sinoatrial node. Sympathetic function is regulated via the rostroventrolateral nucleus of medulla to the intermediolateral column of the thoracic cord to provide sympathetic innervation to the heart and periphery (arterioles and venules).[22] In addition to arterial baroreceptors, there are also low pressure baroreceptors. The effective stimulus is a reduction in central venous pressure; i.e., responsive to changes in volume. Cardiopulmonary receptors in the heart and lungs send mainly nonmyelinated vagal afferents to the nucleus of tractus solitarius. The central pathways and efferents are the same as for arterial baroreceptors. Baroreflex failure, especially if sympathetic efferents are affected, will often results in the triad of OH, supine hypertension, and a loss of diurnal variation in BP. As a result, nocturnal BP is higher than daytime BP.

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 to 30% of total blood volume.[23] Unlike muscle veins, the 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 α-adrenergic receptor mediated.[24] The nerve supply to the mesenteric bed is largely from the greater splanchnic nerve with its cell body in the intermediolateral column (mainly T4 to T9) and synapses at the celiac ganglion, from whence postganglionic adrenergic fibers go on to supply effector cells. There is much clinical and research evidence to support the importance of the splanchnic outflow in the maintenance of postural normotension in man. OH occurs regularly when bilateral splanchnic neurectomy is performed, whereas neither bilateral lumbar sympathectomy nor cardiac denervation alone will cause postural hypotension.[25,26] In patients with complete spinal cord lesions, postural hypotension becomes most pronounced when the splanchnic outflow is affected (above T6). Abnormalities in the splanchnic autonomic outflow have been found in human diabetic neuropathy;[27] there is both demyelination and loss of axons, indicating that preganglionic fibers can be affected.[27]

Cerebral vasoregulation is important in ensuring adequate and stable flow to the brain in spite of changing systemic blood pressure. The maintenance of constant blood flow in spite of variations in blood pressure is termed **autoregulation.**[28] Within a mean blood pressure (MBP) range of approximately 50 - 150 mm Hg MBP, a change in blood pressure results in an insignificant change in cerebral perfusion. Previous studies[29-31] in patients with OH have demonstrated an expansion of the autoregulated range at both the upper and lower limits, so that cerebral perfusion remained relatively constant with the patient in the supine position (when supine hypertension might be present) and in response to standing (when OH occurs).

Management

There are 4 interrelated goals in the treatment of OH. The first is to improve orthostatic BP without excessive supine hypertension. The second is to improve standing time. The third is to relieve orthostatic symptoms. The fourth goal, related to goal 2 is to improve the patient's ability to perform orthostatic activities of daily living.

It is always possible to relieve symptoms of OH, but it is much more difficult to do so without inducing unacceptable supine hypertension, since patients with generalized autonomic failure have impairment of baroreflexes, with the loss of postural regulation of BP as a regular component of such failure. A reasonable practical goal is a regimen that relieves symptoms most of the day with a supine BP that does not usually exceed 180/110. Patients with neurogenic OH with have greater fluctuations than normal (loss of baroreflexes or “buffer nerves”) and will often have supine hypertension. The value we cite is acceptable, since patients are taught to avoid lying flat. With greater reliance on pyridostigmine, it has become considerably easier to attain satisfactory BP control. Recent advances have improved our ability to improve OH without aggravating supine hypertension.

Patients with asymptomatic OH do not require treatment. However, that statement needs to be qualified by the observation that most patients with OH will have symptoms at some time. The orthostatic stresses may be time of day (early AM), a meal, a rise in core temperature, physical activity, or reduced salt or fluid intake. Older patients may become symptomatic after a period of bed rest or after starting certain medications. Common culprits are diuretics, α-antagonists for prostatism, antihypertensive drugs, and calcium channel entry blocking drugs. Insulin, levodopa, or tricyclic antidepressants can also cause vasodilatation and OH in predisposed subjects.

Non-pharmacologic Management

Pharmacologic management alone is never adequate since orthostatic stress varies with circumstances; including time of day, meals, ambient temperature; and orthostatic stress. Patient education is critically important. The patient should understand in simple terms the maintenance of postural normotension and its practical implications (importance of blood volume; venous pooling and muscle contraction; postural training). They need to understand the orthostatic stressors and their mechanisms.

