Orthostatic hypertension: when pressor reflexes overcompensate

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SUMMARY

Orthostatic hypertension—a rise in blood pressure upon assuming upright posture—is an underappreciated and understudied clinical phenomenon. There is currently no widely agreed-upon definition of clinical orthostatic hypertension, the current definitions being operational within the context of particular studies. The underlying pathophysiology is thought to involve activation of the sympathetic nervous system, but the actual etiology is poorly understood. Orthostatic hypertension is observed in association with a variety of other clinical conditions, including essential hypertension, dysautonomias, and type 2 diabetes mellitus. Orthostatic hypertension has been associated with increased occurrence of silent cerebrovascular ischemia and possibly with neuropathy in type 2 diabetes. So, appreciation of the true incidence of orthostatic hypertension, elucidation of the underlying pathophysiology, and an understanding of potentially effective treatment approaches and their associated risks and benefits might all have major clinical significance. Orthostatic hypertension is an aspect of hypertension that is in need of further focused investigation.

KEYWORDS autonomic, baroreflex, dipper, hypertension, orthostatic

REVIEW CRITERIA

A PubMed search using the term "orthostatic hypertension" was the main source of material for this Review. Additional searches were also performed for papers cited in the articles identified via the initial PubMed search.

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INTRODUCTION

It has long been recognized that minor minute-to-minute fluctuations in blood pressure occur in healthy individuals, and that many factors influence these fluctuations. Perhaps the easiest to observe is the influence of posture. Assumption of upright posture from a recumbent position results in a small but measurable decrease in systolic blood pressure (SBP) due primarily to a redistribution of blood volume into the lower abdomen, buttocks and legs under the influence of gravity. In most people, this decrease in blood pressure is very slight and evanescent, as a whole host of response mechanisms are immediately engaged to maintain blood pressure. Chief among these responses is the baroreflex constellation,[1] in which stretch receptors in the carotid artery in the neck, and major vessels and structures in the thorax, quickly sense decreases in arterial pressure and central thoracic volume and trigger a coordinated increase in activity of the sympathetic nervous system, decrease in activity of the parasympathetic nervous system, and modulation of cascades of hormones. These pathways converge to stabilize blood pressure in a normal individual through a wide range of postures. Problems arise when any of these pathways responds inappropriately. The result can have clinical significance in the presence or absence of overt symptoms.

The influence of body position on blood pressure in normal individuals derives from perturbations elicited by gravity with the assumption of an upright posture. The resulting decrease in effective plasma volume is accompanied by a slight decrease in SBP, a slight increase in diastolic blood pressure (DBP), an increased heart rate, and an increase in circulating levels of norepinephrine, epinephrine, active plasma renin, aldosterone, and vasopressin. In addition, rates of sodium reabsorption and potassium excretion are increased at the level of the kidney, without net change in plasma osmolarity.[2] These responses are primarily a reflection of coordinated activation of the sympathetic nervous system and a decrease in activity of the parasympathetic nervous system, both mediated by the baroreflex pathway.

When blood pressure is measured in a clinical setting, the reading can be influenced by the focus and expectation of the individual making the determination. If the examiner is blind to the true blood pressure (for example when a random-zero sphygmomanometer is employed) greater excursions in pressure are often reported. Both orthostatic hypotension and orthostatic hypertension are more commonly encountered when pressures are measured by a blinded observer.[3] Therefore, as blind recording of blood pressure is rarely employed in a clinical setting, there might be widespread underreporting of both these types of orthostatic changes in blood pressure.

Perhaps the most familiar clinical syndrome involving the baroreflex response pathway is orthostatic hypotension. This topic has been reviewed extensively elsewhere[4,5] and will only be briefly discussed here. Orthostatic hypotension occurs when the change in blood pressure upon assumption of upright posture is ineffectively compensated. The objective physical finding is a drop in blood pressure of 20/10 mmHg. Orthostatic hypotension is clinically important when the decrease in blood pressure is accompanied by symptoms of cerebral hypoperfusion, including dizziness or lightheadedness, visual changes, discomfort in the head and neck, fatigue, and frank syncope. The most dramatic examples of orthostatic hypotension are observed in syndromes involving failure of the effector arm of the baroreflex, namely, the autonomic nervous system. These syndromes include pure autonomic failure[6] and multiple system atrophy (Shy–Drager syndrome).[7] It is also noteworthy that a variety of pharmacologic agents, particularly antidepressants and antihypertensives, can cause iatrogenic orthostatic hypotension and must be ruled out initially when considering a differential diagnosis for orthostatic hypotension.[8,9]

