Large Blood Pressure Variability and Hypertensive Cardiac Remodeling
—Role of Cardiac Inflammation—

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An increase in short-term blood pressure (BP) variability is a characteristic feature of hypertensive patients, especially in elderly patients. There is increasing evidence that large BP variability aggravates hypertensive target organ damage and is an independent risk factor for the cardiovascular events in elderly hypertensive patients. However, little is known about the underlying mechanism. We have created a rat model of a combination of hypertension and large BP variability by performing sinoaortic denervation (SAD) in spontaneously hypertensive rats (SHRs). SAD aggravates left ventricular (LV)/myocyte hypertrophy and myocardial fibrosis to a greater extent and impairs LV systolic function without changing mean BP in SHR. SAD upregulates cardiac monocyte chemoattractant protein-1 and transforming growth factor-β, and induces macrophage infiltration. Cardiac angiotensinogen expression is increased and the angiotensin II type 1 receptor is activated by SAD. A subpressor dose of angiotensin receptor blocker abolishes SAD-induced inflammatory changes and cardiac remodeling and subsequently prevents systolic dysfunction in SHR+SAD. Accordingly, it is suggested that cardiac inflammation via activation of the cardiac angiotensin II system would play a role in the aggravation of cardiac remodeling and dysfunction in hypertensives with large BP variability. (Circ J 2009; 73: 2198–2203)

Key Words: Angiotensin II; Cardiac fibrosis; Cardiac hypertrophy; Macrophage

Diurnal blood pressure (BP) change, such as nocturnal BP fall, is an established risk for target organ damage and cardiovascular events. Along with diurnal BP change, an increase in short-term BP variability is a characteristic feature of hypertension, especially in the elderly and in patients with carotid atherosclerosis. Among hypertensive patients with similar BP levels, the degree of hypertensive target organ damage is more advanced in patients with larger BP variability. However, little is known about the mechanism whereby a combination of hypertension and large BP variability aggravates target organ damage. In this article, we review the clinical relevance of BP variability in hypertensive patients, and introduce our recent studies showing that chronic cardiac inflammation plays a role in aggravating hypertensive cardiac remodeling in a novel rat model of hypertension and large BP variability.

Short-Term BP Variability and Hypertensive Target Organ Damage

Twenty-four-hour BP varies not only because of a reduction during night sleep (diurnal BP change), but also because of sudden, fast and short-lasting changes (short-term BP variability) that may occur both during the day and, to a lesser extent, during the night. It has been shown that short-term BP variability increases in hypertensive patients as their BP levels increase, when quantified as the standard deviations (SDs) of the BP values recorded intra-arterially in 30-min intervals. Parati et al investigated the incidence and the severity of target organ damage in 108 hypertensive patients. The patients were divided into 5 groups according to the increasing value of their 24-h average mean BP, and the subjects in each group were further subdivided into 2 classes according to whether their intra-half-hour SD of mean BP, ie, short-term BP variability, was below or above the average of SDs of all the study patients. Within each group, although the 2 classes had a similar 24-h mean BP, the incidence and the severity of target organ damage were greater in the class in which short-term BP variability was higher (Figure 1). Palatini et al studied 67 normotensive patients and 171 borderline, 309 mild, 140 moderate and 41 severe hypertensive patients with noninvasive ambulatory BP monitoring. Each patient was assigned a target organ damage score of 0 to 5 on the basis of funduscopic changes and degree of left ventricular (LV) hypertrophy calculated from ECG and chest roentgenogram. An increased daytime BP variability was associated with a higher degree of hypertensive cardiovascular complications. Moreover, a longitudinal study revealed that the degree of target organ damage and echocardiographic LV hypertrophy at a follow-up examination (4–13 years later, mean 7.4 years) depended on the extent of 24-h BP variability at the time of the initial evaluation, independently of the 24-h mean BP, in 73...
patients with essential hypertension. The European Lacidipine Study on Atherosclerosis (ELSA) demonstrated that 24-h BP variability was more strongly associated with carotid intima-media thickness than 24-h systolic BP and 24-h mean pulse pressure in 1,663 hypertensive patients. A recent study has suggested that circulating inflammatory markers are associated with BP variability in hypertensive patients.