All patients with neurogenic OH require the standard treatment of OH, aimed at expanding blood volume. Generous fluid intake is critically important, and often neglected in the elderly. They need 5-8 eight-ounce glasses of fluid per day. Salt supplementation is essential. Most patients will manage with added salt with their meals. The occasional patient will prefer to use salt tables (available as 0.5 and 1G tablets). It is important to recognize that the vasoconstrictors are ineffective when plasma volume is significantly reduced. Many patients who have inadequate control of OH have an inadequate salt intake. This can be verified by checking the 24-hour urinary sodium. Patients who have a value below 170 mmol/24 hours can be treated with supplemental sodium 1-2G t.i.d. and their weight, symptoms, and urinary sodium checked one or two weeks later.[32]

The head of the entire bed is elevated 4 inches for two reasons. It seems to reduce nocturia. It also reduces the effects of supine hypertension. During the day, it is important to maintain adequate orthostatic stress. Patients with OH who are tilted up repeatedly develop gradual attenuation of OH. It has been suggested that standing results in extravasation of plasma around veins providing a vascular cuff, increasing venomotor tone.

In some subjects, the use of a tightly fitting body stocking results in amelioration of OH and associated symptoms. These have to be well fitted and put on prior to arising. The stockings work by reducing the venous capacitance bed. Disadvantages are the cumbersome application and discomfort in hot weather. A measured Jobst stocking is especially useful. Patients generally, however, prefer a combination of an abdominal binder and leg stockings. An abdominal binder provides two-thirds of the benefits of a full Jobst and is better tolerated by patients.[33]

Water bolus treatment is a useful orthostatic aid. The subject drinks in rapid succession two 8 ounce glasses of water. This results in a rise of standing systolic BP of >20 mm Hg for about 2 hours.[34,35] The mechanism of action is that of sympathetic adrenergic activation. There is an increase in plasma norepinephrine and the action can be abolished with trimetaphan.[35]

Physical countermaneuvers are very helpful in prolonging the duration that the patient can be upright. These include maneuvers such as toe-raise, leg-crossing, thigh contraction, and bending at the waist (Figure 1).[36,37] These maneuvers reduce venous capacity and increase total peripheral resistance. [36,37] There is a training biofeedback effect so that the patient can improve the pressor effect by practicing the maneuver with continuous recording of BP. [36,37]

Pharmacologic Management

Drug treatment is an important part of overall therapeutic regimen, and if well used, will greatly enhance BP control.[38] Midodrine is the only drug that is FDA approved to treat OH. The other drugs are used off-label.

Midodrine

This is the only drug that has been demonstrated, in a double-blind, placebo-controlled study, to improve orthostatic hypotension and improve orthostatic symptoms.[39] It is a directly-acting α_1-agonist. The minimum effective dose of midodrine is 5 mg. Most patients respond best to 10 mg. The duration of action is between 2 - 4 hours, corresponding to the blood levels of the prodrug, midodrine and its active metabolite, desglymidodrine, respectively.[39] The onset of action is between 0.5 - 1 hour. Some patients have a short duration of action of midodrine, lasting less than 4 hours. Since one of the mechanisms of hypertensive swings is severe hypotension, these patient do best with increasing the frequency of dosing (to every 3 hours) during the period of maximal orthostatic stress. The main side-effects are supine hypertension, paresthesias including troublesome scalp-tingling, and goose-bumps. In a subsequent double-blind study, we demonstrated that the drug will dose-dependently improve orthostatic BP.[40] Unfortunately, we also demonstrated that the drug has an even greater effect on supine BP. This is a significant limitation, since baroreflex failure is consistently associated with supine hypertension. Guidelines for the administration of midodrine have become relatively standard. Patients are advised to take the drug prior to getting out of bed, before lunch, and mid afternoon. They are advised to generally avoid the drug after 6 pm, to avoid nocturnal supine hypertension. They are also advised to omit a dose if supine or sitting BP ≥180/110.

Pyridostigmine

To address the issue of improving OH while simultaneously minimizing supine hypertension, we sought a “smart drug” approach. Baroreflex unloading occurs mainly with standing and is minimal with the patient supine. Autonomic ganglionic neurotransmission is cholinergic, and acetylcholine is rapidly hydrolysed by acetylcholinesterase. We argued that since pyridostigmine, a cholinesterase inhibitor, exerts its action (of improving ganglionic transmission) primarily when the patient is standing, this drug should increase ganglionic traffic proportional to the magnitude of orthostatic stress. Hence, it should increase orthostatic

BP without worsening supine BP. We tested this hypothesis in an open study, and demonstrated, in 15 patients with neurogenic OH, that 60 mg pyridostigmine will improve OH, total peripheral resistance and orthostatic symptoms, without aggravating supine hypertension.[41] We followed this study with an inpatient, double-blind randomized, 4-way cross-over study of pyridostigmine in the treatment of 58 patients with neurogenic OH.[42] The primary endpoint, based on the open study, was improvement in standing DBP. Pyridostigmine alone or combined with 5 mg midodrine significantly improved the primary endpoint of standing diastolic BP without aggravating supine BP (Figure 1). The drug improved orthostatic symptoms proportional to the improvement in standing BP (Figure 2).

