

Original Paper

# An Emerging Role for Understanding Orthostatic Hypertension in the Cardiorenal Syndrome

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## Key Words

Cardiovascular disease · Chronic kidney disease · Hypertension · Orthostatic blood pressure

## Abstract

Orthostatic hypertension (OHT) is a clinically important problem increasingly recognized in persons with borderline hypertension, diabetes mellitus, and autonomic neuropathies, and in the elderly. Moreover, the association of OHT with progression of target end-organ damage, especially coronary heart disease and chronic kidney disease (CKD), and the attendant increased cardiovascular disease (CVD) and CKD risk, is gaining attention but is still underappreciated. There are various mechanisms that contribute to the development of OHT: excessive vascular adrenergic sensitivity, baroreceptor reflex abnormalities, and inappropriate activation of the renin-angiotensin-aldosterone system, which are also mechanisms that lead to cardiorenal metabolic disease (CRS). While the evidence is compelling for the clinical importance of OHT, more investigation is needed to evaluate the effects of OHT on CKD and CVD. The notion that the development of OHT is a risk factor for the development of CRS raises the need for further clinical and investigational attention to this clinical dilemma.

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## Introduction

Postural-related fluctuations in blood pressure (BP) can occur normally in all individuals but are usually minimized by autoregulatory mechanisms. Orthostatic BP dysregulation is a measure of cardiovascular reactivity and can result in the two clinical entities ‘ortho-

static hypotension' and 'orthostatic hypertension' (OHT) [1]. An increase in BP within physiological limits on standing is considered a normal response. For example, OHT is characterized by an abnormal increase in BP on standing. The postural variations in BP were studied as early as 1922, and initial observations of OHT were also recorded [2]. In contrast to orthostatic hypotension, which is a well-studied entity especially in the elderly population [2], OHT has been a largely underrecognized phenomenon. OHT has also been referred to as 'postural hypertension' in the past [3]. Over the last few years, there has been an increased interest in OHT as it has been found to be associated with increased risk of developing hypertension in young adults [4], silent cerebral infarcts in elderly hypertensives, and myocardial ischemia and proteinuria [5–7]. Therefore, we will review the current understanding of the pathogenesis, definitions, clinical implications, and possible available treatment options in the context of the cardiorenal metabolic syndrome (CRS).

While there is a general consensus on the definition of orthostatic hypotension, there is currently no consensus on the definition for OHT. However, it should be noted that different studies have used certain parameters for defining OHT. Investigators in a 1998 study of healthy elderly adults defined postural hypertension or OHT as the rise of systolic BP (SBP) >20 mm Hg on standing up from the sitting position [3]. In that study, orthostatic BP was measured twice and the mean difference in SBP was considered for meeting the criteria of OHT. In a 2002 study of elderly hypertensives, investigators performed a 70° head-up tilt (HUT) test for 15 min after 10 min of supine rest [8]. The orthostatic increase in BP was calculated and OHT was defined as SBP increase >20 mm Hg. Other studies have defined OHT as an increase of diastolic BP (DBP) from <90 to ≥90 mm Hg and/or an increase of SBP from <140 to ≥140 mm Hg after 1 min of standing from the supine position [9]. Most studies done on large populations have used the postural measurement of BP to define OHT. A summary of the different definitions used has been listed in table 1. The most commonly used criterion for an accurate diagnosis of OHT appears to be an increase of SBP of >20 mm Hg resulting from an orthostatic change.

The prevalence of OHT has been reported to be varied in the literature due to the lack of a stable definition among various investigators. There is an increased prevalence in patients with borderline hypertension, autonomic neuropathies, and diabetes mellitus, and in the elderly [9, 10]. In a study on healthy airmen, OHT was present in 4.2% of the people [2]. In another study on 21 patients with borderline hypertension, 71% were noted to have OHT [11]. In the context of heart disease, OHT was detected in 16.2% of the young adults in the CARDIA (Coronary Artery Risk Development in Young adults) study [4], classified according to SBP changes of >5 mm Hg. In another study in elderly patients in Japan, the active standing test was used and OHT was defined as an increase of ≥20 mm Hg in BP from the lying position [3]. OHT was noted in 8.7% and orthostatic hypotension in 6% of patients. Another recent study in 1,638 adults found that the prevalence of OHT defined as a change in BP >20 mm Hg was present in 1.1% of patients. Interestingly, they noted that no adult <40 years of age in their group had OHT [12]. In a study including subjects with type-2 diabetes in Japan, the prevalence of OHT was significantly higher in diabetic patients than in control subjects (12.8 vs. 1.8%). The prevalence of OHT in a group of long-standing type-1 diabetics was 15.2% [11].

