Orthostatic Hypertension
—— A Measure of Blood Pressure Variation for Predicting Cardiovascular Risk ——

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Orthostatic hypertension, a measure of blood pressure (BP) variability, is a clinically important pathologic condition associated with the progression of target organ damage and subsequent cardiovascular risk. Orthostatic hypertension precedes hypertension and could be considered as prehypertension if a patient has seated clinic BP <140/90 mmHg. The simple examination of orthostatic BP changes using a self-measured home BP monitoring, through which abnormal pathological conditions can be detected with high reproducibility without the white-coat effect. Orthostatic hypertension is associated with morning hypertension and increased neurohumoral activation; however, the precise mechanism of orthostatic hypertension remains unclear, and accumulation of further clinical evidence is necessary. (Circ J 2009; 73: 1002–1007)

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Elderly patients with hypertension have various blood pressure (BP) regulation disorders, which are associated with the progression of target organ damage and cardiovascular risk. One of these disorders is orthostatic BP dysregulation. In general, orthostatic BP dysregulation presents as the clinical problem “orthostatic hypotension”. Orthostatic hypotension is well-recognized as a risk factor for falls, syncope, and cardiovascular events. In contrast, “orthostatic hypertension”, which is an increase in BP upon standing, has been infrequently reported. However, studies in recent years have shown that orthostatic hypertension is a new cardiovascular risk factor. This review introduces the latest results on orthostatic hypertension, discusses its present status, and provides a new viewpoint.

Definition and Prevalence of Orthostatic Hypertension

Orthostatic hypotension is generally defined as a decrease in systolic BP (SBP) of at least 20 mmHg upon standing, whereas no consensus has been reached on the definition of orthostatic hypertension. In addition, various examination methods have been used in previous studies for the diagnosis of orthostatic hypotension.

A previous study using the active standing test, in which orthostatic hypotension was defined as an increase (mean of increases after 1 and 2 min) of at least 20 mmHg from the BP in the lying position (mean value of 2 measurements) and orthostatic hypotension as a decrease of at least 20 mmHg, showed incidences of 8.7% and 6.0%, respectively, in general subjects. In the Coronary Artery Risk Development in Young Adults (CARDIA) study, young adults were classified according to SBP changes upon standing into groups with orthostatic hypotension (a decrease >5 mmHg), no BP change (from –5 to +5 mmHg), and orthostatic hypertension (an increase >5 mmHg), and the incidences of orthostatic hypotension and hypertension in 2,781 young adults were 26.6% and 16.2%, respectively.

In another study, orthostatic hypertension was defined as both BP in the lying position <140/90 mmHg and BP after 1-min standing ≥140/90 mmHg, and the incidence of orthostatic hypertension in 277 diabetic patients (12.6%) was significantly higher than that in 110 non-diabetic controls (1.8%).

We performed a 70° head-up tilt (HUT) test for 15 min after a 10-min supine rest. The orthostatic increase in BP (mean SBP from 6 to 10 min after tilting–SBP during 5 min before tilting) was calculated, and SBP increase ≥20 mmHg was defined as orthostatic hypertension and an SBP decrease ≥20 mmHg was defined as orthostatic hypotension.

The incidences of orthostatic hypertension and hypotension in elderly patients with hypertension were 11% and 9.5%, respectively.

New Device for Evaluating Orthostatic BP Dysregulation at Home

Because orthostatic BP changes are markedly affected by the circulating blood volume, their reproducibility is considered to be poor. Therefore, it is optimal to diagnose orthostatic hypertension by performing the orthostatic test more than once. However, in daily clinical practice, the HUT test is difficult to perform frequently. In addition, the results of orthostatic tests performed in medical examinations are modified by the white-coat phenomenon. To overcome these problems, we recently developed an automatic BP monitor for the detection of abnormal BP changes upon standing at home (Figure 1). The monitor automati-
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...cally measures BP twice while seated and in the standing position twice on the same occasion. Therefore, changes in orthostatic BP can be readily performed using this home BP monitor and the device facilitates multiple measurements. Figure 2 shows typical cases of orthostatic hypertension and hypotension detected using this monitor. Abnormal BP changes were detected with high reproducibility. In clinical practice, BP values measured by each patient twice while in the seated and standing positions can be used instead of values obtained by orthostatic tests.