Two other conditions are worth mentioning here, as they will be discussed later. Baroreflex failure, which involves loss of afferent input into brainstem blood-pressure control centers, and which is often confused with pheochromocytoma, can involve a component of orthostatic hypotension.[10,11] Unlike pure autonomic failure or multiple system atrophy, however, episodic tachycardia and labile hypertension are prominent features in baroreflex failure.[11–13] The postural tachycardia syndrome (POTS) also presents clinically with symptoms of cerebral hypoperfusion.[14,15] Interestingly, however, this disorder more often involves either no change in blood pressure or orthostatic hypertension of mild severity.

ORTHOSTATIC HYPERTENSION—DEFINITION AND SIGNIFICANCE

Orthostatic hypertension is an underappreciated but potentially clinically important entity. As alluded to above, orthostatic hypertension is defined simply as an increase in blood pressure upon assumption of upright posture. One problem with the literature on this subject is that very few studies have entailed direct measurement of arterial blood pressure in people with orthostatic hypertension. Such measurements would more faithfully reflect intra-arterial pressure and would avoid the introduction of potential artifacts associated with noninvasive blood pressure monitoring (e.g. improper cuff size, incompressibility of atherosclerotic arteries, and the effect of the time required physically to make the measurement). In addition, sphygmomanometers can underestimate blood pressure when it is perturbed by pressor reflexes, such as those engaged by upright posture, or if it is increased by pressor agents.[16] Therefore, the magnitude of the blood pressure increase upon standing might be even larger than is generally reported in orthostatic hypertensive subjects.

The magnitude of increase in sphygmomanometric pressure required for a diagnosis of orthostatic hypertension has often been operationally defined in individual studies, with an increase in SBP of 20 mmHg or more being a common recent diagnostic criterion (Box 1). Recognition of the presence and degree of orthostatic hypertension might be clinically important for a number of reasons. First, orthostatic hypertension might be a symptom of another treatable condition, such as pheochromocytoma[17,18] or mast-cell activation disorder in the context of POTS.[19] Second, orthostatic hypertension resulting from any number of causes might be an important risk factor for silent cerebrovascular ischemia and infarct. Published studies from the Shimada laboratory indicate that, at least in populations of elderly Japanese people with essential hypertension, the incidence of silent cerebrovascular infarct detectable by MRI

Box 1 Definitions of orthostatic hypotension and orthostatic hypertension.

Orthostatic hypotension

- Systolic blood pressure decreases by at least 20 mmHg upon standing
- Diastolic blood pressure decreases by at least 10 mmHg upon standing

Orthostatic hypertension

- Systolic blood pressure increases by at least 20 mmHg upon standing
- No change in diastolic blood pressure has been defined

Although other operational definitions of orthostatic hypertension have been used in various studies, the systolic blood pressure criterion above forms the basis of discussion in this Review as it has been associated with an important clinical condition—silent cerebrovascular ischemia.

is higher in those patients who have clinically identifiable orthostatic hypertension.[20,21]

Orthostatic hypertension has been a recognized phenomenon for quite some time. Some of the earliest reports discussing orthostatic hypertension were written by David HP Streeten in the 1970s and 1980s. The phenomenon was characterized as a DBP above 90 mmHg plus a greater increase in DBP upon standing than that experienced by hypertensives without orthostatic hypertension or by normotensives.[22] Those individuals with orthostatic hypertension also had a greater decrease in cardiac output, greater venous pooling in the lower extremities, and higher plasma norepinephrine levels upon standing. The hypothesis was that excessive venous pooling led to a decrease in cardiac output, the response to which was increased sympathetic activity and increased DBP. Streeten also commented that orthostatic hypertension was probably more common than was generally appreciated, but little or no mention was made of the possible clinical significance of the phenomenon.