### **Pathophysiology**

Maintenance of BP is a dynamic condition influenced by a complex interplay of neuro-humoral factors, including the sympathetic nervous system (SNS) and the renin-angiotensin-aldosterone system (RAAS). The aortic and carotid baroreceptors respond to changes in

**Table 1.** Definitions used for OHT

Author	Test used	SBP/change in SBP	Change in DBP	Subjects, n
Streeten et al. [9]	postural BP recording		>90 mm Hg	1,800
Thomas et al. [4]	postural BP recording	>5 mm Hg		2,781
Yoshinari et al. [19]	postural BP recording	>140 mm Hg	>90 mm Hg	277
Hoshide et al. [5]	home BP monitoring	highest percentile, change >7.8 mm Hg		605
Kario et al. [8]	HUT	>20 mm Hg		241
Kario et al. [29]	HUT	>10 mm Hg		110
Matsubayashi et al. [3]	postural BP recording	>20 mm Hg		334
Wu et al. [12]	postural BP recording	>20 mm Hg		1,638

SBP adjusting the peripheral vasoconstriction and cardiac output to maintain a relatively constant perfusion pressure [13]. These autoregulatory mechanisms help to minimize the diurnal and postural fluctuations in BP. In normal subjects, a change in posture from the recumbent to the standing position results in the redistribution of blood from the intrathoracic vascular compartment to the legs. This gravitational pooling of blood results in reduced end-diastolic volume with a fall in the stroke volume. The decrease in the effective plasma volume leads to sympathetic activation and concurrent tachycardia, a mild increase in DBP, a moderate decrease in SBP and an overall decrease in pulse pressure. The rise in DBP is largely mediated by low-pressure cardiopulmonary receptors [9].

Orthostatic stress responses can be assessed using the HUT test. Varying responses of heart rate and arterial pressure have been noted even among healthy individuals without autonomic dysfunction. Individuals with increased heart rate response to orthostasis have lower SBP, lower pulse pressure, and higher plasma norepinephrine levels [14]. These variations in heart rate and arterial pressure can be considered to be normal baroreflex mechanisms with interindividual variability.

#### *Various Mechanisms Postulated for OHT*

*Excessive Venous Pooling with Exaggerated Physiological Response.* In a majority of patients, the orthostatic change in DBP is thought to be due to excessive gravitational pooling with decreased venous return, lowering of cardiac output and sympathetic stimulation. Gravitational pooling has been found to be significantly higher in OHT than control patients and correlated with an orthostatic rise in BP [9].

*Vascular Adrenergic Sensitivity and Influence of Functional Aortic Properties.* Recent studies have shown that orthostatically induced sympathetic activation might play a direct role in inducing OHT. Orthostatic norepinephrine and vasopressin levels are higher in OHT persons than in those without this problem [9]. An experimental model to study the phenomenon of OHT was developed in Wistar rats, and it was shown that sustained orthostasis elicited a hypertensive response which could be ameliorated by sympathetic blockade [10]. In persons with vascular adrenergic hypersensitivity, there is also an increased pressor response to norepinephrine, which was also present in OHT [15]. These patients have an immediate rise in BP on upright positioning suggesting a primary increase in systemic vascular resistance rather than a reaction to a decreased cardiac output [15]. The impact of arterial properties on orthostatic BP dysregulation has also been studied in older hypertensive patients. Patients with OHT have been found to have an increased augmentation index, which is a reflection of the increased vascular tone likely due to sympathetic activation. Based on

their findings, it has been postulated that the abnormal functional aortic properties in OHT might play a role in the pathogenesis of hypertensive cerebrovascular disease [16].

*Baroreceptor Reflex Abnormalities.* The aortic and carotid baroreceptors act as negative feedback mechanisms to regulate the activity of SNS and RAAS. Baroreceptor afferent mechanisms or central integration of cardiopulmonary baroreflexes may be altered leading to increased SNS and RAAS activity [13, 14]. The role of baroreceptors in hypertension cannot be understated as there have been reports of patients with baroreflex failure presenting with labile hypertension and hypertensive crisis [17, 18]. Patients with OHT have increased sensitivity of the carotid and aortic baroreceptors which results in marked posture-dependent fluctuation in the BP. Baroreflex hypersensitivity has been considered to be one of the mechanisms of OHT, particularly in diabetic patients [19].

