

## Orthostatic Hypertension The Last Hemodynamic Frontier

David Robertson, MD

See related article, pp 167–173

Orthostatic hypertension (OHT) is beneath the radar of many health care professionals. In the clinic, it is generally both unexpected and counterintuitive. After recheck, it may sometimes regress toward the mean. However, at other times the OHT can be dramatic and persistent. Nevertheless, our knowledge about its causes and significance remains circumscribed. It is in many ways the last hemodynamic frontier.

Recently, there has been increasing interest in OHT and its possible consequences on health. The spectrum of degree and clinical context of OHT is very broad.<sup>1</sup> In some cases, it can be a dramatic physical manifestation of 50 mm Hg or more in a disorder such as baroreflex failure. In other situations, it may only be an incidental physical finding.

OHT is usually defined as an increase in blood pressure with upright posture or tilt, but precise criteria have not been established. Furthermore, few studies have entailed direct measurement of blood pressure in people with OHT. Such measurements would more faithfully reflect intraarterial pressure and would avoid the introduction of potential artifacts. 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. Therefore, the magnitude of the blood pressure increase after standing might be even larger than is generally reported in patients with OHT.

OHT has been long recognized. Some of the most thoughtful early studies were conducted by David Streeten and colleagues.<sup>2,3</sup> The authors noted that the individuals with OHT had a greater decrease in cardiac output when upright, a greater venous pooling in the lower extremities, and a higher plasma norepinephrine level after standing. Their hypothesis was that excessive venous pooling led to a decrease in cardiac output and that the response to this was increased sympathetic activity and increased DBP. This hypothesis of excessive venous pooling after standing and

decreased cardiac output initially seems paradoxical. Why is there not reduced rather than increased blood pressure in this circumstance? However, support garments did in fact prevent the OHT during upright posture in the subjects of the study by Streeten and colleagues. Perhaps in the OHT patients, central sympathoexcitation is pathologically excessive. This process could occur in a setting of partial dysautonomia involving capacitance vessels or in individuals with pathological dysregulation in brain stem or higher centers engaged in autonomic control. Why some patients experience orthostatic hypotension and others OHT in this circumstance remains unclear.

OHT occurs in some forms of autonomic dysfunction (Table). It occurs in more than 20% of patients with postural tachycardia syndrome (POTS) in our center and may be especially dramatic in patients with mast cell activation disorder, where 38% of patients who meet criteria for both POTS and disordered mast cell activation had blood pressure elevation after standing. Interestingly, in this “crossover” group of patients, the OHT manifested as either a persistent hypertensive response to upright posture or as a hypertensive crisis with upright BP as high as 240/140.<sup>4</sup>

Patients presenting with acute baroreflex failure experience some of the highest blood pressures encountered in contemporary practice, sometimes with surges of >300 mm Hg.<sup>5</sup> In subsequent days and weeks, the surges moderate, but substantial OHT may continue, although it usually declines somewhat with continued upright posture. In chronic baroreflex failure, labile blood pressure and heart rate track together in response to physical or psychological stress. In a final phase of baroreflex failure, usually months to years after onset, the orthostatic hypertension may be replaced by orthostatic hypotension as the dominant hemodynamic expression.

In the rare syndrome of norepinephrine transporter deficiency, an increase in blood pressure and tachycardia with upright posture is seen.<sup>6</sup>

However, it is not only the dramatic and unusual case of OHT that may be significant. OHT and its potential clinical importance are being recognized in 2 groups of patients with hypertension. The first is elderly patients with essential hypertension. In 1 study, OHT occurred in 11% of 241 elderly Japanese patients with essential hypertension (defined as those whose SBP increased by  $\geq 20$  mm Hg after standing). In this study, the incidence of silent cerebrovascular infarct was higher in patients with OHT than in hypertensives without OHT. Notably, approximately the same proportion of subjects had orthostatic hypotension (23 of 241 patients). These patients were also at increased risk for silent cerebrovascular infarction.<sup>7</sup>

The opinions expressed in this editorial are not necessarily those of the editors or of the American Heart Association.

From the Autonomic Dysfunction Center, Center for Molecular Neuroscience, Departments of Medicine, Pharmacology, and Neurology, Vanderbilt University, Nashville, TN.

Correspondence to David Robertson, Clinical & Translational Research Center, Vanderbilt Institute for Clinical and Translational Research, Elton Yates Professor of Medicine, Pharmacology and Neurology, Vanderbilt University School of Medicine, AA 3228 Medical Center North, 1161 21st Ave South, Nashville, TN 37232-2195. E-mail david.robertson@vanderbilt.edu

(*Hypertension*. 2011;57:158–159.)

© 2011 American Heart Association, Inc.

*Hypertension* is available at <http://hyper.ahajournals.org>  
DOI: 10.1161/HYPERTENSIONAHA.110.163485

**Table. Conditions Associated With OHT**

Chronic primary conditions
Hypertension in elderly
Essential hypertension (“extreme dippers”)
Hypertension with orthostatic blood pooling
Type 2 diabetes mellitus
Peripheral neuropathy
Dysautonomias
Postural tachycardia syndrome
Mast cell activation disorder
Norepinephrine transporter deficiency
Baroreflex failure (early)
Central autonomic dysregulation
Potentially surgically correctable conditions
Pheochromocytoma
Renovascular hypertension
Medullary vascular compression

Some patients with essential hypertension and abnormal diurnal variation in blood pressure (the “extreme dipper” phenotype) exhibit OHT. These patients show a greater than normal decrease in pressure while sleeping. In 1 study,<sup>8</sup> examining the relationship between orthostatic hypertension and diurnal SBP variation, 72% of extreme dippers had OHT, compared with only 11% and 9% of dippers and nondippers, respectively. Extreme dippers have a higher prevalence (53%) of silent cerebrovascular infarction detected by MRI compared with dippers (29%). Moreover, extreme dippers are at increased risk for overt stroke and tend to have a poorer prognosis in the event of a stroke. OHT might have a role in the overall increased risk for stroke in these patients, because two-thirds of strokes in extreme dippers occur in the morning, a time when these patients experience a surge in blood pressure.

