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Review Article

Early morning hypertension: what does it contribute to overall cardiovascular risk assessment?

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Abstract

The early morning surge in blood pressure (BP) in patients with hypertension is associated with an increased risk of cardiovascular events, such as myocardial infarction and stroke, especially in the presence of comorbidities of diabetes, cardiac and renal disease. A variety of nonhemodynamic factors contribute to the early morning prothrombotic state, including increased atherothrombotic plaque vulnerability and endovascular shear stress, increased coagulability, platelet aggregation, and blood viscosity, and reduced fibrinolysis. In addition, there is a strong association between morning hypertension and vascular damage throughout the circulation, which may involve the myocardium, large arteries, and other target organs. Because morning hypertension is often unrecognized, the resultant target-organ damage may progress relentlessly. With recent advances in ambulatory BP monitoring and BP self-measurement and the inclusion of antihypertensive agents that target the underlying pathophysiological mechanisms related to the morning BP surge (ie, the sympathetic nervous system and the renin-angiotensin-aldosterone system), control of morning hypertension is clinically feasible and should be an important therapeutic target. J Am Soc Hypertens 2008;2(6): 397–402.

Keywords: Blood pressure surge; cardiovascular events; ambulatory blood pressure monitoring; target-organ damage.

Introduction

Office blood pressure (BP) is typically used as the primary tool for diagnosis of hypertension, for assessment of severity of hypertension in clinical practice, and in current guidelines. However, the circadian rhythm of BP, in particular the rapid surge to peak values shortly after waking, may contribute to cardiovascular events independently of the office BP.[1] Circumstantial evidence for this is provided by a simultaneous peak in such cardiovascular events as myocardial infarction and stroke.[2] Because BP may vary dramatically among individuals, office and even self-measurement of BP may miss patients with dangerously elevated BPs on arising, a phenomenon now recognized as "masked morning hypertension".[3] Although the circadian variability of BP is largely neglected in current guidelines on hypertension treatment,[4–6] recent advances in ambulatory blood pressure monitoring (ABPM) and BP self-measurement at specific times make the assessment of out-of-office values feasible and clinically relevant.[3] This review considers the evidence that control of morning BP should be an important therapeutic target.

Defining Early Morning Hypertension

Morning hypertension typically conforms to one of two patterns (Figure 1), depending on the nocturnal BP profile.[7] The "surge" pattern is characterized by an exaggerated early morning surge and the "nondipper/riser" pattern by effacement or reversal of the normal nocturnal dip in BP. Either profile may be associated with a variety of nonhemodynamic factors that contribute to an early morning prothrombotic state, including increased atherothrombotic plaque vulnerability and endovascular shear stress, increased coagulation, platelet aggregation and blood viscosity, and reduced fibrinolysis. When hypertension first develops, the

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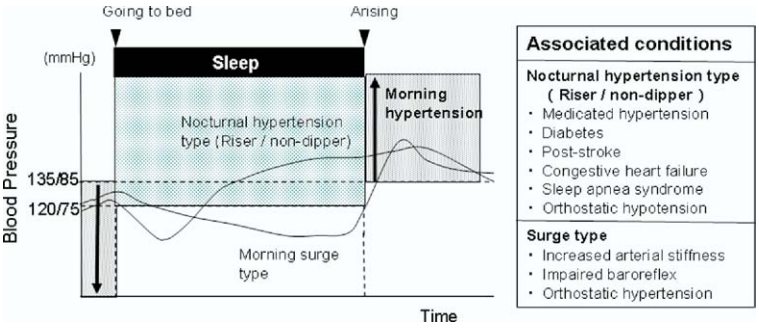

Figure 1. Morning hypertension and diurnal BP variation. Circadian pattern of BP and the 2 types of morning hypertension (nondipper/riser). BP, blood pressure. Modified from Kario K. Time for focus on morning hypertension & pitfall of current antihypertensive medication. Am J Hypertens 2005;18:149–51.[7]

normal circadian BP rhythm is preserved. Later, as target-organ damage compromises the regulation of systemic BP including baroreflex function, the circadian rhythm becomes distorted, with a tendency towards greater variability and excessive morning BP increases. Finally, sleep BP may increase to create a nondipper pattern.