ORTHOSTATIC HYPERTENSION IN THE CONTEXT OF ESSENTIAL HYPERTENSION

More recently, orthostatic hypertension and its potential clinical importance have been recognized in two groups of patients with essential hypertension. The first is elderly patients with essential hypertension. In one study, orthostatic hypertension occurred in approximately 11% of a sample of 241 elderly Japanese patients with essential hypertension[21] (defined as those whose SBP increased by ≥20 mmHg upon standing). In this study, the incidence of silent cerebrovascular infarct was higher in patients with orthostatic hypertension than in hypertensives without orthostatic hypertension. Notably, an approximately equivalent proportion of the study group exhibited orthostatic hypotension (23 of 241 patients). These patients were also at increased risk of silent cerebrovascular infarction.

The second group of essential hypertensives in which orthostatic hypertension has been observed are those who show abnormal diurnal variation in blood pressure—the ‘extreme dipper’ phenotype. These patients show a greater than normal decrease in SBP while sleeping. In one study examining the relationship between orthostatic hypertension and diurnal SBP variation, 72% of extreme dippers were shown to have orthostatic hypertension, compared with only 11% and 9% of dippers and nondippers, respectively.[23] Extreme dippers have been shown to have a higher prevalence (53%) of silent cerebrovascular infarction detected by MRI compared with dippers (29%).[21] Moreover, extreme dippers are at increased risk for overt stroke and tend to have a poorer prognosis in the event of a stroke.[24] It is thought that orthostatic hypertension has an important role in the overall increased risk for stroke in these patients, as two-thirds of strokes in extreme dippers occur in the morning, a time when these patients are known to experience a surge in blood pressure.

Matsubayashi and colleagues reported findings similar to those reported by Kario *et al.*[21] relating to orthostatic blood pressure changes and central nervous system (CNS) changes in a study of 334 elderly Japanese subjects.[25] In this study, 8.7% (29/334) of subjects exhibited orthostatic hypertension using the same definition as the aforementioned study, and 6% (20/334) of subjects exhibited orthostatic hypotension. Both orthostatic hypertensive ($n=15$) and orthostatic hypotensive ($n=15$) subjects had an increased prevalence of CNS lesions detectable by MRI compared with orthostatic normotensives ($n=30$). In addition, scores on a number of cognitive and neurobehavioral metrics were lower in orthostatic hypertensives ($n=29$) and orthostatic hypotensives ($n=20$) than in orthostatic normotensives ($n=285$). An important distinction of the Matsubayashi *et al.* study is that the study population was a general sample of elderly Japanese subjects, of whom only approximately 50% were taking antihypertensive medications. Thus, orthostatic hypertension (and orthostatic hypotension) may be associated with cerebrovascular infarction and with measurable neurocognitive deficits independent of the presence of essential hypertension.

ORTHOSTATIC HYPERTENSION AND DYSAUTONOMIA

Orthostatic hypertension has also been associated with a number of conditions involving some form of autonomic dysfunction. In a recent study of patients with POTS in the context of disordered mast-cell activation, 38% (3/8) were shown to have orthostatic hypertension.[19] Interestingly, in this group of patients, the orthostatic hypertension manifested as either a persistent hypertensive response to assumption of an upright posture or as a hypertensive crisis, with BP as high as 240/140, with upright posture. This has not been observed in patients who have POTS but do not have mast-cell activation disorder. Patients with baroreflex failure may also occasionally experience episodes of orthostatic hypertension.[26–29] These episodes are especially likely to occur in patients presenting with acute baroreflex failure. In the initial days and weeks after onset such patients have orthostatic hypertension immediately on standing, though it usually declines somewhat over the following few minutes. It is not a universal manifestation of baroreflex failure, which is more typically characterized by labile blood pressure and heart rate which track together. In a final phase of baroreflex failure, usually months to years after onset, orthostatic hypotension is more typically the dominant hemodynamic expression of the disorder. In the rare syndrome of norepinephrine transporter deficiency, an increase in blood pressure with upright posture can also be seen.[30]

