Ambulatory blood pressure (BP) exhibits significant diurnal variation with modification of various psychological and physical stimulations during daily living. There is a consensus that the average ambulatory BP levels over 24 hours are more closely associated with hypertensive target organ damage and cardiovascular event than clinical BP. In addition, exaggerated ambulatory BP variation may be important in addition to the average BP level. However, results of previous studies that attempted to demonstrate the association between BP variability and cardiovascular disease are inconsistent. Some studies have found that ambulatory BP variability is a significant and independent determinant of target organ damage and poor cardiovascular prognosis, whereas others have not found an independent association. The reason for these inconsistent results is partly the modification of diurnal BP variation. Abnormal diurnal BP variation, such as marked nocturnal BP falls (extreme dippers) or the exaggerated morning BP surge, and reverse diurnal BP variation patterns with higher sleep BP than awake BP (risers) are risks for target organ damage and cardiovascular events. These phenotypes of ambulatory BP variability are associated partly with each other and with 24-hour ambulatory BP variability. Abnormal diurnal BP variability is associated with other relatively shorter BP variability, such as orthostatic BP variabilities in elderly hypertensives.

In this issue, Zakopoulos et al newly introduce time rate of BP variation, which is a measure of speed of BP variation, to evaluate the effect of BP variability components on target organ damage. They found the steeper BP variability, which is greater in hypertensives than in normotensives, is closely associated with increased carotid artery intima-media thickness (CA-IMT) independently of ambulatory BP level, the magnitude of BP variability, and nocturnal BP dipping. This indicates that a steeper rate of BP variability, which more closely triggers shear stress and wall tension, is a potential independent cardiovascular risk in hypertensive patients. Interestingly, they found that a greater rate of BP variability during the morning BP surge (6:00 AM to 10:00 AM) was also associated with increased CA-IMT, independently of the morning BP level. Because baroreceptor sensitivity reduces in the morning, the impact of BP variability and its rate may be more markedly enhanced in the morning than in other periods. The increased morning surge and rate of variability in BP may partly explain the fact that cardiovascular events occur more frequently in the morning. In fact, there are 2 prospective studies to support the possible risk of exaggerated morning BP surge and cardiovascular events independently of 24-hour BP level in hypertensive patients.

Various mechanisms may be involved in the association between BP variability and cardiovascular disease, and the impact of this association may be augmented in the morning. Experimentally, increased BP variability impairs endothelial function by inhibiting NO production and enhances neointimal formation after balloon injury, and may thereby contribute to atherogenesis. Neurohumoral activation, which is increased in those with increased BP variability, may also increase the risk of cardiovascular disease. Increased sympathetic activity, particularly the α-adrenergic component, increases vascular tone in the resistance arteries and may contribute to the morning BP surge. In addition, coronary spasms are more likely to occur in the morning. One mechanism by which the morning BP surge may trigger vascular spasm is by increased shear stress on the vascular wall. An increase in plasma cortisol levels could enhance coronary artery sensitivity to the vasoconstrictor effects of catecholamines. In particular, morning BP surge associated with α-adrenergic activity is closely associated with multiple silent cerebral infarcts in older hypertensive patients. The renin-angiotensin-aldosterone system (RAAS) is also activated in the morning and could contribute to morning BP surge and morning increase in cardiovascular risk. It was demonstrated recently that in addition to circulating factors in the cardiovascular system, the tissue RAAS also exhibits diurnal variation, possibly in relation to a clock gene. In addition to systemic RAAS, morning activation of the tissue RAAS could be suppressed effectively, leading to increased protection against hypertensive target organ damage and cardiovascular events in hypertensive patients.

In addition to augmented mechanical stress on the cardiovascular system (which leads to cardiovascular remodeling), increased variability of blood flow by augmented BP variability increases shear stress on endothelial cells advancing atherosclerosis. Even in healthy subjects, flow-mediated dilatation of the brachial artery was diminished in the early morning when compared with the other periods (later in the morning and in the evening), whereas nonflow-mediated dilatation was comparable in the morning and in the other
periods. The degree of morning endothelial cell dysfunction found in healthy subjects was similar to that found in high-risk patients with cardiovascular risk factors, such as diabetes and hyperlipidemia.

Other contributory changes are thrombophilic tendencies including increased platelet aggregation and an increase in levels of hematocrit and fibrinogen, which leads to increased blood viscosity. Potentiation of these factors is partly triggered by getting out of bed in the morning. Platelets could be activated by high shear stress occurring at stenotic areas of atherosclerotic arteries, morning BP surge per se could trigger increased platelet aggregation in the morning. Plasminogen activator inhibitor-1 (PAI-1), which inhibits tissue-type plasminogen activator leading to impaired fibrinolysis, also shows a morning increase. A clock gene has been identified recently in peripheral tissues, as well as in the central suprachiasmatic nucleus of the brain. PAI-1 production levels are partly regulated by a peripheral clock gene and partly by components of the RAAS system, shown by the infusion of angiotensin II causing an increase in PAI-1 levels. Further experimental studies are necessary to study the synergic effect of BP variability in the morning on hypertensive target organ damage in relation to neurohumoral and cardiovascular risk factors partly regulated by central and peripheral clock genes.

In international guidelines of hypertension management, cardiovascular risk stratification depends on the BP level and the status of the target organ damage. In addition to these 2 major predictors, BP variability may be the possible third axis of risk stratification. Further prospective and interventional studies are necessary to establish the clinical impact of BP variation, particularly in the morning, on target organ damage and cardiovascular events in hypertensive patients. Clinically, in addition to conventional hypertension management, the specific antihypertensive treatment targeting morning hypertension and exaggerated morning BP surge may achieve more beneficial target organ protection and prevention of cardiovascular events.

References

Morning Surge and Variability in Blood Pressure: A New Therapeutic Target?
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