CONTROVERSIES IN HYPERTENSION

Prognosis in Relation to Blood Pressure Variability

Pro Side of the Argument
Kazuomi Kario

It is well known that cardiovascular events occur more frequently in the morning and that blood pressure (BP) levels increase on waking in the morning (morning surge).1,2 In a previous study, we first defined morning BP surge (MBPS) by ambulatory BP monitoring (ABPM), and the results demonstrated that MBPS in elderly hypertensive patients is associated with silent cerebral infarcts defined by brain magnetic resonance imaging and future clinical stroke events independently of age or average 24-hour BP level.3 We also stressed the importance of controlling morning hypertension in clinical practice.1,4,5 Many studies indicate that MBPS is a risk factor for cardiovascular disease, independently of 24-hour BP levels in both hypertensive outpatients and community-dwelling subjects.1,6,7 although a few studies have struck a discordant note.8,9 In this debate article, I demonstrate the evidence that MBPS and related BP variability (BPV) are risk factors for organ damage and cardiovascular events, and I discuss perspectives related to this issue.

Evidence of Cardiovascular Events
The major prospective studies on MBPS in which the number of study subjects was >800 are summarized in Table 1.

JMU-ABPM Study
The first prospective study was our Jichi Medical University School of Medicine (JMU)-ABPM Study.3 We first defined 2 MBPSs by ABPM as follows: (1) a sleep-trough surge defined as morning BP (2-hour average of 4 BP readings taken at 30-minute intervals just after wake-up) minus the lowest nocturnal BP (1-hour average of the 3 BP readings centered on the lowest nighttime reading); and (2) a prewaking surge defined as morning BP minus the prewaking BP (2-hour average of 4 BP readings just before wake-up). The exaggerated MBPS group, defined as the top-tenth percentile of patients with a sleep-trough surge (≥55 mm Hg), exhibited a significantly increased stroke risk even after matching for age, 24-hour BP, and nocturnal BP dipping status. The prewaking surge tended to be associated with stroke risk, although the association was not significant (P=0.07). Among the 519 study subjects, only 5 acute myocardial infarctions (definitive) occurred during the same 42 months period (one in the sleep-trough surge ≥55 mm Hg group and 4 in the sleep-trough surge <55 mm Hg group).

Ohasama Study
In the Ohasama study of a community-dwelling Japanese population, both sleep-trough and prewaking MBPSs were associated with intracranial hemorrhage.6

IDACO
The results of the large International Database on Ambulatory Blood Pressure in Relation to Cardiovascular Outcome (IDACO) study of 8 populations (n=5645) indicated that individuals with sleep-trough MBPS or prewaking MBPS values in the top-tenth percentile were at high risk of mortality and total cardiovascular events (only for cardiac events), even after controlling for covariates, including age and 24-hour BP.7

PIUMA Study
In the Progetto Ipertensione Umbria Monitoraggio Ambulatoriale (PIUMA) Study of a cohort of 3012 initially untreated hypertensive patients, the top-tenth percentile of sleep-trough MBPS was not associated with the cardiovascular prognosis. In addition, blunted MBPS (the lowest quartile,
In the linear model of a recent meta-analysis, although some of the negative studies were not included because of the lack of data, a 10-mm Hg increase in MBPS was associated with an 11% increased risk of stroke.\(^8\) In a recent prospective study of medicated elderly hypertensives, mildly exaggerated MBPS (tertile, >23 mm Hg systolic) was a risk only for dippers, and the nondippers were at higher stroke risk with or without MBPS.\(^1\)

**Interpretation of Discrepancy**

As shown earlier, there are discrepancies in the findings regarding the clinical relevance of MBPS among the previous studies. Several explanations are presented below.