ORTHOSTATIC HYPERTENSION AS A FEATURE OF OTHER CONDITIONS

Finally, orthostatic hypertension has been described as a clinical feature of a variety of other conditions, not all of which have blood pressure disturbances as a major symptom cluster. Patients exhibiting baroreflex failure are discussed above. Patients with pheochromocytoma, much like patients with baroreflex failure, may present with impressive labile hypertension that can be exacerbated by standing. Also like patients with baroreflex failure, however, this orthostatic hypertension may more properly be thought of as a manifestation of an underlying labile hypertension that in some patients will manifest as orthostatic hypertension. Interestingly, Yoshinari *et al.* have described orthostatic hypertension as a feature of type 2 diabetes mellitus.[31] Diabetic and non-diabetic subjects were classified as normotensive or hypertensive at the beginning of the study, and blood pressure was measured in the supine, sitting, and standing position. Orthostatic hypertension was defined as either an increase in DBP from <90 mmHg to ≥90 mmHg or an increase in SBP from <140 mmHg to ≥140 mmHg. In this sample, 12.8% of the normotensive diabetic patients had orthostatic hypertension, as compared to 1.8% of normotensive non-diabetic subjects. Hypertensive and normotensive diabetic subjects had a similar incidence of orthostatic hypertension. Interestingly, diabetic patients with orthostatic hypertension had decreased vibratory sense compared to diabetics without orthostatic hypertension and to non-diabetics. While this difference did not reach statistical significance, it may point to an important clinical correlation between orthostatic hypertension and neuropathy in this diabetic population. Jannetta and colleagues have emphasized a relationship between hypertension, including orthostatic hypertension, and medullary vascular compression.[32,33] These patients are believed to have compression from vascular loops which may interfere with medullary cardiovascular control centers. Jannetta has reported successful surgical treatment in some of these patients.

PATHOPHYSIOLOGY OF ORTHOSTATIC HYPERTENSION

The pathophysiology underlying orthostatic hypertension remains relatively poorly understood (Figure 1). This is due in part to an underappreciation of the phenomenon and in part to the diverse clinical conditions that can have orthostatic hypertension as a feature. As discussed above, Streeten *et al.* described a process of excessive venous pooling in the lower extremities upon standing, which leads to a decrease in cardiac output, a vigorous activation of the sympathetic nervous system, and excessive

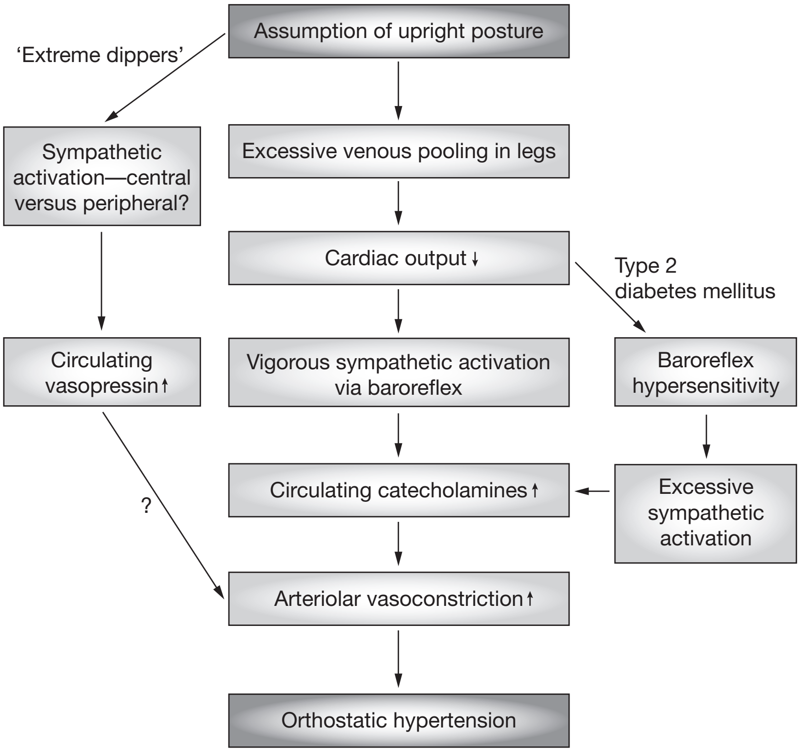

Figure 1 Pathophysiological mechanisms proposed to underlie orthostatic hypertension.

arteriolar vasoconstriction.[22] This process may be analogous in some ways to the mechanism proposed for POTS by Streeten *et al.*[34] and Jacob *et al.*,[35] which involves a partial dysautonomia in the lower extremities as an immediate upstream cause for excessive venous pooling. There must be substantive differences, however, as patients with POTS do not always exhibit orthostatic hypertension.