Matsubayashi et al<sup>9</sup> reported similar findings relating to orthostatic blood pressure changes and central nervous system changes in a study of 334 elderly Japanese subjects. 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 central nervous system 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 this study is that the study population was a general sample of elderly Japanese subjects, of whom only ≈50% were taking antihypertensive medications.<sup>9</sup> Thus, orthostatic hypertension (and orthostatic hypotension) may be associated with cerebrovascular infarction and with measurable neurocognitive deficits independent of the presence of essential hypertension.

A study this year from China also suggests that OHT is independently associated with target organ damage and

stroke in hypertensive subjects, although this study was limited by its cross-sectional design.<sup>10</sup>

In this issue of *Hypertension*, still more robust data emerge. These data derive from Yatsuya et al<sup>11</sup> in the Atherosclerosis Risk in Communities (ARIC) Study, which had its baseline in 1987 to 1989. It assessed orthostatic BP change within 2 minutes after supine to standing, and the incidence of subsequent stroke through 2007 was examined. The investigators focused on 680 ischemic strokes, classified as lacunar (153), nonlacunar thrombotic (383), and cardioembolic (144), during a mean follow-up of 18.7 years. There was a greater incidence of lacunar stroke in both orthostatic hypotension and orthostatic hypertension. These meticulously collected observations demonstrate that OHT is associated with a greater effect on cardiovascular health than has previously been recognized. Perhaps the time has come to bring emerging investigative strategies to bear on this neglected phenomenon.

### Sources of Funding

Supported by National Institutes of Health grants P01 HL056693, R01 HL071784, U54 NS065736.

### Disclosures

None.

### References

- Fessel J, Robertson D. Orthostatic hypertension: when pressor reflexes overcompensate. *Nat Clin Pract Nephrol*. 2006;2:424–429.
- Streeten DH, Auchincloss JH Jr, Anderson GH Jr, Richardson RL, Thomas FD, Miller JW. Orthostatic hypertension: pathogenetic studies. *Hypertension*. 1985;7:196–203.
- Streeten DH, Anderson GH Jr, Richardson R, Thomas FD. Abnormal orthostatic changes in blood pressure and heart rate in subjects with intact sympathetic nervous function: evidence for excessive venous pooling. *J Lab Clin Med*. 1988;111:326–335.
- Shibao C, Arzubiaga C, Roberts LJ II, Raj S, Black B, Harris P, Biaggioni I. Hyperadrenergic postural tachycardia syndrome in mast cell activation disorders. *Hypertension*. 2005;45:385–390.
- Ketch T, Biaggioni I, Robertson R, Robertson D. Four faces of baroreflex failure: hypertensive crisis, volatile hypertension, orthostatic tachycardia, and malignant vagotonia. *Circulation*. 2002;105:2518–2523.
- Shannon JR, Flattem NL, Jordan J, Jacob G, Black BK, Biaggioni I, Blakely RD, Robertson D. Orthostatic intolerance and tachycardia associated with norepinephrine-transporter deficiency. *N Engl J Med*. 2000;342:541–549.
- Eguchi K, Kario K, Hoshida S, Hoshida Y, Ishikawa J, Morinari M, Hashimoto T, Shimada K. Greater change of orthostatic blood pressure is related to silent cerebral infarct and cardiac overload in hypertensive subjects. *Hypertension Res*. 2004;27:235–241.
- Kario K, Eguchi K, Nakagawa Y, Motai K, Shimada K. Relationship between extreme dippers and orthostatic hypertension in elderly hypertensive patients. *Hypertension*. 1998;31:77–82.
- Matsubayashi K, Okumiya K, Wada T, Osaki Y, Fujisawa M, Doi Y, Ozawa T. Postural dysregulation in systolic blood pressure is associated with worsened scoring on neurobehavioral function tests and leukoaraiosis in the older elderly living in a community. *Stroke*. 1997;28:2169–2173.
- Fan XH, Wang Y, Sun K, Zhang W, Wang H, Wu H, Zhang H, Zhou X, Hui R. Disorders of orthostatic blood pressure response are associated with cardiovascular disease and target organ damage in hypertensive patients. *Am J Hypertens*. 2010;8:829–837.
- Yatsuya H, Folsom AR, Alonso A, Gottesman RF, Rose KM; for the ARIC Study Investigators. Postural changes in blood pressure and incidence of ischemic stroke subtypes: the ARIC study. *Hypertension*. 2011;57:167–173.

## Orthostatic Hypertension: The Last Hemodynamic Frontier David Robertson

*Hypertension*. 2011;57:158-159; originally published online January 3, 2011;  
doi: 10.1161/HYPERTENSIONAHA.110.163485

*Hypertension* is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231  
Copyright © 2011 American Heart Association, Inc. All rights reserved.  
Print ISSN: 0194-911X. Online ISSN: 1524-4563

The online version of this article, along with updated information and services, is located on the  
World Wide Web at:

<http://hyper.ahajournals.org/content/57/2/158>

**Permissions:** Requests for permissions to reproduce figures, tables, or portions of articles originally published in *Hypertension* can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the [Permissions and Rights Question and Answer](#) document.

**Reprints:** Information about reprints can be found online at:  
<http://www.lww.com/reprints>

**Subscriptions:** Information about subscribing to *Hypertension* is online at:  
<http://hyper.ahajournals.org/subscriptions/>