**Definition of MBPS**

There is no consensus on the definition or threshold of MBPS.\(^5\) We first defined sleep-trough MBPS and prewaking MBPS by ABPM because we wanted to detect conceptually the different dynamic and phasic components of ambulatory MBPS, aiming to minimize the effect of 24-hour diurnal BP rhythm.\(^3\) Some definitions of MBPS used the average of nocturnal BP values during sleep.\(^12\) When we use this definition, half of the BP measure is the same as that used for the definition of nocturnal BP dipping.

However, there remains a significant association between MBPS and 24-hour BPV, especially with nocturnal BP dipping.\(^3,5,8,9\) The positive association between MBPS and cardiovascular prognosis disappeared in the PAMELA study after adjustment for components of 24-hour BPV.\(^3\) In the PIUMA study, blunted MBPS was associated with cardiovascular risk after adjustment for nocturnal BP dipping.\(^8\) The adjustment of nocturnal BP dipping status may have overcompensated for the effect of MBPS. In fact, similarly, a study of patients referred for ABPM showed that an increased MBPS was significantly associated with decreased mortality, especially among nondippers.\(^13\)

However, the JMU-ABPM study,\(^7\) the Ohasama study,\(^6\) and IDACO\(^7\) demonstrated the remaining significant positive associations between exaggerated MBPS and cardiovascular risk even after controlling for the covariates, including nocturnal BP dipping.

**New Measures of MBPS**

Although sleep-trough and prewaking MBPSs are defined based on the BP difference, theoretically the speed of the surge (ie, the slope of increase in morning BP against time) may be a better indicator of the risk of morning surge.\(^14\) A recently proposed measure of MBPS, derived by the product of the rate of morning surge and the amplitude (day–night difference), giving an effective power of MBPS, may better clarify the cardiovascular risk in the morning.\(^15\) In addition, as the magnitude of MBPS is significantly associated with the physical activity in the hours after arising,\(^3\) morning BP reactivity (ie, the slope of degree of MBPS against physical activity) may reflect the characteristics of individual cardiovascular properties in the morning. In fact, in a community-dwelling sample, exaggerated morning BP reactivity was associated with left ventricular hypertrophy.\(^16\) Analyses using these new measures may detect the risk of MBPS more precisely.

---

**Table 1. Five Major Prospective Studies of Sleep-Trough Morning Surge in Blood Pressure (n>800)**

<table>
<thead>
<tr>
<th>Variable</th>
<th>JMU-ABPM</th>
<th>Ohasama</th>
<th>IDACO</th>
<th>PIUMA</th>
<th>PAMELA</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>811</td>
<td>1430</td>
<td>5645</td>
<td>3012</td>
<td>2011</td>
</tr>
<tr>
<td>Race</td>
<td>Japanese</td>
<td>Japanese</td>
<td>Various</td>
<td>Italian</td>
<td></td>
</tr>
<tr>
<td>Subjects</td>
<td>HT Pts</td>
<td>Pop</td>
<td>Pop</td>
<td>HT Pts</td>
<td>Pop</td>
</tr>
<tr>
<td>Mean age, y</td>
<td>72</td>
<td>61</td>
<td>53</td>
<td>51</td>
<td>51</td>
</tr>
<tr>
<td>Mean follow-up, y</td>
<td>3.4</td>
<td>10</td>
<td>11</td>
<td>8.4</td>
<td>16</td>
</tr>
<tr>
<td>Hypertensives, %</td>
<td>100</td>
<td>ND</td>
<td>100</td>
<td>ND</td>
<td>ND</td>
</tr>
<tr>
<td>Medication, %</td>
<td>53</td>
<td>27</td>
<td>21</td>
<td>ND*</td>
<td>19</td>
</tr>
<tr>
<td>Threshold of top-tenth</td>
<td>55</td>
<td>40‡</td>
<td>37</td>
<td>44</td>
<td>35–40</td>
</tr>
<tr>
<td>Percentile of MBPS, mm Hg</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Daytime</td>
<td>146</td>
<td>128</td>
<td>130</td>
<td>143</td>
<td>ND</td>
</tr>
<tr>
<td>Night-time</td>
<td>127</td>
<td>112</td>
<td>112</td>
<td>125</td>
<td>ND</td>
</tr>
<tr>
<td>Morning</td>
<td>146</td>
<td>129</td>
<td>126</td>
<td>144</td>
<td>ND</td>
</tr>
<tr>
<td>Night-time trough</td>
<td>113</td>
<td>ND</td>
<td>105</td>
<td>116</td>
<td>ND</td>
</tr>
<tr>
<td>Hazard ratio</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
| All-cause death                 | ND       | ND      | 1.32‡ | 1.00  | 1.19 (1.98§|}
| Cardiovascular death            | ND       | ND      | 1.18  | ND    | 1.24 (2.15¶) |
| Total cardiovascular events     | ND       | ND      | 1.30¶ | 0.98  | ND     |
| Cerebrovascular events          | 2.7‡     | 8.88¶#  | 0.95  | ND    | ND     |
| Cardiac events                  | ND       | ND      | 1.52‡ | ND    | ND     |
| Coronary events                 | ND       | ND      | 1.45¶ | ND    | ND     |

