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COMMENT

Home blood pressure variability and target organ damage

Takashi Hisamatsu[1] · Takayoshi Ohkubo[2]

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High blood pressure (BP) is one of the most important modifiable risk factors for cardiovascular disease (CVD). The prevalence of elevated BP remains high, and the greatest absolute burden of elevated BP is especially found in the East Asian and Pacific regions [1]. Recent international hypertension management guidelines confer increasing weight to methods of measuring BP outside the medical office (e.g., self-measurement at home) to assess CVD risk [2]. The major advantage of out-of-office BP measurement is that it provides a large number of BP measurements with minimization of the white-coat effect and observer bias, facilitating highly reliable assessment of actual BP [3]. In fact, several studies have shown that BP self-measured at home is more strongly associated with CVD risk than BP measured in the office setting [3]. Independent of the mean BP, higher day-to-day variability in home BP has also been shown to be associated with CVD risk [4, 5].

Experimental studies have suggested that enhanced BP variability, even in the absence of hypertension, can induce arterial remodeling (including vascular smooth muscle cell proliferation and extracellular matrix deposition) and can also lead to increased oscillatory shear stress on the vascular wall, promoting endothelial dysfunction [6]. BP instability may also reflect abnormal autonomic function and environmental and behavioral factors [7]. Increased sympathetic activity may directly accelerate the development of arterial damage [7]. These factors can consequently contribute to the development of atherosclerosis across multiple vascular beds and related organ systems.

✉ Takashi Hisamatsu
hisamatsu@okayama-u.ac.jp

[1] Department of Public Health, Okayama University Graduate School of Medicine, Dentistry and Pharmaceutical Sciences, Okayama, Japan

[2] Department of Hygiene and Public Health, Teikyo University School of Medicine, Tokyo, Japan

In this issue of *Hypertension Research*, Kubozono, et al. [8] present a cross-sectional observational study of 315 community-dwelling older Japanese (mean age of 70 years) to assess the association of day-to-day BP variability derived from self-measured BP across 1 month with multiple target organ damages (TODs), including cardiac dysfunction (N-terminal pro B-type natriuretic peptide [NT-pro BNP] and high-sensitivity troponin T), hepatic dysfunction (Fibrosis-4 index), and renal dysfunction (estimated glomerular filtration rate [eGFR]). Kubozono, et al. [8] found that independent of the mean BP, higher day-to-day BP variability was associated with a higher NT-pro BNP concentration and Fibrosis-4 index and a lower eGFR. This is one of the first studies on home BP variability to evaluate the association with multiple TODs within the same persons from a general population. Similarly, we also reported that higher day-to-day variability in home BP was independently associated with a greater burden of subclinical atherosclerosis in the carotid (carotid intima-media thickness), aortic (aortic artery calcification), and peripheral (ankle-brachial index) arteries within the same middle-aged to older individuals ($n = 1033$; mean age, 64 years) from a population-based cohort [9]. Several markers of TOD, including higher left ventricular mass in patients with untreated hypertension [10], macroalbuminuria in patients with diabetes [11], and cognitive decline or dementia in community-dwelling participants [12, 13], showed an independent association with day-to-day home BP variability. Thus, several studies have indicated an effect of higher day-to-day variability in BP measured at home on a greater burden of multiple TODs (Fig. 1).

The finding by Kubozono, et al. [8] supports the first report, from the Ohasama Study, of the effect of home BP variability on NT-pro BNP [14]. Furthermore, interestingly, Kubozono, et al. [8] demonstrated an association of day-to-day variability in home BP with the Fibrosis-4 index. The Fibrosis-4 index is a simple, noninvasive scoring method for the detection of liver impairment and liver fibrosis [15]. In particular, this method has been validated for the evaluation of liver fibrosis in patients with liver diseases of various