Recently, a large analysis (n = 1,419) of patients with essential hypertension detected a mean BP surge of 29/24 mm Hg, with 60% of patients experiencing a systolic blood pressure (SBP) surge of >25 mm Hg (equating to an increase of approximately 10 mm Hg per hour in the transition from sleep to wakefulness).[8] Patients who smoked and/or drank alcohol, or who were older than 60 years, had a greater surge. Another study found that the early morning BP surge is augmented in cold weather, particularly in elderly subjects, even when treated with multiple antihypertensive drugs.[9] This finding may partly account for the observation that cardiovascular events occur more frequently in the winter than summer in temperate locations.[10]

In addition to physical environmental influences, daily ABPM has demonstrated that the early morning BP surge is substantially greater on Monday than other days of the week.[11] It is noteworthy that cardiovascular deaths are also more common on Mondays.[12] Thus, variations in ambulatory BP appear to parallel the patterns of cardiovascular events not only during the day, but also during the week and with the seasons. Clinical studies, including those of an interventional nature, are needed to clarify the impact of these variations in BP on cardiovascular events in hypertensive patients.

A small increase in the morning BP (eg, <15 mm Hg) seems to be physiological, while an exaggerated surge is pathological and may trigger cardiovascular events, particularly in high-risk hypertensive patients. Evidence-based studies have not fully established a definition of thresholds of the morning BP surge that induces harm. Morning hypertension could reasonably be defined as a high morning BP level >135/85 mm Hg, even if BPs during other times of day (eg, office, evening, and just going to bed) are normotensive as shown in Figure 1.

Morning Hypertension and Target-Organ Damage

Cross-sectional observations of hypertensive patients in Japan and in European countries have demonstrated a strong association between morning hypertension and vascular damage throughout the circulation, including the myocardium, large arteries, and other target organs.

Atherosclerosis and Arterial Stiffness

A high morning BP surge appears to be linked to arterial stiffness. The aortic pulse-wave velocity (an indicator of vascular stiffness) correlates with the early morning BP ($r = 0.434$; $P < .0001$).[13] Furthermore, carotid intima-media thickness (a noninvasive marker of systemic atherosclerosis) is greater in patients with a high early morning BP than those with a lower early morning BP (1.096 mm vs. 0.796 mm; $P = .005$).[14]

Cardiac Remodeling

An exaggerated early morning BP surge is associated with abnormalities in ventricular repolarization, including prolongation and increased dispersion of the corrected QT interval.[15] Conduction abnormalities appear to be connected to effects of excessive morning BP on left ventricular mass index (LVMI). In a study of 23 elderly hypertensive patients, ABPM showed that the magnitude of the SBP surge predicted both LVMI and relative left ventricular (LV) wall thickness ($P < .05$).[16] Similar findings were observed in a study using the average values from 3 months of home BP self-measurement in 297 hypertensive patients treated with amlodipine.[17] Using a stepwise, multivariate regression model to account for 44% of LVMI variability, the most powerful predictor of LV hypertrophy was the difference between morning and evening home SBP ($r^2 = 0.362$; $P < .001$).

A strong correlation has also been detected between morning hypertension and LV hypertrophy in cross-sectional observations of a cohort of hypertensive patients in Bordeaux, France.[18,19] BP measurement triggered manually by the patient upon arising in the morning correlated better with LVMI and LV wall thickness than did the clinic BP (*P*

$< .05$).[18] Using an ABPM device with an integrated position sensor, LV hypertrophy correlated best with the morning SBP surge (mean, 14 mm Hg) independently of the mean 24-hour BP.[19] Similarly, in a study by Polonia et al[13] involving 743 treated and untreated hypertensives, type 2 diabetics, and healthy individuals, a 185-patient subset showed LVMI correlated with the early morning BP at the moment of rising ($r = 0.447$; $P < .0001$) more powerfully than with either the difference between morning and evening BP or the daytime BP variability.

Cerebrovascular Disease

The early morning BP surge may be particularly harmful to the white matter of the brain. In a prospective study, baseline magnetic resonance imaging revealed that early morning BP correlated with cerebral infarction in 519 elderly hypertensive patients with no history of clinically overt stroke or transient ischemic attack.[20] Comparison of patients with an early morning BP surge in the top decile (>55 mm Hg; n = 53) with those in all other deciles combined (n = 466) revealed that multiple cerebral infarctions were more common in those with the largest morning surge (57% vs. 33%; $P < .001$). Follow-up of this cohort also demonstrated a significantly greater risk of future strokes with functional impairment in patients with the top decile of early morning BP surges (19% vs. 7%; $P = .004$).

Cardiovascular Events

Long-term prospective studies have now demonstrated the importance of the early morning BP surge in predicting cardiovascular events. With over 41 months of follow-up, Kario et al[20] found that for each 10 mm Hg increase in baseline early morning SBP surge, the risk of stroke increased by 22% ($P = .008$). The change in BP on rising predicted cardiovascular events ($P < .0001$) independently of age and the average of 24-hour SBP. Another population-based study of 1,430 people with a 10-year follow-up period showed that a large early morning BP surge was associated with the development of hemorrhagic stroke ($P = .04$).[21] During a 92-month follow-up of 507 patients in a cohort in France, 23 cardiovascular events and six deaths occurred in the 253 patients with the highest morning BP surge, compared with eight events and no deaths in those with lower morning BP increases.[19] The associations between the morning BP surge and risk of cardiovascular events were independent of clinic BP or 24-hour BP.