ABPM indicates ambulatory BP monitoring; HR, hazard ratio; HT Pts, hypertensive patients; IDACO, International Database on Ambulatory Blood Pressure in Relation to Cardiovascular Outcome; JMU, Jichi Medical University School of Medicine; MBPS, morning BP surge; ND, not determined; PAMELA, Pressioni Arteriose Monitorate E Loro Associazioni; PIUMA, Progetto Ipertensione Umbria Monitoraggio Ambulatoriale; Pop., population sample; and SBP, systolic blood pressure.

*The most frequently used antihypertensive drugs.
†The 5th Q5.
‡P<0.01.
§P<0.001.
¶Unadjusted.
#HR of intracranial hemorrhage (the 5th Q5 vs. the 2nd Q5).

<19.5 mm Hg) was an independent predictor of cardiovascular events (hazard ratio, 1.66; P<0.01).\(^8\)

**PAMELA Study**

The Pressioni Arteriose Monitorate E Loro Associazioni (PAMELA) study demonstrated that the top-tenth percentile of sleep-trough MBPS was associated with all-causes death and cardiovascular death during 10 years or more of follow-up, whereas prewaking MBPS was not associated with these end points.\(^9\) However, sleep-trough MBPS was related to indices of 24-hour BPV, including those made independently of the magnitude of the day–night BP difference. The significance of the risk disappeared after controlling for these confounders.
Threshold of Pathological MBPS

Differences in the pathological threshold of MBPS may affect the discrepancy in results. The association between BPV and the risk of cardiovascular disease should not be linear. As adequate, MBPS is a physiological circadian phenomenon to adjust to the day–night cycle of the earth, and exaggerated MBPS above some threshold should be pathological, resulting in excessive hemodynamic stress to the vessel.

MBPS increases with aging and with higher BP levels. In the JMU-ABPM study, as the study subjects were all hypertensive and their ages were highest among the studies previous to the present study, the top-tenth percentile of sleep-trough MBPS was the highest (55 mm Hg). In other community-dwelling population studies (Ohasama, IDACO, PAMELA) with a majority of normotensive subjects, the top-tenth percentile was between 35 and 40 mm Hg and was smaller by 15 mm Hg or more than that of the JMU-ABPM study. In the PIUMA study of hypertensive subjects, the top-tenth percentile of MBPS (44 mm Hg) was lower by 11 mm Hg than that of JMU-ABPM study. This may be because of the 21-year difference in the mean age of the patients between the 2 studies. Thus, the threshold of pathological MBPS should be identified in the future.

In contrast, the absence of MBPS or an inverse MBPS may be an inadequate compensation. Thus, both extremes of MBPS—the absence (or a negative value) of MBPS and exaggerated MBPS—may be pathological, resulting in nonlinear J-shaped (or U-shaped) associations with specific upper and lower thresholds between MBPS and cardiovascular events.