**BP Variability as a Cardiovascular Event Risk**

Recent studies have shown that large short-term BP variability is a risk factor for cardiovascular events in elderly hypertensive patients. A sub-analysis of the Syst-Eur trial demonstrated that the risk of stroke in the placebo group increased by 80% for every 5 mmHg increase in night-time systolic BP variability on admission to the trial. It was suggested that large night-time BP variability was an independent risk factor for stroke. Eto et al investigated the clinical significance of the increase of BP variability in 106 elderly hypertensive patients. The prevalence of cardiovascular events, including cerebral infarction and myocardial infarction, was significantly higher in patients with large BP variability than those with normal BP variability (Figure 2). Accordingly, it is suggested that large BP variability not only aggravates hypertensive target organ damage, but is also an independent risk factor for future cardiovascular events in elderly hypertensive patients.

**A Rat Model of a Combination of Hypertension and Large BP Variability**

Very recently, we have proposed a rat model representing a combination of hypertension and large short-term BP variability by performing bilateral sinoaortic denervation (SAD) in spontaneously hypertensive rats (SHRs). Arterial baroreflex is the neural regulatory mechanism used to dampen rapid BP fluctuation. SAD disrupts the afferent pathway of the arterial baroreflex system. This procedure...
includes ablation of the aortic depressor nerve and superior laryngeal nerve, resection of the superior cervical ganglia and cervical sympathetic trunks, and denervation of the aortic and carotid sinus baroreceptors. Sympathetic nerve activity is transiently increased soon after SAD and activation wanes within a couple of weeks. Seven weeks after the SAD operation, and myocardial nor-epinephrine levels were similar in WKY with sham operation (WKY+sham), WKY with SAD (WKY+SAD), SHR with sham operation (SHR+sham) and SHR with SAD (SHR+SAD). The hemodynamic, histological and functional features of these rats were investigated at 7 weeks after the SAD operation. As shown in Figure 3A, SAD exaggerates BP variability to a similar extent without changing the average mean BP in WKY and SHR. Thus, SHR+SAD is considered as a model that represents hypertensive patients with large short-term BP variability, whereas SHR+sham is considered as a model that represents hypertensive patients with normal BP variability.

**SAD-Induced Cardiac Remodeling**

In WKY, SAD induces mild LV hypertrophy associated with modest perivascular fibrosis and little interstitial fibrosis (Figure 3B). SHR+sham shows concentric LV hypertrophy and mild perivascular fibrosis. In SHR, SAD augments LV/myocyte hypertrophy and myocardial fibrosis by not only enhancing perivascular fibrosis, but also inducing massive reparative interstitial fibrosis. SAD induces much greater myocardial fibrosis in SHR than in WKY, whereas
Figure 4. Effects of a subdepressor dose of an angiotensin receptor blocker on myocardial remodeling, macrophage infiltration and left ventricular (LV) function in spontaneously hypertensive rats (SHRs) with or without sinoaortic denervation (SAD). (A) Representative photographs of the whole LV sections and microphotographs (inlets) at 7 weeks after SAD. (B) Pooled data of the effects of an angiotensin receptor blocker on echocardiographic LV fractional shortening at 7 weeks after SAD. (C) Pooled data of the effects of an angiotensin receptor blocker on the number of infiltrated macrophages at 7 weeks after SAD. Bar = 1×SD (n=10 per group).*P<0.05 and **P<0.01, vs SHR + sham. ††P<0.01 vs SHR + SAD. Modified from Kudo et al.17 ARB, angiotensin receptor blocker; SD, standard deviation.