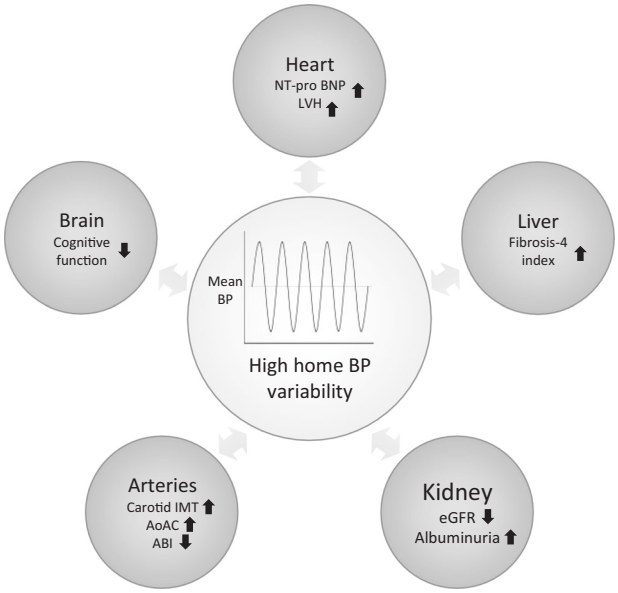

Fig. 1 Home blood pressure variability and multiple target organ damage. ABI ankle-brachial index, AoAC aortic artery calcification, BP blood pressure, eGFR estimated glomerular filtration rate, IMT intima-media thickness, LVH left ventricular hypertrophy, NT-pro BNP N-terminal pro B-type natriuretic peptide

etiologies, including nonalcoholic fatty liver disease (NAFLD) and chronic hepatitis C virus infection [15]. The underlying mechanism of the association between home BP variability and liver fibrosis remains unclear. One possible explanation is that unfavorable cardiovascular risk factor profiles, such as obesity, diabetes mellitus, hypertension, and dyslipidemia in people with NAFLD, promote arterial stiffening and thus lead to higher BP variability [16]. Another explanation is that given the association between NAFLD and dysfunction of the autonomic nervous system, NAFLD may contribute to higher instability of BP [16]. Therefore, Kubozono, et al. [8] concluded that home BP variability may also be useful as a marker for liver fibrosis.

BP variability and TOD may bidirectionally affect each other. Because the majority of prior studies were cross-sectionally analyzed, whether higher BP variability can cause a higher burden of TOD or vice versa remains unclear because TOD (e.g., cardiac, renal, or liver dysfunction) can also accelerate BP variability. Importantly, however, both higher home BP variability and higher TOD burden were shown to be independent predictors of CVD, which may imply that individuals with higher home BP variability and TOD burden have an increased risk of future CVD.

Several concerns should be addressed in future research on BP variability. First, BP variability is a complex phenomenon that can be classified into various types: ambulatory (short-term [24 h]), self-measured home (day-to-day), and conventionally measured office (visit-to-visit) BP variability. However, which type of BP variability can more accurately predict CVD or TOD remains unknown. Second, there are no standard guidelines to determine the minimum number of BP readings and the optimal intervals between them to reliably estimate BP variability. However, more frequent measurement may be related to better assessment, which could lead to identification of a more precise association with CVD or TOD risk. Third, various indices have been proposed to accurately evaluate BP variability: the standard deviation, coefficient of variation, average real variability, maximum and minimum difference, and variability independent of the mean. Each of these indices of BP variability may have advantages or disadvantages in obtaining a better understanding of its actual relationship with CVD or TOD risk and, consequently, of the potential therapeutic implications. We found similar relationships to multiple TODs between these indices, suggesting that the indices of BP variability may represent the same pathophysiologic background in relation to TODs [9]. Despite the accumulated evidence, the question of which index is more clinically useful remains inconclusive and warrants further investigation. Finally, whether BP variability is an indicator of future CVD or TOD or an interventional target for their prevention remains unclear. Therapeutic interventions are needed to investigate whether and how a higher magnitude of variability in BP should be treated with the purpose of reducing CVD risk. Importantly, it is essential to first evaluate and control the BP levels sufficiently by accurate BP measurement, and this should be followed by assessment of various indicators of BP variability to take actions needed [2].

Compliance with Ethical Standards

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