Age and Antihypertensives

The risk of MBPS would differ among the different age groups, as well as among patients with different severities of concomitant vascular disease (Table 2). The risk of MBPS would be greater in older patients in whom increased stiffness of the large arteries and remodeling of the small arteries impairs the autoregulation of the blood flow to the target organ.

In addition, the leading mechanism underlying exaggerated MBPS may partly differ among different age groups. Increased cardiac output may predominantly contribute to increased MBPS in younger adults (the cardioreactive type), whereas the age-related increase in reflection wave and impaired baroreceptor sensitivity as a result of increased vascular stiffness may contribute to increased MBPS in older subjects (the vascular stiffness type; Table 2).

Vascular stiffness–related MBPS in the elderly might be more difficult to control than in younger hemodynamic MBPS. In the PIUMA study, in which the mean age was much lower than that in the JMU-ABPM subjects (51 versus 72 years), the longer follow-up with antihypertensive medication (mean 8.4 years) in hypertensive patients may have weakened the impact of exaggerated MBPS evaluated under an unmedicated condition at the baseline.

Racial Difference

BPV is closely associated with behavioral patterns. Different lifestyles would affect the degree of MBPS, resulting in different clinical impacts on cardiovascular events. Conflicting results positive for Japanese subjects and not for Italian populations may be based partly on differences in environmental conditions and lifestyles, which may also contribute to different racial demographics of cardiovascular events. In Japan, among medicated hypertensive patients, stroke events are 3x more frequent than myocardial infarction. However, in Westerners, this ratio is the opposite. The degree of MBPS may partly explain this racial difference in the demographics of cardiovascular disease.

Associated Organ Damage and Risk Factors

Independently of clinic and 24-hour BP levels, MBPS is associated with organ damage, such as left ventricular hypertrophy, albuminuria, and large and small artery disease, such as carotid atherosclerosis, arterial stiffness, silent cerebrovascular disease, and reduced coronary flow reserve. Even in well-controlled hypertensive patients with 24-hour BP values <130/80 mm Hg, MBPS was significantly associated with left ventricular hypertrophy and an increase in carotid intima-media thickness.

Hypertensive patients with exaggerated MBPS had increased values of carotid intima-media thickness and urinary catecholamine excretion, as well as higher levels of inflammatory markers, such as C-reactive protein, interleukin-6, interleukin-18 (P<0.001), and uric acid compared with those without MBPS. The association between exaggerated MBPS and vascular inflammation may be a cause–effect association resulting in a vicious cycle.

A thrombotic tendency in the morning augments the morning risk of cardiovascular events. In the JMU-ABPM study, an additive increase in stroke risk was found for MBPS, as well as for increased plasma levels of prothrombin fragment 1+2 and tissue-type plasminogen activator inhibitor-1. In addition, MBPS was associated with increased platelet aggregation in hypertensive patients.

Poor glycemic control and insulin resistance are independently associated with exaggerated MBPS in diabetic patients, which might be significantly associated with endothelial dysfunction.

MBPS and Systemic Hemodynamic Atherothrombotic Syndrome

Concept

The exaggerated MBPS is one of the specific phenotypes of BPV that ABPM detects. We recently proposed a novel disease

Table 2. Age-Related Characteristics of Morning Surge in Blood Pressure

<table>
<thead>
<tr>
<th>Type</th>
<th>Cardiac Reactive-Type</th>
<th>Vascular Stiffness-Type</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>Younger adult</td>
<td>Elderly</td>
</tr>
<tr>
<td>Clinical implication</td>
<td>Prehypertension</td>
<td>Advanced vascular disease</td>
</tr>
<tr>
<td>BP characteristics</td>
<td>Increased heart rate</td>
<td>Systolic hypertension</td>
</tr>
<tr>
<td>Response to treatment</td>
<td>Easy to treat</td>
<td>Difficult to treat</td>
</tr>
<tr>
<td>Day-by-day variability</td>
<td>Stable</td>
<td>Variable</td>
</tr>
<tr>
<td>Morning BP surge</td>
<td>Lower</td>
<td>Higher</td>
</tr>
</tbody>
</table>