What is the role of pyridostigmine in the management of OH? The main limitation of the drug is its modest pressor effect (Figure 1). For patients with mild OH, pyridostigmine alone is adequate. The drug is started at 30 mg b.i.d. or t.i.d. and the dose gradually increased to 60 mg t.i.d. Its effectiveness can be enhanced, without causing supine hypertension, by combining each t.i.d. dose of pyridostigmine with midodrine 5 mg.[42] When full doses have been attained, some patients prefer the use of the timespan (Mestinon timespan 180 mg) taken once daily. The main side-effects of pyridostigmine are cholinergic (abdominal colic, loose motions).

Other Drugs

L-threo-3,4-dihydroxyphenlyserine (L-DOPS; also known as Droxidopa) is a drug under study for the treatment of neurogenic OH. The drug has been reported to improve OH.[43-45] There is considerable interest in whether the drug improves OH with less supine hypertension than standard pressor drugs such as midodrine. Key to this discussion is the site of action of the drug. If its primary role is to replete the postganglionic adrenergic axon, its release of norepinephrine should be proportional to ganglionic traffic and should result in less supine hypertension. It appears to improve OH even where there is a severe loss of postganglionic fibers (as in pure autonomic failure) and an extraneural source has been suggested.[43] Clinical pharmokinetic studies suggest that it has both an extraneuronal and neuronal mode of action.[46] It appears to variably also increase supine BP. In a small double-blind placebo-controlled study of 10 patients with OH, the drug increased both supine and standing BP and norepinephrine.[44] It sometimes is effective when other drugs have failed.[47] It is currently not an approved drug for the treatment of neurogenic OH. The drug is dramatically effective in the treatment of OH due to dopamine-β-hydroxylase deficiency.

Fludrocortisone expands plasma volume and increases α-adrenoreceptor sensitivity.[48,49] The drug is usually used at a dose of 0.1 to 0.2 mg/day but occasionally at higher doses of 0.4-0.6 mg/day. Especially at higher doses supine hypertension and hypokalemia are very common.[48,50] A pressor effect has been described for a number of drugs including yohimbine, indomethacin, somatostatin and dihydroergotamine but at this time their value is controversial.[51]

Management of Supine Hypertension

The best approach to management of supine hypertension is prevention. Midodrine and other pressor drugs should not be taken after 6PM. Patient sleep with the head of the bed elevated. Taking a mild vasodilator such as a glass of wine may be sufficient to reduce supine BP. If supine BP ≥180/110, then it can be gently reduced using transdermal nitroglycerine at a dose that should be individualized. A dose of 0.025 to 0.1 mg/h has been reported to reduce BP by 36±7 mm Hg.[52]

Synthesis and Conclusions

The management of neurogenic OH can be synthesized as follows. The presence of OH, its manifestations, influence on activities of daily living and relationship to orthostatic stresses should be determined. All patients need need volume expansion with increased fluids and salt intake, supplemented in some cases with low dose fludrocortisones. The patient receives education on management of OH, need to sleep with the head of the entire bed elevated, the use of physical countermaneuvers, compression garments and the judicious use of water bolus. If medication is needed the combination of pyridostigmine and midodrine can be titrated. A major responsibility of management shifts to the patient. To optimize the role of the physician, it is helpful to have the patient provide a set of recordings taken over a couple of days of BP sitting and standing up on awakening, before lunch, 1 hour after lunch, and before retiring. If the patient has an automated BP unit, they stand for 1 minute and then activate the recording.

