Renovascular hypertension is the most common cause of secondary hypertension. Although many physicians have encountered cases in which angioplasty for atherosclerotic renal artery stenosis (ARAS) achieved a dramatic reduction in BP, and presumably an eventual reduction in cardiovascular events, recent clinical trials involving percutaneous transluminal renal angioplasty (PTRA) were unable to demonstrate a beneficial clinical effect compared with standard medical antihypertensive therapy.

In an attempt to resolve this discrepancy between the clinical trials and actual clinical practice, Jujo et al. in this issue of the Journal investigate the features of patients with a satisfactory BP response to PTRA using ABPM. They found that, in hypertensive patients with functionally significant ARAS, responders (average decrease in 24-h systolic BP from baseline >10 mmHg at 1 month after PTRA) had higher 24-h, awake and sleep systolic BP, and diminished nocturnal BP fall as assessed by ABPM before PTRA, but there was no significant difference between responders and non-responders in clinic SBP at baseline.

High blood pressure (BP) has been recognized as an important and modifiable risk factor for cardiovascular disease and death. A recent trial investigating whether strict BP control truly reduces the incidence of cardiovascular events clearly showed that a systolic BP target of <120 mmHg resulted in a lower incidence of cardiovascular events than a systolic BP target of <140 mmHg among patients at high risk for cardiovascular events but without diabetes. Many studies have demonstrated that there is a better correlation between organ damage and prognostic values of out-of-clinic BP measurement [ie, ambulatory BP monitoring (ABPM)] and home BP measurement, than between organ damage and office BP measurement in the general population or treated hypertensives. ABPM is used not only in the clinical setting but also in the research field to explore the pathogenesis of cardiovascular disease.

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Division of Cardiovascular Medicine, Department of Medicine, Jichi Medical University School of Medicine, Shimotsuke, Japan
Mailing address: Kazuomi Kario, MD, PhD, FACP, FACC, FAHA, Division of Cardiovascular Medicine, Department of Medicine, Jichi Medical University School of Medicine, 3311-1 Yakushiji, Shimotsuke 329-0498, Japan. E-mail: kkario@jichi.ac.jp
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Importance of ABPM for PTRA

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sham-control group. However, both studies raise the concern that much of the efficacy data on BP reduction might be overinflated by bias, particularly a “regression to the mean.” This phenomenon occurs when a variable such as BP and a corresponding patient group are selected based on the high values of that variable. When patients experiencing higher-than-usual BP are selected, a larger statistical expectation of a fall in BP is observed without any intervention. Although the sham-controlled, double-blind SYMPLICITY HTN-3 trial was designed to mitigate this bias, no significant differences in BP response were observed between the RDN and the sham-group.

On the other hand, the post-hoc-analysis in SYMPLICITY HTN-3 and SYMPLICITY HTN-Japan clearly showed that RDN contributed to the reduction in those BP components of ABPM that were most related to cardiovascular events, such as morning and sleep BPs. These findings suggest that RDN might continue to contribute to BP reduction and thus cardiovascular protection over a specific period of time.

Thus, for example, in the current study by Jujo et al because “responders” were defined based on ABPM, it would be inevitable that patients with higher ABPM values at baseline would tend to exhibit greater falls in this parameter (ie, regression to the mean). This phenomenon occurs when a variable such as BP and a corresponding patient group are selected based on the high values of that variable. When patients experiencing higher-than-usual BP are selected, a larger statistical expectation of a fall in BP is observed without any intervention. Although the sham-controlled, double-blind SYMPLICITY HTN-3 trial was designed to mitigate this bias, no significant differences in BP response were observed between the RDN and the sham-group. On the other hand, the post-hoc-analysis in SYMPLICITY HTN-3 and SYMPLICITY HTN-Japan clearly showed that RDN contributed to the reduction in those BP components of ABPM that were most related to cardiovascular events, such as morning and sleep BPs. These findings suggest that RDN might continue to contribute to BP reduction and thus cardiovascular protection over a specific period of time.