BP indicates blood pressure.
entity, systemic hemodynamic atherothrombotic syndrome (SHATS), that is characterized by a vicious cycle between hemodynamic stress and vascular disease and is a risk factor for cardiovascular events and organ damage (Figure 1).

The novel contribution of SHATS is its synergistic consideration of various types of BPV and hemodynamic stress (including high heart rate) in relation to vascular disease.

**MBPS and Related BPV**

Different BP variabilities from short-term (beat-by-beat) to long-term (yearly) are phenotypes of SHATS (Figure 2), and all were associated with organ damage, as well as with the risk of cardiovascular events. These phenotypes of BPV could be detected by repeated measurement of clinic BPs (eg, visit-to-visit), self-measured home BP monitoring (eg, day-by-day, seasonal), and ABPM (eg, MBPS, nocturnal BP dipping). Some of these specific phenotypes of BPV and nonspecific 24-hour BPV are associated with each other. MBPS is associated with nocturnal BP dipping, orthostatic BP dysregulation, and 24-hour BPV. The phenotypes of the extremes of hyper-reactive BPV, such as exaggerated MBPS, extreme dipping of nocturnal BP, and orthostatic hypertension, are closely associated with each other, whereas extreme hyporeactive edges, such as blunted/inverse MBPS, risers of nocturnal BP, and orthostatic hypotension are also closely associated with each other (Figure 3).

**Target Vessels and Organs**

SHATS targets arteries of different sizes and microcirculation–organ interactions. In high-risk patients, advanced vulnerable plaque may be the first target. MBPS triggers plaque rupture by the mechanical stress of BP and shear stress from the exaggerated variability of blood flow, resulting in the onset of cardiovascular events. The small arteries branching perpendicularly from large arteries may be an appropriate second target. These vessels are the so-called strain vessels that are anatomically exposed to high pressure and that must maintain strong vascular tone to provide large pressure gradients from the parent vessels to the capillaries, for example, near the large artery (arcuate artery) and the greater pressure overload in the afferent arterioles of the glomeruli.

The first source of microalbuminuria is the glomeruli near the arcuate arteries. The structure of the strain vessels is also found in the cerebral perforating arteries, the culprit arteries of both cerebral hemorrhage and infarction. In fact, in elderly hypertensive patients, silent cerebral infarcts were more frequently detected by brain magnetic resonance imaging in an exaggerated MBPS group than in a normal MBPS group. An age-related increase in

---

**Figure 1.** Systemic hemodynamic atherothrombotic syndrome (SHATS): acceleration of the cardiovascular risk via a vicious cycle of hemodynamic stress and vascular disease. BNP indicates B-type natriuretic peptide; BP, blood pressure; CAVI, cardio ankle vascular index; FMD, flow-mediated dilatation; MRI, magnetic resonance imaging; PWV, pulse wave velocity; NT-proBNP, N-terminal pro-BNP; and UACR, urinary albumin/creatinine ratio.

**Figure 2.** Information technology (IT)-based assessment of differences in blood pressure variability (BPV) and vascular damage for systemic hemodynamic atherothrombotic syndrome (SHATS). BP indicates blood pressure.
in large-artery stiffness will augment the impact of exaggerated MBPS on cardiovascular events because of diminished attenuation of the pulse transmitted to the peripheral arteries.