Figure 5. Schematic showing the role of inflammatory changes in the aggravation of myocardial remodeling induced by a combination of hypertension and large blood pressure (BP) variability. MCP-1, monocyte chemoattractant protein-1.
the magnitude of the SAD-induced LV/myocyte hypertrophy is similar in WKY and SHR (Figure 3B). It is noteworthy that echocardiographic fractional shortening is reduced only in SHR+SAD, but not in WKY+SAD and SHR+sham.17 These findings suggest that the superimposition of large BP variability onto hypertension causes massive myocyte damage and loss, which results in reparative fibrosis to replace the damaged myocardium. This may account for the deterioration of LV function in SHR+SAD. It is noteworthy that massive myocardial fibrosis, especially reparative fibrosis, has been shown to be a critical determinant of the deterioration of LV function in hypertensive patients.23

Chronic Cardiac Inflammation Induced by a Combination of Hypertension and Large BP Variability

In WKY, SAD induces mild perivascular macrophage infiltration (Figure 3C). Also, SHR+sham shows mild macrophage infiltration in the perivascular space. In contrast to WKY, SAD causes massive perivascular and interstitial macrophage infiltration in SHR. Myocardial expression levels of monocyte chemotactic protein-1 (MCP-1), a chemokine for monocytes/macrophages, and transforming growth factor-β (TGF-β), a pro-fibroinflammatory cytokine, are similar in WKY+sham and SHR+sham.17 In WKY, SAD upregulates MCP-1 and TGF-β expression. In SHR, SAD induces much greater upregulations of MCP-1 and TGF-β. The circulating levels of norepinephrine, the active form of renin, interleukin-1β and tumor necrosis factor-α are similar in the 4 groups,17 suggesting that the SAD-induced myocardial inflammation is independent of systemic inflammation, sympathetic nerve activation and the systemic renin-angiotensin system (RAS). Interestingly, the time course experiment shows that these inflammatory changes, namely MCP-1 and TGF-β induction and macrophage infiltration, precedes myocardial remodeling in SHR+SAD.17

Role of the Cardiac Angiotensin II System in SAD-Induced Aggravation of Hypertensive Cardiac Remodeling

It is interesting to note that myocardial angiotensinogen expression is upregulated only in SHR+SAD.17 Moreover, the tyrosine phosphorylation level of the angiotensin II type 1 receptor (AT1R), an indicator of the AT1R activation,24 is increased in SHR+SAD compared with SHR+sham. A subdepressor dose of an angiotensin receptor blocker prevents the SAD-induced aggravation of myocardial remodeling (LV/myocyte hypertrophy and myocardial fibrosis) and LV dysfunction in SHR (Figures 4A, B), whereas the magnitude of BP variability is not changed.17 Importantly, the angiotensin receptor blocker not only inhibits the SAD-induced MCP-1 and TGF-β induction,17 but also prevents macrophage infiltration (Figure 4C). Because angiotensinogen induction is inhibited by the angiotensin receptor blocker in SHR+SAD, the angiotensin receptor blocker may block the positive feedback loop between the fibro-inflammatory process and the angiotensin II system. Therefore, it is suggested that the cardiac angiotensin II system may participate in the mechanism whereby large BP variability induces chronic fibroinflammatory changes and subsequently aggravates cardiac remodeling and LV dysfunction in hypertensive hearts (Figure 5).

We have shown that in rats with a supranidal aortic constriction, a rapid BP rise provokes cardiac angiotensin II system-mediated perivascular fibroinflammatory changes, which exerts a role in hypertensive cardiac remodeling.25–29 Thus, it is considered that large BP variability repeatedly provokes abrupt BP rises. A long exposure to repetitive, abrupt BP rises may cause chronic inflammation in SHR+SAD. The precise molecular mechanism whereby the combination of hypertension and large BP variability activates the cardiac angiotensin II system remains to be addressed in future studies.

Conclusions

SHR with SAD is a model of a combination of hypertension and large BP variability without activation of systemic RAS, and systemic and cardiac sympathetic nerve activity. In this context, sympathetic nerve activity is not always increased in hypertensive patients with large BP variability, especially elderly patients.30 Thus, this model can also be considered as a model representing the characteristic features of hypertension in elderly patients. Large BP variability provokes chronic inflammation through the cardiac angiotensin II system, which leads to aggravation of cardiac remodeling and LV function in hypertensive hearts. Angiotensin receptor blocker may inhibit large BP variability-induced aggravation of hypertensive cardiac remodeling independent of its BP-lowering effect. The present study provides a rationale for treatment with RAS inhibitors in hypertensive patients with large BP variability.

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