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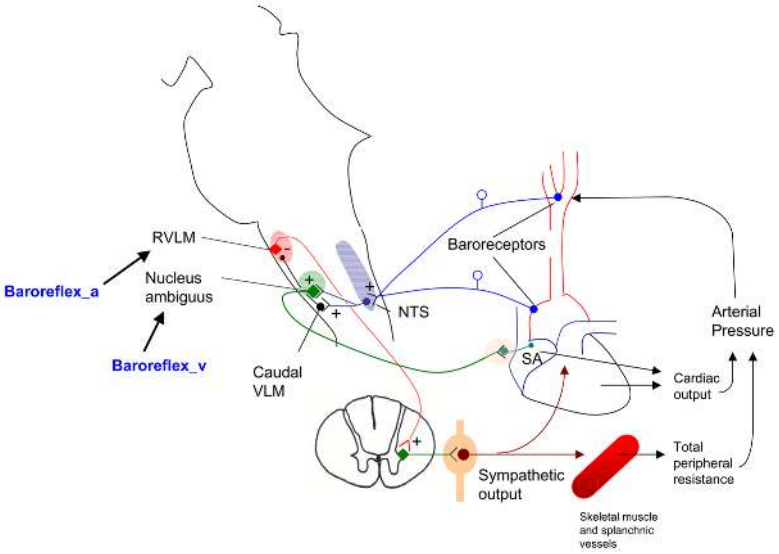

Figure 1.

Baroreceptor afferents synapse at nucleus of tractus solitarius. From this nucleus vagal baroreflex (baroreflex_v) and adrenergic baroreflex (baroreflex_a) loops diverge. Baroreflex_v pathways synapse at nucleus of tractus solitarius and send efferents to sinoatrial node (SA). Baroreflex_a is mediated by connections to rostroventrolateral nucleus of medulla (RVLM) with preceding connection at caudal VLM. Sympathetic efferents from RVLM travel to intermediolateral column and thence synapse at autonomic ganglia then innervate the heart and arterioles and venules.

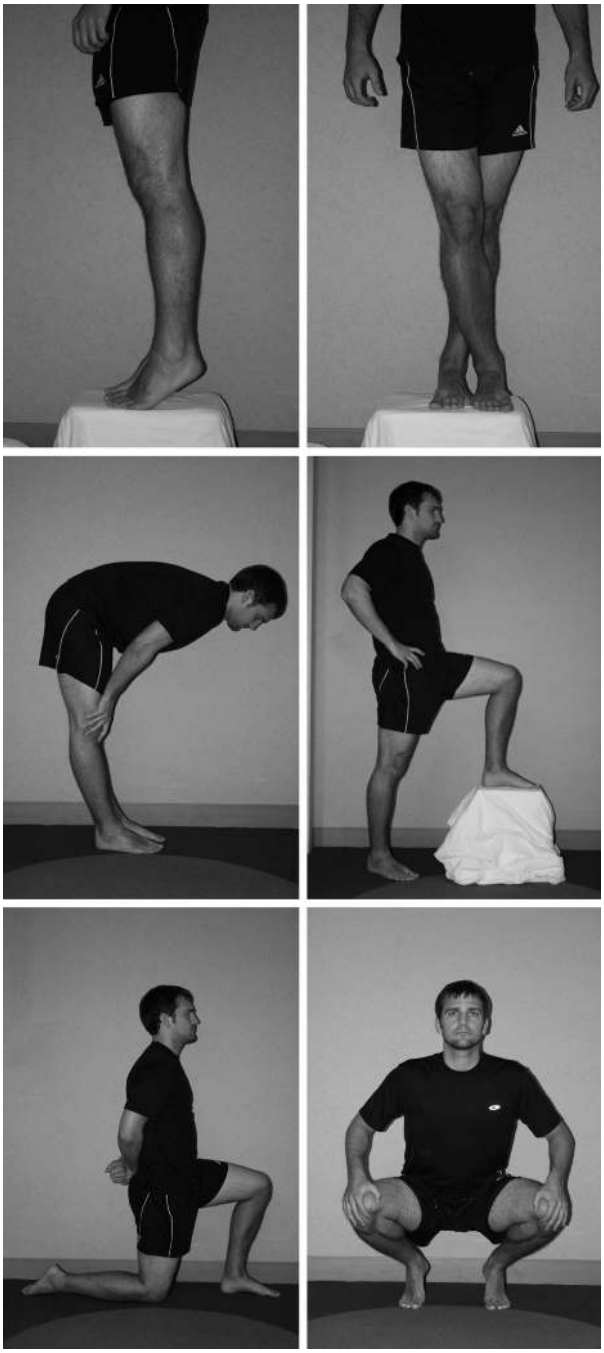

Figure 2.
Examples of some physical countermaneuvers that can raise orthostatic BP. a. Toe-raise; b. Leg-cross; c. forward lean; d. step up; e. genuflection-contraction; f. squat