*Orthostatic RAAS Activation in Nephroptosis.* Nephroptosis, also known as floating kidney, is a condition characterized by the descent of a kidney by more than 2 vertebral bodies or >5 cm after changing the posture from supine to upright. In patients with nephroptosis, assumption of the upright posture is thought to result in stretching of the renal artery and a change in the size of the lumen with subsequent activation of the RAAS [20–22]. This OHT has an entirely different pathogenesis from the mechanisms suggested above and is specific for nephroptosis.

## The Clinical Spectrum of OHT

### *OHT as an Indicator of (Future) Hypertension*

The implication of orthostatic changes in BP in normotensive, pre-hypertensive and stage-I hypertensive patients has been of particular interest. In the HARVEST study which was conducted on a group of 1,029 young stage-I hypertensives, patients with exaggerated orthostatic response had higher whole-day BP on ambulatory BP measurements [23]. Interestingly, there were no differences in the clinical BP between the group of hyperreactors to orthostatic stress and normal patients. Other studies have also shown that a diastolic orthostatic response may be predictive of sustained hypertension [24]. In the CARDIA study including 2,781 young adults to assess the relationship between positional BP change and incidence of hypertension over a follow-up period of 8 years, there was a significantly increased risk of developing hypertension in OHT persons [4]. The cardiovascular reactivity to orthostatic stress has been used to devise a hemodynamic instability score which has been shown to be associated with the development of hypertension [25]. Potentially, detection of OHT might help to identify a subset of pre-hypertensive patients that might have progression of their hypertension and develop hypertensive target organ damage (table 2).

### *OHT in Elderly Hypertensives*

OHT has been well studied in elderly hypertensive patients. In a study from Japan of elderly hypertensive patients, the incidence of OHT was about 11% [8]. Many factors, including autonomic nervous dysfunction, baroreceptor reflex abnormalities, and altered aortic properties in the elderly, predispose to increased occurrence of OHT in the elderly. OHT has been established to be a risk factor for cerebrovascular disease and CVD in the elderly [3, 8, 16, 26] and an independent predictor of cardiovascular death in the very elderly patients [27].

### *OHT and the Relationship between Diurnal BP Variations*

In normal subjects, there is diurnal variation in BP with a fluctuation of >10 mm Hg throughout the day. Typically, a BP variation of 20–30 mm Hg is noted, with the highest pressure seen during the morning hours and a nocturnal dip in BP [28]. The decrease in SNS

**Table 2.** Conditions associated with OHT

Common

- Elderly patients with hypertension
- Patients with borderline hypertension
- Extreme dippers
- Patients with diabetes mellitus
- Young patients with hypertension

Rare

- Autonomic disorders
  - Postural orthostatic tachycardia syndrome with mast cell activation
  - Sympathetic denervation hypersensitivity
- Baroreceptor reflex abnormality
  - Baroreflex buffering, baroreflex hypersensitivity, inadequate baroreflex-mediated vasopressin release
  - Brain stem stroke
  - Monogenetic hypertension
- Nephroptosis

activity during sleep is one of the most obvious explanations for the nocturnal dip in BP. The ‘extreme dippers’ have a marked nocturnal fall in BP, >20% of the mean awake SBP [29]. Extreme dippers have also been found to have OHT with postural increase in both SBP and DBP. There is now increasing evidence to suggest that persons who are extreme dippers are at risk for developing silent myocardial ischemia and non-fatal ischemic stroke [16, 30, 31].

A surge in morning BP has now been well recognized and is known to be about 2 mm Hg/h of DBP and 3 mm Hg/h of SBP from 6 AM to about 12 PM. The morning surge in BP is attributed to multiple factors, including  $\alpha$ -adrenergic activity [32], RAAS changes, oxidative stress, and plasminogen activator inhibitor, for example. Also, in some studies, the early morning surge has been known to be associated with OHT [33]. SNS hyperactivity seems to be the common pathophysiology underlying all these diurnal and postural BP variations.

*OHT in Diabetics*

OHT is a newly recognized complication in normotensive and hypertensive diabetics. A study done on type-2 diabetes mellitus patients showed that the prevalence of OHT was significantly higher in normotensive diabetic patients in comparison to control subjects (12.8 vs. 1.8%, respectively) [19]. Another recent study on type-1 diabetes patients found that the incidence of OHT was 15.2%, and postural changes were more common in patients <40 years of age [11]. In other studies, the prevalence of diabetes mellitus in the OHT group was high [16]. The hypersensitivity of the cardiopulmonary baroreceptor reflex and the SNS has been implicated in the pathogenesis of OHT in diabetic patients.