**Mechanism of Orthostatic Hypertension**

The mechanism of orthostatic hypertension is unclear. During HUT tests, changes in neurohumoral factors have been evaluated by my group. The norepinephrine and vasopressin levels after standing were higher in the group with orthostatic hypertension than in the group with orthostatically normal BP (Figure 3). On the other hand, changes in the renin level did not differ between the 2 groups. Because both the level of and response to resin are decreased in...
elderly people, vasopressin may be markedly influenced by changes in humoral distribution upon standing, compensating for the decreased renin.

There is also a possibility that overstimulation of the sympathetic nervous system, particularly α sympathetic nerve activity, upon standing is involved in the pathology of orthostatic hypertension. When doxazosin as an α-patholytic agent was administered to patients with hypertension, hypertensive patients with normal orthostatic BP showed similar decreases in BP on standing and BP in the prone position but no significant changes in orthostatic BP changes, whereas those with orthostatic hypertension showed the disappearance of only the orthostatic BP increase (Figure 4).

**Association With Target Organ Damage**

In my group’s study of elderly patients with hypertension, orthostatic hypertension was a risk for silent cerebral infarcts and advanced deep white matter lesions (Figure 5).

Silent cerebral infarcts detected by brain MRI are often
accompanied by microbleeds, and are a future risk for clinical stroke. A study involving general subjects also showed decreases in cognitive function and activities of daily living, as well as progression of deep white matter lesions, in patients with orthostatic hypotension or hypertension compared with the group with normal orthostatic BP. Other studies have shown progression of cardiovascular remodeling, such as carotid intimal/medial thickening and left ventricular hypertension in patients with orthostatic hypertension in comparison with a group with normal orthostatic BP.

Patients with diabetes mellitus complicated by orthostatic hypotension reportedly show a decrease in vibratory sensation in the lower limbs, an increase in the cardiothoracic ratio, and an increased triglyceride concentration. My group recently performed the Japan Morning Surge-1 (JMS-1) study in patients with early morning hypertension and evaluated orthostatic BP changes in the early morning and before bedtime. The baseline data revealed increases in urinary albumin excretion and plasma levels of B-type natriuretic peptide (BNP: a useful marker of hypertensive heart disease) in patients with orthostatic hypertension independent of BP in the seated position (Figure 6).

**Chronic Kidney Disease (CKD)**

Urinary albumin excretion has attracted attention as a risk for CKD and cardiovascular disease, and, together with the estimated glomerular filtration rate, is an important index of CKD. Concerning the association between urinary albumin excretion and cardiovascular risk, no threshold is considered to be present. Even in the early stage of high-normal albuminuria before microalbuminuria, the risks of progressing to hypertension and experiencing cardiovascular events have been reported to increase.

Among the results of the JMS-1 study, the finding worthy of special mention is the existence of an association between orthostatic hypertension based on BP evaluated at home and not only the risk of microalbuminuria but also the risk of high-normal albuminuria (14.0–29.9 mg/g Cr), even in patients with normoalbuminuria (<30 mg/g Cr). These results suggest that orthostatic hypertension is associated with the risks of developing hypertension and cardiovascular disease, and that CKD is associated with the pathology of early-stage hypertension characterized by slightly enhanced BP responsiveness before an increase in resting BP.
The progression of hypertension is known to accelerate from a certain stage. An increase in BP to 140 mmHg may require 60 years, but an increase from 140 to 180 mmHg may require less than 20 years. This phenomenon can be explained by Folkow’s principle, showing an exponential association between vasoconstriction and vascular resistance.

With the annual progression of organic vasoconstriction at the small vessel level (100–350 μm) as resistance vessels, vascular resistance exponentially increases. When there are no changes in cardiac function, BP also exponentially increases. This small vessel remodeling precedes BP increase at the BP level <140/90 mmHg. Studies in humans have shown small vessel remodeling in all patients with a BP ≥140/90 mmHg. In the young, arteriolar stenosis is observed with high-normal BP.