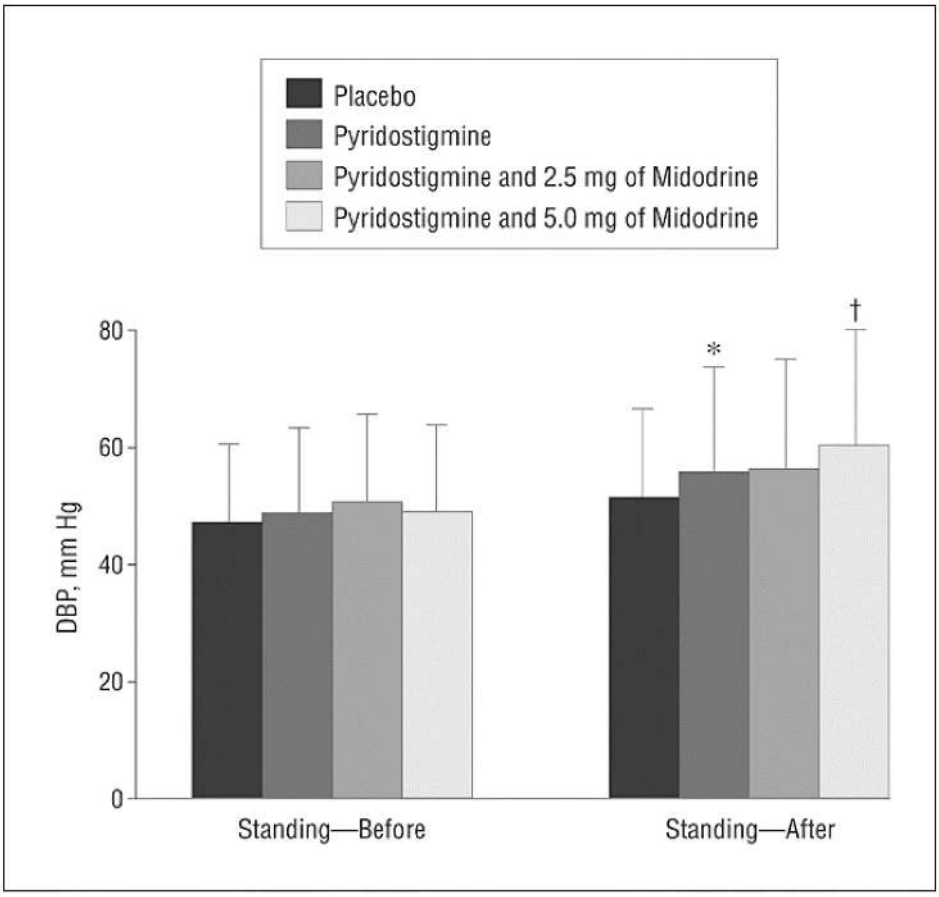

Figure 3.
Diastolic blood pressure (DBP) before and after administration of study drug. Each group (placebo, pyridostigmine bromide, pyridostigmine and 2.5 mg of midodrine hydrochloride, pyridostigmine and 5.0 mg of midodrine hydrochloride) averaged for the supine position and standing position. Asterisk indicates *P*_.05; dagger, *P*_.01. Error bars represent mean±SD. (From Singer W, Sandroni P, Opfer-Gehrking TL, Suarez GA, Klein CM, Hines S, O'Brien PC, Slezak J, Low PA. Pyridostigmine treatment trial in neurogenic orthostatic hypotension. Arch Neurol 63:513-518, 2006. Reproduced with permission.)