*OHT in Special Circumstances*

*Nephroptosis.* OHT related to nephroptosis has been recognized as early as 1940 and was frequently discussed in the literature as a treatable cause of hypertension [34]. Nephroptosis has also been associated with fibromuscular dysplasia and torsion of the kidneys [20, 22, 35]. Detection of OHT associated with nephroptosis can be of considerable therapeutic value as patients could be treated with nephropexy resulting in resolution of OHT and hypertension as well. Patients with associated fibromuscular dysplasia may also be effectively treated with percutaneous renal angioplasty [36].

*Autonomic Disorders with OHT.* OHT may occur in a subset of patients with postural orthostatic tachycardia syndrome with mast cell activation. This syndrome is characterized

**Table 3.** Comparison of methods used for the detection of OHT

	HUT test	Orthostatic BP in clinic	Ambulatory BP recording
Advantages	gold standard	easy to perform	accurate reproducible
Disadvantages	time consuming requires trained personnel impractical in clinical setting	inaccurate needs to be repeated	expensive instrument availability may be limited
Effect of white-coat phenomenon	yes	yes	no
Usefulness for screening	no	yes, commonly used in large-scale population studies	yes, but expensive
Detection of other hypertension-related phenomena (dippers/morning surge)	no	no	yes

by orthostatic intolerance presenting with fatigue, tachycardia, syncope, and shortness of breath on standing and OHT [37]. Similarly, other autonomic disorders like sympathetic denervation hypersensitivity may present with OHT [38].

*Neurogenic OHT.* Neurogenic OHT may result due to conditions affecting the brain stem. Neurovascular contact of the ventrolateral medulla can result in interference with baroreflex functions [39]. This has been noted in a group of patients with monogenic hypertension who presented with OHT. A similar entity can be found in patients with brain stem stroke which may result in baroreflex failure and paroxysmal hypertension precipitated by positional change [17].

## Diagnosis

Most commonly, OHT is discovered as an incidental finding during routine evaluation of patients. OHT patients may present with symptoms of orthostatic intolerance in specific conditions [17, 40, 41]. Various methods can be used to diagnose postural BP variations in patients (table 3). Each of these methods has their advantages and disadvantages and has to be employed in a judicious fashion to improve the yield of detection.

*HUT Test.* The HUT test is the gold standard for diagnosing postural BP and pulse changes. This test is performed by placing the patient on 60–80° on a tilt table for 15–20 min and recording the BP in that position. BP is also recorded in the supine resting position and the difference is noted. This test has been widely used in clinical studies on OHT [8, 29]. The HUT test is time consuming, requires trained personnel and is not very practical in the clinical setting.

*Postural BP Evaluation.* Measurement of orthostatic BP in an office setting is a much simpler way to diagnose OHT and has been used in many large-scale and population-based studies to evaluate the long-term effects of OHT [9, 12, 19, 23]. BP is measured first in the supine position and then again after 1–2 min of standing. The recordings have to be repeated at least twice in order to offset variations such as the white-coat effect. Though this form

of recording may not be very accurate, due to the relative ease of testing it is more likely to be used.

*Ambulatory BP Monitoring.* Ambulatory BP monitoring is a very useful tool and gives better prediction of clinical outcome than clinical or casual BP measurements. The technique of ambulatory BP monitoring is specialized, and appropriate quality control measures should be used. The monitor is a small device worn in a pouch that has a BP cuff attached to it. The cuff is fitted on the patient's arm and inflates and deflates automatically at 30- to 60-min intervals throughout the 24- or 48-hour period. Ambulatory BP has been identified as a measure of cardiovascular morbidity independent of clinical BP recording [42]. Newer models of ambulatory BP monitors have been designed, which have a body position sensor and measure BP twice in the sitting and standing positions automatically [7]. The results from ambulatory BP monitoring are more accurate and reproducible. However, the availability of the instruments and cost for routine assessment of OHT may be prohibitive.

### **Target Organ Damage Associated with OHT**

*CKD.* Patients with an orthostatic rise in BP >7.8 mm Hg have a higher urinary albumin to creatinine ratio (209.1 vs. 34.1 mg/g creatinine) [5]. The presence of microalbuminuria has been identified as a risk factor for the onset of future albuminuria and renal disease in diabetic individuals with increased rates of mortality [43]. Also, in non-diabetic patients, microalbuminuria is a predictor of future CVD and peripheral vascular disease [44, 45].