**Mechanism of the Vicious Cycle**

MBPS is potentiated by neurohumoral activation, such as that of the sympathetic nervous system or the renin–angiotensin–aldosterone system, in the morning. The overall underlying mechanisms of exaggerated MBPS and SHATS may include impaired neural or vascular components of the baroreflex because of increased central sympathetic activity or decreased carotid dispensability, respectively. 25–27,34

In addition, small-artery remodeling contributes to increases in BPV.25–27 Arterial stiffness and pressure wave reflections are important components of pulsatile hemodynamics. Beat-by-beat BPV in particular is another possible determinant of the vicious cycle of SHATS.

Evidence suggests the clinical relevance of SHATS in organ damage, based on the finding of a synergistic association between BPV and vascular disease.27,35 In our study, delta systolic BP (SBP); the peak SBP minus the lowest SBP over 12 months, a measure of visit-to-visit variability of clinic BP and vascular disease (evaluated by intima-media thickness and the β-stiffness of the carotid artery) had a synergistic impact on cognitive impairment evaluated by the reduction in Mini-Mental State Examination scores in elderly patients.35

**Morning BP as a Therapeutic Target**

There are no solid outcome data showing that targeting MBPS is more beneficial than targeting clinic BP. However, morning BP seems to be the important target of antihypertensive treatment in current clinical practice for the management of hypertension for the reasons listed in Table 3. Our recent large prospective observational study using home BP monitoring demonstrated that home morning BP during treatment is essentially a more important risk factor for cardiovascular events than clinic BP in medicated hypertensive patients.17

In addition, among the various phenotypes of BP variability in SHATS, morning BPV—including MBPS defined by ABPM and home BPV (peak home morning SBP, the standard deviation [SD] of morning SBP, and the morning-evening [ME] difference [morning SBP minus evening SBP]) defined by home BP monitoring—is closely associated with organ damage1,36 and the risk of cardiovascular events.37,38

In the PAMELA study, MBPS was closely associated with nonspecific 24-hour BPV.9 After controlling for nonspecific 24-hour BPV, the impact of MBPS on prognosis was diminished. However, this does not imply that MBPS is less important in clinical practice, because nonspecific BPV could not be a direct therapeutic target of specific antihypertensive medication.

In contrast, morning BP could be a target by specific chronotherapy, such as bed time dosing, resulting in the reduction of MBPS.31,39 The bedtime administration of angiotensin receptor blockers improves microalbuminuria more effectively than morning dosing, especially in patients with morning hypertension.39 An integrated approach targeting morning BP and renin–angiotensin–aldosterone system activation by bedtime dosing of a renin–angiotensin–aldosterone system inhibitor, in combination with statin or antithrombotic agents, may be effective for high-risk hypertensive patients.

Information technology (IT)–based home BP monitoring and evaluation systems in combination with the evaluation of vascular disease may be feasible, and a morning BP–guided antihypertensive strategy would be more effective in clinical practice (Figure 2).

**Conclusions and Perspectives**

BPV is most extensively exaggerated in the morning, and the risk of cardiovascular events is highest in the morning. Night-time BP levels are the most dangerous if elevated, and risers and nondippers have an increased risk, but BP levels seem to be the most important. MBPS would have an additive risk; it could be particularly relevant in extreme dippers and is related to BPV. MBPS should be investigated together with the other patterns of BPV in perspective with the night-time BP level per se and the other patterns of night-time BP in different populations.

The current guidelines for the management of hypertension stress the importance of out-of-office BP, and the BP control status is assessed by the average of clinic, home, or 24-hour BP values. The BP level is the most important; however, even if the average value of BP measures is well below the recommended threshold of target BP level, there is still a blind spot. Namely, an exaggerated MBPS and related BPV still pose the risks of advancing organ damage and triggering cardiovascular events.