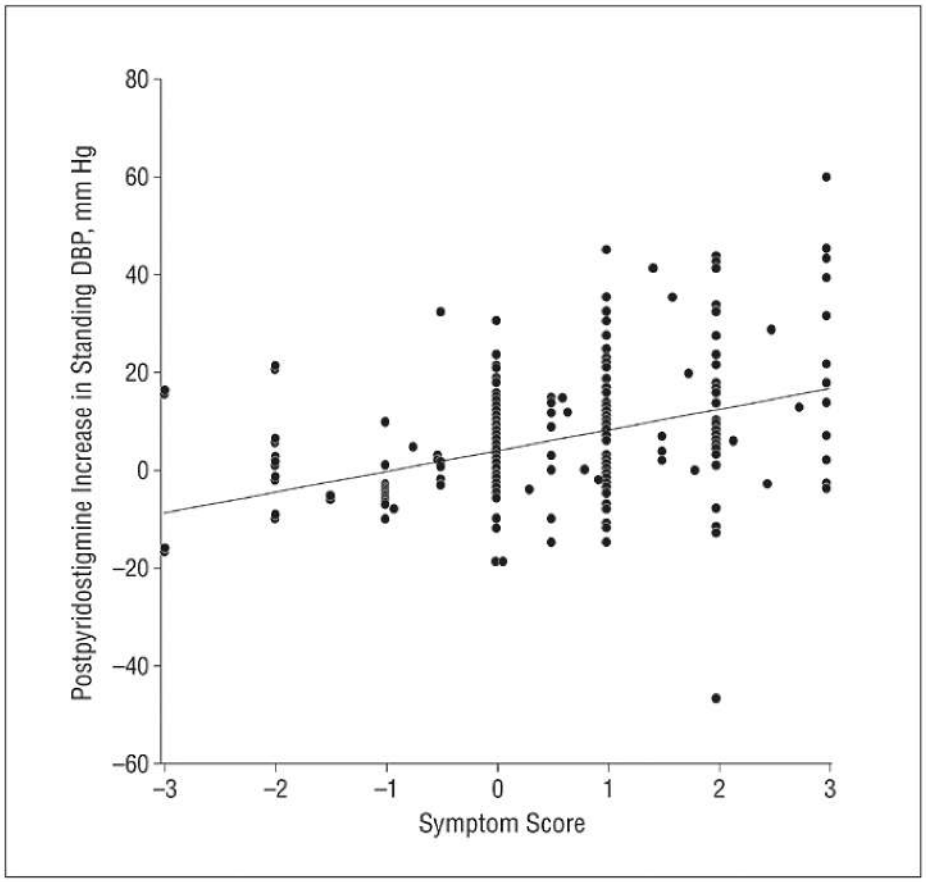

Figure 4.

Regression of change in diastolic blood pressure (DBP) with symptom score. The regression equation is as follows: symptom score=0.524_0.0272_DBP increase (*R*=0.34). Pyridostigmine was administered as pyridostigmine bromide. (From Singer W, Sandroni P, Opfer-Gehrking TL, Suarez GA, Klein CM, Hines S, O'Brien PC, Slezak J, Low PA. Pyridostigmine treatment trial in neurogenic orthostatic hypotension. Arch Neurol 63:513-518, 2006. Reproduced with permission.)

Table 1

Symptom grade of orthostatic intolerance

Grade I	
1	Orthostatic symptoms are infrequent, inconstant, or only under conditions of increased orthostatic stress
2	Standing time typically ≥15 minutes
3	Unrestricted activities of daily living
4	Blood pressure indices may or may not be abnormal
Grade II	
1	Orthostatic symptoms are frequent, developing at least once a week. Orthostatic symptoms commonly develop with orthostatic stress
2	Standing time ≥5 minutes on most occasions.
3	Some limitation in activities of daily living.
4	Some change in cardiovascular indices. These might be OH, reduction in pulse pressure ≥50%, excessive oscillations in BP.
Grade III	
1	Orthostatic symptoms develop on most occasions, and are regularly unmasked by orthostatic stressors.
2	Standing time ≥1 minute on most occasions.
3	Marked limitation in activities of daily living.
4	Orthostatic hypotension is present on ≥50% of the time, recorded on different days.
Grade IV	
1	Orthostatic symptoms consistently present.
2	Standing time <1 minute on most occasions.
3	Patient is seriously incapacitated, being bed- or wheel-chair bound because of orthostatic intolerance. Syncope/presyncope is common if the patient attempts to stand.
4	Orthostatic hypotension is consistently present.

Table 2

Orthostatic Symptom Score. The patient is instructed to select appropriate answer.

1	**Frequency of Orthostatic Symptoms**
	0 I *never or rarely* experience orthostatic symptoms when I stand up.
	1 I *sometimes* experience orthostatic symptoms when I stand up.
	2 I *often* experience orthostatic symptoms when I stand up.
	3 I *usually* experience orthostatic symptoms when I stand up.
	4 I *always* experience orthostatic symptoms when I stand up.
2	**Severity of Orthostatic Symptoms**
	0 I *do not* experience orthostatic symptoms when I stand up.
	1 I experience *mild* orthostatic symptoms when I stand up.
	2 I experience *moderate* orthostatic symptoms when I stand up and *sometimes* have to sit back down for relief.
	3 I experience *severe* orthostatic symptoms when I stand up and *frequently* have to sit back down for relief.
	4 I 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 I *never or rarely* experience orthostatic symptoms under any circumstances.
	1 I *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 I *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 I *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 I *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.