Physicians should be careful to select appropriate candidates for interventional therapy for hypertension, because there are procedure-related complications, albeit infrequent ones. Therefore, it is important to predict responders to device-based hypertensive therapy. We suggest that out-of-clinic BP measurement using ABPM is among the essential components for assessing potential responders to this therapy.

Although their study was retrospective in nature, the results confirm that evaluation of out-of-clinic BP using ABPM is more important than clinic BP for discriminating the patients whose BP will respond to PTRA.

In renovascular hypertension, reduced renal perfusion pressure resulting from stenosis of the renal artery stimulates renin release by the kidney, which increases circulating levels of angiotensin II (AII) and aldosterone by activating the renin-angiotensin-aldosterone system (RAAS). These hormones increase the circulating volume by enhancing renal reabsorption of sodium and water. In addition, the increased AII causes systemic vasoconstriction and enhances the activation of sympathetic nervous activity. Increased AII also increase sleep BP to compensate for the excretion of sodium from the kidney, based on the observation that natriuresis is BP-dependent, and manifests as diminished nocturnal BP fall with increasing sleep BP. Sympathetic nerve overactivity caused by activation of the RAAS has also been associated with increasing sleep BP, in addition to awake BP, resulting from excessive retention of sodium. PTRA would suppress this pathological mechanism of increasing BP in renovascular hypertension, resulting in an improvement of 24-h BP and diminished nocturnal BP fall as assessed by ABPM (Figure 1). Figure 2 shows the results of ABPM performed before and after PTRA in a patient with refractory hypertension. This case also shows that PTRA reduced 24-h BP, awake BP, and sleep BP, and improved the diminished nocturnal BP fall.

Although device-based hypertensive therapy has the potential to provide an alternative treatment option for patients with resistant hypertension or who are intolerant to antihypertensive medication, its efficacy remains a matter of debate. Percutaneous catheter-based renal denervation (RDN) by radiofrequency ablation of the renal artery nerves is reported to be a promising device-based hypertensive therapy to achieve BP control in resistant hypertension. In initial studies, namely, the SYMPLICITY HTN-1 and HTN-2 trials, RDN achieved an impressive BP reduction, although these studies lacked a sham-control group. However, both studies raise the concern that much of the efficacy data on BP reduction might be overinflated by bias, particularly a “regression to the mean.” This phenomenon occurs when a variable such as BP and a corresponding patient group are selected based on the high values of that variable. When patients experiencing higher-than-usual BP are selected, a larger statistical expectation of a fall in BP is observed without any intervention. Although the sham-controlled, double-blind SYMPLICITY HTN-3 trial was designed to mitigate this bias, no significant differences in BP response were observed between the RDN and the sham-group. On the other hand, the post-hoc-analysis in SYMPLICITY HTN-3 and SYMPLICITY HTN-Japan clearly showed that RDN contributed to the reduction in those BP components of ABPM that were most related to cardiovascular events, such as morning and sleep BPs. These findings suggest that RDN might continue to contribute to BP reduction and thus cardiovascular protection over a specific period of time.

Thus, for example, in the current study by Jujo et al because “responders” were defined based on ABPM, it would be inevitable that patients with higher ABPM values at baseline would tend to exhibit greater falls in this parameter (ie, regression to the mean). In regard to renovascular hypertension, therefore, there is need for a randomized clinical trial comparing the results of PTRA with those of standard medical anti-hypertensive therapy using BP reduction with ABPM. Moreover, it will be important to assess the strategy of using ABPM to target BP reduction over a specific period of time in future studies on interventions for renovascular hypertension.

Physicians should be careful to select appropriate candidates for interventional therapy for hypertension, because there are procedure-related complications, albeit infrequent ones. Therefore, it is important to predict responders to device-based hypertensive therapy. We suggest that out-of-clinic BP measurement using ABPM is among the essential components for assessing potential responders to this therapy.
Disclosures

The authors declared no conflict of interest.

References


