Vascular Damage in Exaggerated Morning Surge in Blood Pressure

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Recent clinical studies demonstrated that an exaggerated morning blood pressure (BP) surge is a risk for cardiovascular events, such as ischemic and hemorrhagic stroke.1–3 Simultaneously, neurohumoral factors and various cardiovascular risk factors are exaggerated in the morning. Although the precise molecular mechanisms remain unclear, exaggerated morning BP surge has been closely associated with other cardiovascular risk factors potentiated in the morning (Figure). The main mechanisms of morning BP surge and associated neurohumoral activation on cardiovascular disease consist of progression of cardiovascular remodeling and atherosclerosis, as well as direct effects of BP surges that may trigger cardiovascular events.

An exaggerated morning BP surge may advance vascular remodeling from the larger arteries to the small resistance vessel through increased mechanical pressure and shear stress of an exaggerated fluctuation of blood flow on the vessel wall. In hypertensive patients, morning BP surge and time of morning BP variability in the morning were significantly correlated with increased carotid intima–media thickness, and these associations were independent of 24-hour BP levels.4 On the other hand, increased stiffness of large arteries increases BP variability through impaired baroreceptor sensitivity. This increase in BP variability is pronounced particularly in the morning, when compared with the other periods,5 leading to cardiac hypertrophy.6 In addition, small artery disease may also be associated with exaggerated morning BP surge. In our previous study on elderly hypertensive patients, silent cerebral infarcts, assessed by brain MRI, were significantly associated with exaggerated morning BP surge.7 This association was prominent between multiple cerebral infarcts and morning BP surge and appeared to depend on α-adrenergic sympathetic activity. The reactivity of morning BP surge depends on the α-adrenergic vasoconstrictor response of small resistance vessel, and it may be closely related to remodeling of the small vessel. Thus, morning BP surge and vascular remodeling of various arterial sizes could form a vicious cycle of cardiovascular risk.

As shown in the Figure, the morning BP surge also seems to have some role in the initial stage and the progression of atherosclerosis. In the model of sinoaortic denervation rat, which exhibits the marked BP variation, the neointimal formation after vascular injury was significantly increased.8 In healthy subjects without atherosclerotic disease, flow-mediated vasodilation, which reflects endothelial function, was reduced early in the morning. Reduced endothelial function could contribute to the high BP reactivity in the morning.9 In addition, because activity of the sympathetic nervous system and renin–angiotensin–aldosterone system is the highest in the morning, the impact of exaggerated BP variability in the morning to lead to endothelial cell damage and subsequent atherosclerosis would be greater than in other periods of the day.

In this issue, Marfella et al10 demonstrated that exaggerated morning surge in BP was significantly associated with vulnerable plaques and stressed the importance of oxidative stress and activation of the ubiquitin–proteasome system as the mechanism of morning BP surge-related plaque instability. Plaques obtained from the group with exaggerated morning BP surge exhibited higher numbers of macrophages and T-lymphocytes and increased expression of HLA-DR antigen than the nonsurge group, while exhibiting less vascular smooth muscle cells and intimal collagen. With higher levels of matrix metalloproteinase-9, the most important enzyme in plaque rupture, their study suggests that exaggerated morning BP surge is associated with plaque instability. These factors were significantly associated with increased oxidative stress and activation of the ubiquitin–proteasome system, which might induce inflammatory reaction through the activation of nuclear factor κB. In addition, hypertensive patients with exaggerated morning BP surge had higher levels of systemic inflammatory markers, such as high-sensitive C-reactive protein and interleukin-6, than those without surge. Morning BP surge-dependent increase in shear stress and increased pressure on vascular walls would increase the level of oxidative stress. In a previous report, reactive oxygen species formation was measured by gated flow cytometry, and hypertensive patients with exaggerated morning BP surge had higher reactive oxygen species formation by mononuclear cells.11

Although the morning BP surge is a physiological phenomenon, in the hypertensive patients, the degree of morning BP surge is exaggerated and is an independent risk for advancing the atherosclerotic process and target organ damage and triggering cardiovascular events. Thus, in addition to strict BP control, antihypertensive therapy targeting the morning BP surge along with plaque-stabilizing strategies using statins, peroxisome proliferator-activated receptor-γ agonists,
and inhibitors of the renin–angiotensin system could achieve more beneficial effect for prevention of cardiovascular disease in high-risk hypertensive patients.

Disclosures
None.

References