**Table 3. Reasons Why Morning Blood Pressure and Surge Are More Important Types of Blood Pressure Variability**

<table>
<thead>
<tr>
<th>Reason</th>
<th>Explanation</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Morning BP and BP variability are measured in the riskiest period of cardiovascular events.</td>
<td></td>
</tr>
<tr>
<td>2. BP variability is most exaggerated in the morning.</td>
<td></td>
</tr>
<tr>
<td>3. Morning potentiation of other risk factors augments the impact of morning BP surge.</td>
<td></td>
</tr>
<tr>
<td>4. Morning BP and surge are associated with organ damage and cardiovascular events, independent of clinic BP.</td>
<td></td>
</tr>
<tr>
<td>5. Morning BP is the blind spot for the current once-daily antihypertensive drugs.</td>
<td></td>
</tr>
</tbody>
</table>

BP indicates blood pressure.
The currently used intermittent BP measurement may underestimate the risk of MBPS and BV. More effective organ protection and the prevention of cardiovascular events would be achieved by the identification of BP phenotypes with which to assess SHATS (especially in high-risk patients with vascular disease), by specific anti-hypertensive medications administered in timed dosing targeting BP peaks, by measures to confer vascular protection, or by neuromodulation with renal denervation or baroreceptor sensitization.

Disclosures

Dr Kario received Research Grant from Novartis, Teijin, and Takeda; Speakers Bureau from Takeda, Mochida, Sumitomo Dainippon Pharma, and Daiichi Sankyo.

References

28. Mitchell GF, van Buchem MA, Sigurdsson S, Gotaal JD, Jonsdottir MK, Kjartannsson O, Garcia M, Aspelund T, Harris TB, Gudmunsdottir V, Launer LJ. Arterial stiffness, pressure and flow pulsatility and brain structure and

Downloaded from http://hyper.ahajournals.org/ by guest on December 14, 2017
Response to Prognosis in Relation to Blood Pressure Variability: Pro Side of the Argument

Kei Asayama, Fang-Fei Wei, Azusa Hara, Tine W. Hansen, Yan Li, Jan A. Staessen

We concur with Dr Kario1 that research on the morning blood pressure surge stood at the cradle of enticing hypotheses on the pathogenesis of acute vascular events that occur at daybreak. However, temporal parallelism between cardiovascular complications and the morning rise in blood pressure does not imply causation, in particular in the light of the manifold physiological processes driving the transition from sleep to wakefulness. As highlighted in our position paper, the morning surge is of little value in the clinical management of patients or in risk stratification. Indeed, this elusive risk indicator has even no standardized definition. Irrespective of its definition, the morning surge is a weak predictor of cardiovascular risk, attaining statistical significance only in the top end of the distribution in large cohorts. The confidence limits for risk stratification in individual patients are too wide to be clinically applicable. Furthermore, the risk associated with the morning surge is confounded by the day-to-night difference in blood pressure level and by the intake of antihypertensive medications. Finally, determining the morning surge reliably requires frequent nighttime readings, which cause discomfort to patients. In conclusion, we support Dr Kario’s viewpoint that the morning blood pressure surge is an interesting instrument in research, but, however, we propose that it has equivocal clinical utility. The message for clinicians is that blood pressure level, not variability, requires treatment, regardless of the period of the day during which blood pressure is elevated.

Reference

Prognosis in Relation to Blood Pressure Variability: Pro Side of the Argument
Kazuomi Kario

Hypertension. 2015;65:1163-1169; originally published online April 27, 2015;
doi: 10.1161/HYPERTENSIONAHA.115.04800

The online version of this article, along with updated information and services, is located on the
World Wide Web at:
http://hyper.ahajournals.org/content/65/6/1163

Data Supplement (unedited) at:
http://hyper.ahajournals.org/content/suppl/2016/04/11/HYPERTENSIONAHA.115.04800.DC1

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published
in Hypertension can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial
Office. Once the online version of the published article for which permission is being requested is located,
click Request Permissions in the middle column of the Web page under Services. Further information about
this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Hypertension is online at:
http://hyper.ahajournals.org//subscriptions/
临床试验- ACS1研究（摘要）