Mechanism of Morning Surge in BP and Associated Cardiovascular Risk

The precise mechanisms that exaggerate the morning BP surge and by which the morning BP surge might increase hypertensive target-organ damage and trigger cardiovascular events in the morning hours is unclear. Morning increases in neurohumoral factors, such as the sympathetic nervous system[22] and the renin-angiotensin system (RAS)[23] may contribute in part to the exaggerated morning BP surge and in turn to its relation to enhanced cardiovascular risk.

Increased sympathetic activity, particularly the alpha-adrenergic component,[24] increases vascular tone in the resistance arteries and may contribute to the morning BP surge. In addition, coronary vasospasm is more likely to occur in the morning. An increase in plasma cortisol levels could enhance coronary artery sensitivity to the vasoconstrictor effects of catecholamine. In fact, morning BP surge associated with alpha-adrenergic activity is closely associated with multiple silent cerebral infarcts in older hypertensive patients.[25]

The RAS is activated in the morning and could contribute to morning BP surge and increases in cardiovascular risk. Recently, it has been demonstrated that, in addition to circulating factors in the cardiovascular system, the tissue RAS also exhibits diurnal variation, possibly in relation to a "clock gene".[26,27] In addition to the reduction in the morning BP level, if morning activation of tissue RAS could be suppressed effectively, it could theoretically lead to increased protection against hypertensive target-organ damage and cardiovascular events in hypertensive patients.

Recently, Tissot et al[28] reported that a vaccine targeting angiotensin II significantly reduced the ambulatory BP throughout a 24-hour period. Of interest, the reduction in the BP was most prominent in the morning hours. This unexpected result implies that both the RAS and its related pressor effect are highly activated in the morning. The morning BP surge-dependent increase in shear stress and the increased pressure on vascular walls is thought to increase oxidative stress that causes an inflammatory reaction through the activation of nuclear factor kappa B.[29] Activation in oxidative stress is also known to be closely affected by tissue RAS. Therefore, the results of this new vaccine therapy targeting angiotensin II indicates that complete 24-hour RAS inhibition may, therefore, be a promising modality for more effectively achieving synergistic cardiovascular protection by the suppression of the morning BP surge and tissue RAS (Figure 2) in addition to lowering the 24-hour BP.

Thrombotic Tendency in the Morning

Prothrombotic tendencies are additively or partly synergistically involved in cardiovascular risk in the morning. Platelet aggregability and determinants of blood viscosity such as hematocrit and fibrinogen are increased in the morning.[30] Sympathetic nervous activity is known to activate platelet aggregability. In addition, as platelets may be directly activated by high shear stress occurring at stenotic areas of atherosclerotic arteries,[31] morning BP surge, per se, could trigger increased platelet aggregation in the morning. The potentiation of these

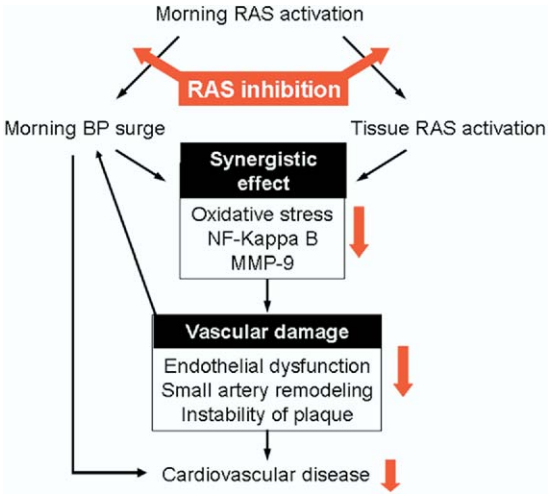

Figure 2. Cardiovascular protection of morning RAS inhibition. MMP-9, matrix metalloproteinase-9; NF-kappa B, nuclear factor kappa B; RAS, renin-angiotensin system.

factors is partly activated by getting out of bed in the morning.[30] One mechanism by which the morning BP surge may generate vascular spasm is by increased mechanical stress (pressure and shear stress) on the vascular wall.

In addition, plasminogen activator inhibitor-1 (PAI-1), which inhibits tissue-type plasminogen activator leading to impaired fibrinolysis, also increases in the early morning period.[32] PAI-1 production levels are regulated, in part, by a peripheral clock gene[33] and by components of the RAS system as demonstrated in studies in which infusion of angiotensin II caused an increase in PAI-1 levels.[34] Presumably, the potentiation of these various stimuli could lead to the development of thrombogenic tendencies in the early morning period.