In general, hypertension is diagnosed based on BP in the seated position at rest. At rest, the constriction of resistance blood vessels is minimal. However, even if the BP at rest is normal, functional vasoconstriction occurs in the early morning and upon standing, or during stress and episodes of sleep apnea, when neurohumoral factors are activated (Figure 7). As the association between vascular contraction and vascular resistance is exponential, the difference in the vascular resistance between those with small vessel remodeling and those without remodeling is greater under stress conditions than in the resting condition. Therefore, in patients with advanced remodeling of small blood vessels, the increase in BP would be greater. Indeed, studies in humans have shown a positive correlation between an increase in the morning surge of BP and an increase in the media/lumen ratio or arterioles evaluated in biopsy specimens as a gold standard parameter for the evaluation of small vessel remodeling.

Based on these findings, I consider that a prehypertensive state characterized by progression in small vessel remodeling is present in patients with early morning hypertension, sleep apnea-induced nocturnal hypertension, workplace stress-induced hypertension or orthostatic hypertension in whom the clinic BP is normal at rest, but increases with high reproducibility during the time period showing enhanced vascular constriction (Figure 8). These conditions may be the phenotypes of masked hypertension in which in-office BP is <140/90 mmHg and out-of-office BP ≥135/85 mmHg. These BP surges create a vicious cycle leading to the progression of vascular damage. In the development of hypertension, a genetic predisposition, the intrauterine environment, community/family characteristics during infancy, gustatory preferences formed during this process, aging, obesity/metabolic factors, and CKD may be involved.

Indeed, a follow-up study has shown that orthostatic hypertension is a risk factor for the development of hypertension in the future. The incidence of hypertension over 8 years in 2,781 young adults who participated in the CARDIA study was the highest in the group with orthostatic hypertension and the lowest in the group without orthostatic BP changes (12.4% vs 6.8%, P=0.001), and intermediate in the group with orthostatic hypotension (8.4%). The risk (odds ratio) of hypertension after correction in the group with orthostatic hypertension as compared with the group without BP changes was 2.85 in black males, 2.17 in white males, 2.47 in black females, and 4.74 in white females. These results suggest that orthostatic hypertension reflects enhanced sympathetic activity and arteriolar remodeling and is a risk for the development of hypertension in the future.
Orthostatic BP Dysregulation and Abnormal Diurnal BP Variation

We previously reported that extreme BP dippers with marked nocturnal BP fall and nocturnal BP risers with higher sleep BP than daytime BP often have silent cerebral infarcts and ischemic lesions in deep white matter as complications, and run a high risk of clinical stroke in the future. These abnormal diurnal BP variations are associated with other BP dysregulation. Extreme dippers often have orthostatic hypertension while risers often exhibit orthostatic hypotension (Figure 9). In extreme dippers, because the nocturnal BP decreases, the increase from night to the early morning (ie, the BP morning surge) is marked and, indeed, the extreme-dipper group considerably overlaps with the marked morning surge group in elderly patients with hypertension. In patients with orthostatic hypertension, BP in the early morning is high, which may be associated with the increase in BP from the lying to the standing position when arising in the morning.

Clinically, in patients with orthostatic BP changes, even if the BP in the seated position measured in the examination room is normal, masked hypertension in which the BP is increased at other times should be suspected, and the measurement of home or 24-h BP is recommended. It is important not to overlook masked morning hypertension (BP morning surge type) in patients with orthostatic hypertension and masked nocturnal hypertension (non-dipper/riser type) in patients with orthostatic hypotension.

Conclusion

Orthostatic hypertension increases BP variability and is a clinically important pathologic condition associated with progression of target organ damage and future cardiovascular risk, but accumulation of further evidence is necessary. The simple examination of orthostatic BP changes using home BP monitoring, by which abnormal pathological conditions can be detected with high reproducibility without the involvement of the white-coat phenomenon, is recommended as a new practical examination of autonomic dysfunction.

References