The underlying mechanisms for orthostatic hypertension in extreme dipper patients are especially unclear. Kario *et al.* suggest that orthostatic hypertension in this patient population may involve enhanced arteriolar vasoconstriction that is mediated by the sympathetic nervous system.[23] It is plausible that the orthostatic hypertension in these patients is in fact the result of sympathetic activation, though the specifics are not understood. For example, it is unknown whether the phenotype is primarily due to central or peripheral sympathetic activation. Further clouding the picture is the finding by Kario and Shimada that circulating levels of vasopressin in extreme dippers are higher following a head-up tilt challenge than in dippers and non-dippers, but extreme dippers did not have significantly higher levels of norepinephrine or plasma renin activity.[24] It also seems plausible that there is some mechanistic connection between orthostatic hypertension and the unusually large drop in SBP that is the defining feature of the extreme dipper phenotype, though what the connection may be remains obscure.

The connection between orthostatic hypertension and type 2 diabetes mellitus is similarly obscure. Yoshinari *et al.* suggest that hypersensitivity of the baroreflex may be the underlying cause for orthostatic hypertension in these patients.[31] In support of this hypothesis, they point out that the patients with orthostatic hypertension also had evidence of neuropathy; however, the coefficient of variation of the RR interval on electrocardiograms of patients with orthostatic hypertension was higher than that of those without. This coefficient is known to decrease with parasympathetic dysfunction, and parasympathetic dysfunction precedes sympathetic dysfunction in diabetic patients. These investigators suggest that the disconnect between clinical evidence of neuropathy and the elevated coefficient of variation of the RR interval could point to baroreflex hypersensitivity as a contributing factor to orthostatic hypertension in type 2 diabetes. The mechanism underlying baroreflex hypersensitivity, however, is not at all clear.

There is some experimental evidence in animal models that orthostatic hypertension is sympathetically mediated. Raffai *et al.* exposed normotensive and experimentally hypertensive (via blockade of nitric oxide production) rats to either repeated or sustained 45-degree head-up tilt.[36] Both normotensive and hypertensive rats responded to head-up tilt with an increase in blood pressure. This response was blocked by the administration of prazosin, an alpha-1 adrenergic receptor antagonist, or a subanesthetic dose of chloralose. The conclusion of these authors was that the hypertensive response of these rats to head-up tilt was likely due to stress-mediated activation of the sympathetic nervous system. The anesthetic reduced the animals' stress, while the prazosin prevented the increase in blood pressure at the level of the vasculature. While this model differs substantially from orthostatic hypertension observed in humans, it offers a potential mechanism at work in patients that can be tested with currently available pharmacologic tools.

