Editorial Comment

Blood Pressure Variability Reduction and Organ Protection in Hypertension Treatment

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It is estimated that approximately 1 billion individuals worldwide have hypertension, and more than 7 million deaths per year may be attributable to hypertension-induced complications and organ damage (*1*). The mechanisms underlying hypertension are complex and incompletely understood. To better control hypertension-induced end-organ damage, it is important to investigate new and effective targets for therapeutic intervention. Besides blood pressure level itself, recent studies have demonstrated that the spontaneous variation in blood pressure, called blood pressure variability (BPV), is another key determinant of hypertensive end-organ damage.

Clinical trials have demonstrated that, for nearly any level of 24-h mean arterial blood pressure, hypertensive subjects with low 24-h BPV had a significantly lower prevalence and severity of organ damage than those with high BPV (*2*). Furthermore, the cardiovascular complications of hypertension may in fact depend on the degree of 24-h BPV (*3*). Tatasciore *et al*. showed that awake systolic BPV, *via* non-invasive ambulatory blood pressure monitoring, correlates with subclinical target-organ damage that is independent of mean blood pressure level in hypertensive subjects (*4*). In contrast, ambulatory blood pressure levels and BPV are closely associated with carotid artery alteration, as found in the Ohasama study, suggesting that these parameters are independent risk factors and/or predictors of carotid artery alteration (*5*).

Recent experimental studies have provided some important insights into the relationship between BPV and organ damage. Martinka *et al*. found that an elevated frequency of blood pressure rises in mice with high BPV activates mechano-sensitive and autocrine pathways, resulting in cardiac hypertrophy and dysfunction even in the absence of hypertension (*6*). Eto *et al*. showed that increased blood pressure lability, independent of average blood pressure level, impairs endothelial function by inhibiting NO production and enhances neointimal formation after balloon injury, and may thus contribute to atherogenesis (*7*).

Over the past decade, the research group of Su has published a series of systemic studies elucidating the mechanistic relationship between BPV and end-organ damage (reviewed in Su and Miao (*8*)). Their experimental findings led them to propose four possible mechanisms underlying BPV-induced end-organ damage: 1) lesions of arterial endothelial cells, 2) activation of tissue renin-angiotensin system RAS), 3) initiation of inflammation, and 4) augmentation of cardiomyocyte apoptosis (*8–10*). Collectively, their studies suggest that BPV is an independent determinant of end-organ damage and hence may become an important target for therapeutic interventions (Fig. 1). In the treatment of hypertension, antihypertensive drugs often decrease both blood pressure level and BPV. Therefore, a key question is whether or not the reduction of BPV comes from the effect of blood pressure reduction. To this end, Su *et al*. have demonstrated that BPV reduction is not necessarily associated with decreased blood pressure during treatment (*8*, *11*). Moreover, their studies suggest that a number of commonly used antihypertensive drugs affect BPV reduction, the most effective of which are those acting on arterial baroreflex and calcium channels (*12*).

In this issue of *Hypertension Research*, the same authors

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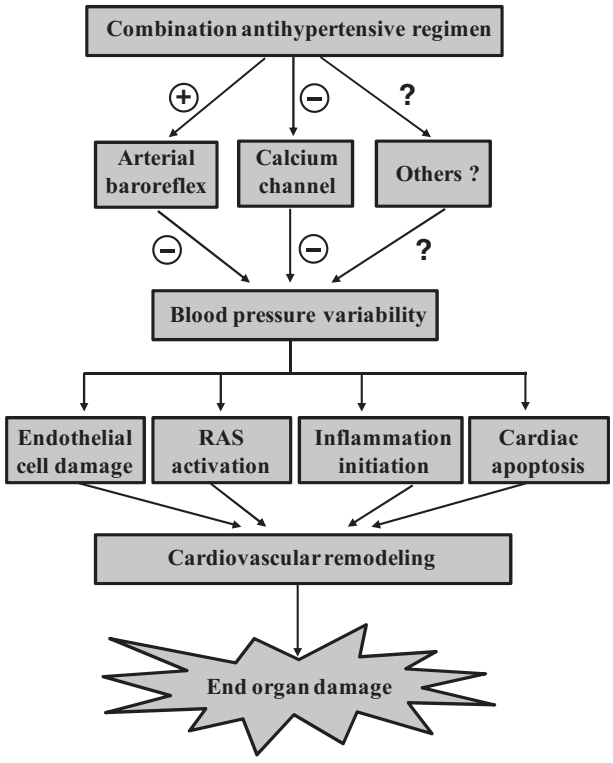

Fig. 1. *Proposed major mechanisms underlying blood pressure variability's induction of end-organ damage in hypertension as depicted in this diagram: 1) lesion of arterial endothelial cells, 2) activation of tissue renin-angiotensin system (RAS), 3) initiation of inflammation, and 4) augmentation of cardiomyocyte apoptosis. Certain combinations of antihypertensive regimens may synergistically reduce blood pressure variability, thereby reducing end-organ damage. ⊕, stimulation; ⊖, inhibition.*

further address the effects of a hydrochlorothiazide-nifedipine combination on hemodynamic parameters and organ protection in spontaneously hypertensive rats (SHR) (*13*). They found that long-term treatment with this combination produces a significant synergistic effect on BPV reduction, baroreflex sensitivity enhancement, and organ protection in SHR. Furthermore, multiple-regression analysis showed that organ protection is most closely associated with the decrease in BPV and/or the increase in baroreflex sensitivity. These results suggest that long-term treatment with a combination of hydrochlorothiazide and nifedipine results in a significant synergistic effect on BPV reduction and organ protection in SHR, and the decrease in BPV may contribute importantly to the observed effect of organ protection. Thus, the study by Xie *et al*. (*13*) in this issue not only provides new evidence but also novel insights into the relationship between BPV and organ damage in hypertension. Although their experimental data reveal that therapeutic intervention has a clear effect on BPV and organ damage in hypertension, these experimental observations need to be validated in hypertensive subjects. Therefore, future studies in humans are warranted to ascertain the clinical impact of BPV on organ damage in hypertension.

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