Should Early Morning Hypertension Be a Therapeutic Target?

Although there are no definitive outcome data relating a specific reduction in early morning BP to declines in early morning cardiovascular events, there are consistent findings that relate the impact of uncontrolled early morning hypertension and clinical outcomes. Thus, therapy aimed at reducing morning hypertension should target the underlying pathophysiological mechanisms associated with the morning BP surge: the sympathetic nervous system[25] and the renin-angiotensin-aldosterone system.[35]

Results with adrenergic-blocking agents suggest varying benefits for reducing the early morning BP surge. In one study, 128 patients with an elevated early morning BP were randomized to once-nightly therapy with either the selective β_1-blocker metoprolol 100 to 200 mg or the nonselective α/β-blocker carvedilol 12.5 to 25 mg.[14] After 12 months, a greater decrease in early morning BP occurred with carvedilol (27.3 vs. 20.2 mm Hg; $P = .001$). Moreover, a higher proportion of patients treated with carvedilol displayed net regression of carotid atherosclerosis with (49% vs. 18%; $P < .01$). In another study, we assessed the impact of targeted treatment of morning BP on microalbuminuria by bedtime administration of alpha-adrenergic blockade with doxazosin, in an open-label multicenter trial involving 611 patients with uncontrolled morning hypertension.[36] The urinary albumin/creatinine ratio (UACR) was significantly reduced in the doxazosin group and was more marked in the patients with microalbuminuria at baseline (−27.9 vs. −8.1 mg/gCr; $P < .001$). The reduction of UACR was significantly associated with the use of doxazosin, the baseline morning BP, and the change in morning BP, and these associations were independent of each other.

The RAS inhibitors that maintain pharmacodynamic effects into the early morning period are likely to have a superior effect on the early morning BP surge.[37] In 76 patients with hypertension treated once daily in the morning with the angiotensin receptor blocker (ARB) valsartan 40 to 160 mg (mean dose: 124 mg/day) or the calcium-channel blocker amlodipine 2.5 to 10 mg (mean dose: 6.4 mg/day), the two agents were similarly effective in reducing clinic and 24-hour mean BP. However, the mean change from baseline in the early morning BP was −6.1 mm Hg for amlodipine, compared with +4.5 mm Hg for valsartan ($P < .02$).[38] The most readily apparent explanation for the observed treatment difference is the pharmacokinetic profiles of the two agents: the half-life of amlodipine (about 34 hours) is substantially longer the value for valsartan (about 9 hours). Similarly, among the angiotensin-converting enzyme (ACE) inhibitors, longer-acting agents, such as trandolapril,[39] appear to reduce the early morning BP more effectively than shorter-acting ones, such as ramipril.[40] Chronopharmacological formulations, such as controlled-onset extended-release verapamil, have also been shown to reduce the early morning BP surge quite effectively.[41]

The evaluation of the effect of renin-angiotensin blocking agents on early morning BP has been evaluated in a pooled analysis of two prospective, randomized, open-label, blinded-endpoint trials comparing the ARB telmisartan 80 mg and the ACE inhibitor ramipril 10 mg.[42] In 1,383 patients meeting inclusion criteria for the pooled analysis of early morning BP surge, the mean change from baseline to endpoint in morning SBP surge was −1.5 (SE, 0.47) mm Hg for telmisartan and +0.3 (0.47) mm Hg for ramipril ($P = .0049$). Of interest, in patients with a baseline morning BP surge in the highest quartile, the changes in systolic early morning BP surge were −12.7 (0.91) mm Hg for telmisartan, compared with −7.8 (1.02) mm Hg for ramipril ($P = .0004$). Similarly, pooled data comparing once-daily treatment with telmisartan 80 mg or valsartan 160 mg showed that telmisartan offers more sustained BP control, especially at the end of the dosing period.[43] Presumably, the pharmacodynamic and pharmacokinetic differences between

these agents convey the differential BP-lowering effects on the early morning BP values. The early morning hour before administration of medications coincides with the end of the dosing period and attenuation of efficacy of antihypertensive therapy when administered once daily.

Conclusion

There are compelling data that demonstrate the clinical relevance of the early morning BP surge in patients with hypertension, especially in the presence of comorbidities of diabetes, cardiac and renal disease.[13] Because morning hypertension is often unrecognized (ie, "masked"), target-organ damage may progress relentlessly. Self-monitoring of BP at home by patients is the most practical means to detect early morning hypertension and should be considered in all hypertensive patients with excessive cardiovascular risk. Management of early morning hypertension should include revision of therapy to include a specific antihypertensive agent that provides an effective pharmacodynamic profile that counteracts neurohumoral mechanisms involved in the morning BP surge, and maintains antihypertensive efficacy throughout the 24-hour dosing cycle.

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