血管紧张素受体拮抗剂和钙通道拮抗剂在亚裔高血压患者中降低睡眠血压作用的年龄相关性差异——ACS1研究

Age-Related Difference in the Sleep Pressure-Lowering Effect Between an Angiotensin II Receptor Blocker and a Calcium Channel Blocker in Asian Hypertensives-The ACS1 Study

Kazuomi Kario, Satoshi Hoshide

李勇 译

睡眠血压水平部分取决于盐敏感性及盐摄入，是高血压患者的一个重要心血管风险。然而，目前尚无研究考察血管紧张素受体拮抗剂（angiotensin II receptor blockers, ARB）和钙通道拮抗剂（calcium channel blockers, CCB）对亚裔人群睡眠血压降低作用的年龄相关差异。阿齐沙坦昼夜节律和睡眠血压（Azilsartan Circadian and Sleep Pressure）第一项研究（ACS1）是一个多中心、随机、开放标签、2个平行组对照研究，比较口服ARB（阿齐沙坦20 mg）或CCB（氨氯地平5 mg）治疗对动态血压监测评估的睡眠血压的疗效。总体上，与阿齐沙坦相比，氨氯地平治疗降低睡眠血压、清醒血压及24小时平均血压的幅度更大。对>60岁的老年高血压患者，氨氯地平降压作用更加显著。在>60岁患者中，氨氯地平治疗后睡眠血压达标率趋向高于阿齐沙坦，但未达到统计学差异。在清醒血压及24小时平均血压的达标率上亦呈相似结果。这些结果提示，氨氯地平降压疗效及血压控制能力优于阿齐沙坦，对老年高血压人群，氨氯地平的降压及血压控制作用均优于阿齐沙坦。正如美国高血压学会（American Society of Hypertension）/国际高血压学会（The International Society of Hypertension），以及美国国立健康和临床优秀研究所（National Institute for Health and Clinical Excellence）等指南推荐，根据年龄选择降压治疗药物时，氨氯地平应作为老年人起始治疗的选择之一。

（Hypertension. 2015;65:729-735.）

高血压的介入治疗（摘要）

一项随机假手术对照试验评估去肾交感神经术对轻度顽固性高血压患者的降压疗效

Randomized Sham-Controlled Trial of Renal Sympathetic Denervation in Mild Resistant Hypertension

Steffen Desch, Thomas Okon, Diana Heinemann, Konrad Kulle, Karoline Röhnert, Melanie Sonnabend, Martin Petzold, Ulrike Müller, Gerhard Schuler, Ingo Eitel, Holger Thiele, Philipp Lurz

孙颖 译 程标 审校

目前关于去肾交感神经术治疗轻度顽固性高血压患者的研究数据较少。轻度顽固性高血压（24小时动态血压监测日间收缩压：135~149，舒张压：90~94 mmHg）患者，按1:1比例随机分为去肾交感神经术组（Symplicity Flex导管，美敦力公司）或假手术组。主要疗效终点为在意向性治疗（intention to treat, ITT）人群中比较两组患者术后6个月时24小时收缩压的变化。共有71例患者参与随机分组。去肾交感神经术组的基线日间收缩压为144.4±4.8 mmHg，假手术对照组为143.0±4.7 mmHg。6个月后ITT分析显示，去肾交感神经术组24小时平均收缩压下降7.0 mmHg（95% CI：-10.8←3.2），假手术组下降3.5 mmHg（95% CI：-6.8←0.2）（P=0.15）；完成治疗方案（per protocol）人群分析显示，去肾交感神经术组24小时平均收缩压下降8.3 mmHg（95%CI：-11.7←5.0），假手术组下降3.5 mmHg（95% CI：-6.8←0.2）（P=0.042）。对于轻度顽固性高血压患者，ITT分析显示去肾交感神经术与假手术组6个月后的24小时收缩压没有显著差异。

（Hypertension. 2015;65:1202-1208.）