Beat-to-Beat Blood Pressure Variation and Cardiovascular Organ Injuries in Hypertension

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Epidemiological studies have shown that the risk of cardiovascular diseases such as stroke and coronary artery disease (CAD) increases with increasing levels of blood pressure (BP) over a wide range. This linear relationship can be extended to the normal BP range to as low as 115/75 mmHg. As for the changes in BP with antihypertensive therapy, 10 mmHg reduction in systolic BP is estimated to yield 40% reduction in the incidence of stroke and 20% reduction in the incidence of CAD. In addition to the BP level, a considerable number of recent studies have focused on the effects of BP variation on the development of hypertensive organ injuries and the occurrence of cardiovascular diseases.

There are several types of BP variation according to the length of cycle or period of time. For example, the longest one is the seasonal variation, with BP generally highest in the winter and lowest in the summer. The most abundant information about BP variation regards diurnal changes in BP evaluated by 24-h ambulatory monitoring or home BP measurements, and abnormal patterns such as masked hypertension, including morning surge and non-dipper, have been shown to facilitate cardiovascular organ injuries and events.

Regarding beat-to-beat BP variation, the shortest time change in arterial pressure, not as much information is available on the effect on cardiovascular organ and tissue injuries. However, it has been reported that the beat-to-beat BP variation evaluated by tonometry (Finapres) shows a relationship with left ventricular mass index and urinary albumin excretion in hypertensive patients. Regarding the prognosis of patients with cardiovascular diseases, higher beat-to-beat BP variation was shown to be associated with the incidences of death and dependency in stroke patients. It has been also observed that the beat-to-beat BP variation is an independent predictor of cardiovascular events.

Figure. Outline of the renin-angiotensin-aldosterone system and the biological actions elicited by its components. ACE, angiotensin-converting enzyme.
BP variation showed a significant relationship with cerebral white matter lesions and carotid artery intima-media thickness in hypertensive patients.\textsuperscript{6,7}

The rats with sinoaortic denervation used in the current study by Aoki et al,\textsuperscript{8} are assumed to be an animal model of increased beat-to-beat BP variation. Sinoaortic denervation impairs the baroreflex sensitivity and thereby augments the beat-to-beat BP variation in the rats. It has been reported that sinoaortic denervation facilitates the development of hypertensive organ injuries in the heart, kidney and small arteries of hypertensive rats without affecting the 24-h mean BP level.\textsuperscript{9} Even in the normotensive rats, sinoaortic denervation has been reported to impair left ventricular diastolic function and promote cardiac remodeling such as left ventricular wall thickening and fibrosis.\textsuperscript{10} Interestingly, this deleterious effect of increased beat-to-beat BP variation has been also shown to affect the function and structure of the right ventricle as well. Therefore, it is speculated that increased beat-to-beat BP variation may injure not only the cardiovascular organs and tissues but also the function of respiratory system, either of which greatly worsens prognosis.

Among the neural and endocrine systems, it is generally considered that the sympathetic nervous activity and the renin-angiotensin-aldosterone (RAA) axis play pivotal roles in the regulation of BP. Figure outlines the components of the RAA system and their relationships. Among these, angiotensin II and aldosterone have prominent biological actions in the regulation of the cardiovascular system. The main actions of angiotensin II are vasoconstriction and promotion of aldosterone secretion by the adrenal cortex. However, basic research has shown that angiotensin II also promotes cardiovascular tissue hypertrophy, increases oxidative stress and elicits inflammation. In addition, aldosterone has been also shown to promote cardiovascular tissue fibrosis, cause endothelial dysfunction and elicit inflammation. The short-term changes in heart rate and BP are largely influenced by the autonomic nervous activity, and the actions of the RAA system take longer time to become apparent. As for the mechanism of the deleterious effects of sinoaortic denervation on the cardiovascular system in addition to the hemodynamic and mechanical changes, it has been reported that the tissue concentration of angiotensin II increased in the heart and the kidney, although plasma angiotensin II was unchanged, in rats after long-term sinoaortic denervation.\textsuperscript{11} It has been also reported that the mineral corticoid receptor is activated in the arterial medial cells and cardiomyocytes of SAD rats.\textsuperscript{12} Thus, it is speculated that short-term changes in BP such as beat-to-beat variation enhances the RAA system in cardiovascular tissues and thereby injures cardiovascular organs such as the heart and the kidney.

The current study further provides information on treating the renal injuries induced by increased BP variation in SAD rats. Namely, a subdepressor dose of an angiotensin II receptor blocker was effective in ameliorating arteriosclerotic and glomerulosclerotic lesions in the kidney of SAD rats. The authors have reported previously that a subdepressor dose of eprelepine, an aldosterone blocker, reduced cardiac hypertrophy, fibrosis and dysfunction in the same animal model.\textsuperscript{12} In addition, β-blockers, which inhibit renin secretion via the β1 adrenergic receptor, have been shown to attenuate short-term BP variation and are expected to alleviate cardiovascular tissue and organ injuries in SAD rats.\textsuperscript{13} Also in a human study, it has been reported that treatment with an angiotensin-converting enzyme inhibitor improved baroreflex sensitivity,\textsuperscript{14} and is expected to reduce short-term BP variation. Thus, inhibition of an enhanced RAA system in the cardiovascular tissue seems an effective therapeutic approach for cardiovascular organ injuries induced by increased short-time BP variation.

It is anticipated that the aged population will further increase in the coming decades, and the management of hypertension in elderly patients will become a subject of growing importance. Generally in elderly patients, baroreflex function is deteriorated and the compliance of cardiovascular system is decreased, both of which augment the BP variation especially in the short term. The experimental and clinical evidence indicates such increases in short-term BP variation facilitate the development of cardiovascular organ injuries. In the treatment of hypertension, it is primarily important to control BP to the optimal level. In addition to this, alleviation of short-term variation may contribute to further protecting the cardiovascular system and improving the prognosis of hypertensive patients, especially in the aged population.

**Disclosures**

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**References**