DIAGNOSIS AND TREATMENT

Fortunately, although orthostatic hypertension is an underappreciated clinical phenomenon, diagnosis of the condition is relatively straightforward. What is lacking in terms of diagnosis, however, is a standardized value for the increase in SBP and/or DBP to make the diagnosis of orthostatic hypertension. The criteria used in the study by Kario *et al.* that linked orthostatic hypertension to an increased incidence of silent cerebrovascular disease defined orthostatic hypertension as a ≥20 mmHg increase in SBP upon assumption of an upright posture (specifically in the study, head-up tilting to 70 degrees) from the supine position.[21] This definition, in the absence of other more rigorous diagnostic criteria, seems an appropriate definition to use, as this is a diagnostic criterion that has been associated with a clinically relevant endpoint. Although different studies have varied in their use of either passive tilting or active standing to elicit orthostatic hypertension, the phenomenon and associated clinical findings are seen with passive tilting[21] and active standing.[25] Evaluation of any patient in either the setting of a health maintenance visit or the setting of a work-up for a blood pressure abnormality should include measurement of blood pressure in the supine, sitting, and standing positions. A problem that arises immediately with the current state of knowledge is what the next step should be for a patient who is found to have orthostatic hypertension. Certainly the phenomenon should be considered a real finding if a patient shows an increase of ≥20 mmHg SBP upon standing from a supine position on more than one occasion. A demonstration of reproducibility is important for any orthostatic blood pressure changes, as patients with underlying blood pressure dysregulation (e.g. essential hypertension) and/or comorbidities that can impact upon blood pressure (e.g. diabetes mellitus) may well have more variable blood pressure readings than otherwise healthy normotensive subjects. The indications for further work-up should be based upon other findings independent of the orthostatic hypertension itself. For example, if a patient is found to have labile hypertension that is refractory to aggressive therapy, a diagnostic work-up for baroreflex failure and/or a search for surgically correctable causes of hypertension should be undertaken. Currently there is not sufficient data to suggest expensive or invasive testing for patients who are either normotensive or essentially hypertensive who also have asymptomatic orthostatic hypertension.

Box 2 Conditions in which orthostatic hypertension is a notable feature.

Chronic primary conditions
- Essential hypertension in the elderly
- Essential hypertension with abnormal diurnal variation (‘extreme dippers’)
- Type 2 diabetes mellitus

Dysautonomias
- Postural tachycardia syndrome with disorder of mast-cell activation
- Norepinephrine transporter deficiency
- Baroreflex failure (acute)

Potentially surgically-correctable conditions
- Pheochromocytoma
- Medullary vascular compression

Therapeutic considerations are currently as challenging as recommendations for diagnostic measures. Treatment should primarily be guided by the condition that is the context for the orthostatic hypertension. For example, treatment for a patient with essential hypertension who has a component of asymptomatic orthostatic hypertension should be geared toward achieving optimal blood pressure control as for any patient with essential hypertension. The sum of the existing data would suggest that therapy targeted at controlling orthostatic hypertension would be aimed at controlling the effects of sympathetic activation. This could include therapies such as alpha-1 adrenergic receptor antagonists such as prazosin, used in the study by Raffia *et al.*, or central alpha-2 adrenergic receptor agonists such as clonidine. There are currently no data to indicate whether orthostatic hypertension should be specifically targeted therapeutically, which therapy would be optimal, or what the therapeutic endpoints would be.

CONCLUSIONS

Orthostatic hypertension is a real clinical phenomenon that is associated with a variety of underlying conditions (Box 2). It has been associated with important clinical correlates such as silent CNS ischemia/infarct, overt stroke, and neuropathy in the context of type 2 diabetes. The underlying pathophysiology is poorly understood at present but seems to involve activation of the sympathetic nervous system. A better understanding of the underlying pathophysiology is very important, as it could have direct implications for possible therapies. Diagnostic criteria are ill-defined at present, and a consensus should be reached regarding the clinical diagnosis of orthostatic hypertension. There are essentially no data regarding what the further diagnostic or therapeutic implications are for a diagnosis of orthostatic hypertension. Should the condition be treated as an independent therapeutic target in the context of hypertension? What are the optimal treatment strategies? What are the benefits and risks of treating orthostatic hypertension? These and many other questions have yet to be addressed. Clearly orthostatic hypertension represents an aspect of hypertension that is poorly understood and is in need of focused basic science and clinical inquiry.

KEY POINTS

- Orthostatic hypertension—in contrast to orthostatic hypotension—is an understudied and often overlooked form of blood pressure dysregulation
- There is no generally accepted definition of orthostatic hypertension; an increase in systolic blood pressure of 20 mmHg or more upon standing has been proposed
- Physiological processes that might underlie orthostatic hypertension include excessive venous pooling leading to decreased cardiac output, activation of the sympathetic nervous system, and increased levels of circulating hormones
- Orthostatic hypertension is a feature of several conditions and patient subgroups, including essential hypertension in the elderly and 'extreme dippers', dysautonomias, and pheochromocytoma
- In the absence of data on specific therapies, management of orthostatic hypertension should be a function mainly of the condition of which it is a feature, and might include adrenergic receptor antagonists

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