*CVD.* Exaggerated sympathetic stimulation and baroreflex hypersensitivity are implicated in the pathogenesis of OHT. These factors also influence the risk and outcomes in CVD patients. OHT has been associated with increased brain natriuretic peptide, which might reflect increased left-ventricular systolic load [5, 6]. In a large epidemiological study performed on 13,340 men and women to assess the characteristics of persons with a BP change with posture, persons with increased SBP on standing had a higher predicted risk of developing coronary artery disease after 8 years [1]. OHT has also been a strong predictor of CVD death in very elderly patients (>80 years) [27].

*Cerebrovascular Disease.* The relationship between OHT and cerebrovascular disease particularly in the elderly has been well studied. Investigators reported that silent cerebral ischemia (SCI) detected by MRI was significantly higher in OHT elderly after adjusting for confounding variables [8]. Other studies on the elderly have also shown that the prevalence of SCI, number of SCI and number of multiple SCI was the highest in the OHT group compared to the orthostatic normo- and hypotensive groups [6]. Orthostatic rise in SBP has also been associated with intima-media thickness and carotid atherosclerosis [46]. It has also been noted that asymptomatic elderly patients with postural hypertension had poorer scores on neurobehavioral tests and a higher incidence of periventricular hyperintensities on MRI [3].

### **Treatment Options for Patients with OHT**

#### *Non-Pharmacological Options*

Patients with orthostatic intolerance should be advised and cautioned against sudden changes in posture. In a majority of OHT patients with no underlying cause, gravitational pooling is a major factor. If this pooling was decreased by the use of anti-gravity suits, the consequent orthostatic fluctuation in BP could be minimized [9].

### Pharmacological Options

The  $\alpha$ -adrenergic activity is presumed to be the predominant pathophysiological mechanism in patients with OHT with no associated secondary causes. In a study in elderly hypertensives,  $\alpha$ -adrenergic blockade led to decreases in the orthostatic response [8]. This provides credence for recommending  $\alpha$ -adrenergic blockers in those patients with significant OHT. Clonidine, which is a centrally acting  $\alpha_2$ -agonist, has been shown to lower norepinephrine levels in patients with baroreflex failure and to be helpful in reducing hypertensive episodes [18]. As baroreceptor hypersensitivity may play a part in OHT, clonidine may be a useful drug. Some recent studies have suggested that the new calcium channel blocker azelnidipine has greater effect on baroreflex sensitivity compared to the older analogues like amlodipine [47]. More evidence will be required to see if this could have a noticeable effect on target organ damage. There is also some evidence that patients with OHT tend to tolerate diuretic therapy poorly [9].  $\beta$ -Blockers may potentiate the  $\alpha$ -mediated vasoconstriction leading to decreased pulse pressure, which could be beneficial in patients with orthostatic hypotension, but it is controversial whether  $\beta$ -blockers might accentuate OHT [48, 49].

### Conclusion

OHT is a disorder of postural regulation of BP which results due to overactive SNS and increased sensitivity of chemoreceptors. It may also be a manifestation of rare underlying autonomic, baroreflex, or neurogenic disorders or nephroptosis. The prevalence of this disease process is significant and warrants further testing. Most of the studies consistently point towards an association between OHT and target organ damage. It can be detected most easily by postural recording of BP in the clinic, but for more accurate diagnosis the HUT test or ambulatory BP monitoring is preferred. From the data available so far, it could be used as a screening tool for prognostication for borderline hypertension, diabetes, proteinuria, and kidney disease as well as future autonomic dysfunction. It could also be of value in long-standing hypertensives to assess possible target organ injury, and particularly in the elderly as a marker of CVD and cerebrovascular disease. The treatment options are fairly limited due to a lack of studies based on intervention. Most would agree that all patients once diagnosed with OHT should undergo counseling similar to patients with orthostatic hypotension. The utility of compression grade stocking or anti-gravity suits has yet to be established, but the effect of blunting orthostatic changes is well known and therefore recommended. Pharmacologic intervention with  $\alpha$ -blockers may be of benefit in hypertensive patients with coexisting OHT. However, to date no studies have addressed the issue of targeted treatment of OHT and its potential benefits on morbidity and mortality. Since this entity is still underrecognized and undervalued, further studies are required to ascertain the potential benefits of routine screening for OHT [50] and the target organ damage associated with OHT. Further studies are needed to evaluate the role of OHT in causing end-organ damage.

### Disclosure Statement

The authors have nothing to disclose.



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