Blood Pressure Variability and Its Management in Hypertensive Patients

Review

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Optimizing treatment for hypertension has focused on reducing cardiovascular risk through reduction of mean blood pressure (BP) under the basic assumption that lower is better, as long as diastolic BP is sufficient to maintain coronary perfusion. However, antihypertensive therapy as currently practiced does not eliminate all hazards associated with BP elevation. Blood pressure variability (BPV) correlates closely with target-organ damage independent of mean BP and transient increases in BP are also triggers of vascular events. So far, there is no definitive outcome data relating specific reduction in BPV to decline cardiovascular events or death. Thus, the decision whether BPV should be considered a new therapeutic target is left to the clinical judgment of physicians and individualized for each patient. However, new evidence suggests that taking an antihypertensive medication at bedtime significantly affects BPV and lowers the risk of cardiovascular events and death. This strategy may provide a means of individualizing treatment of hypertension according to the circadian BPV of each patient and may be a new option to optimize BP control and reduce risk.

Keywords: Hypertension; Blood Pressure; Cardiovascular Diseases; Circadian Rhythm

INTRODUCTION

Hypertension is the most common treatable risk factor for stroke, coronary artery disease, heart failure, chronic kidney disease, and aortic and peripheral arterial disease, accounting for about 50% of risk.[1] The ultimate goal of blood pressure (BP) control is to reduce the incidence of target-organ damage and prevent cardiovascular disease or premature death in hypertensive patients. However, current antihypertensive therapy does not eliminate all hazards associated with hypertension. Rather, it decreases them by approximately one-third, a meaningful, but clearly suboptimal result.[2]

Usual BP, the theoretical true underlying level of blood pressure, is widely considered the main determinant of BP-related vascular risk and of benefit from antihypertensive treatment. The American Heart Association guidelines[3] on measurement BP state that it is generally agreed that conventional clinic readings are a surrogate marker for a patient's true BP and are thought to be the most important component of BP in determining its adverse effects. Like this, clinic BP is used as the primary tool for diagnosis and assessment of hypertension and its severity in clinical practice and in current guidelines. Also, physicians treat hypertension under the basic assumption that lower is better so long as diastolic BP is sufficient to maintain coronary perfusion.

Which component of BP causes vascular events is poorly understood. Mean BP (average of several readings of either systolic or diastolic BP) is clearly important, but other factors, such as variability (variation in BP with time) or instability of BP (transient fluctuations in BP) might also play a part when

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most vascular events occur. According to the current paradigm, however, an effective pharmacological regimen is one that provides continuous, indiscriminate BP reduction throughout 24 hours. The results of the Monitorizacion Ambulatoria para Prediccion de Eventos Cardiovasculares (MAPEC, Ambulatory Blood Pressure Monitoring for Prediction of Cardiovascular Events) study challenge conventional understanding, and have the potential to effect important changes in the management of hypertension.[4]

CIRCADIAN VARIATION OF BLOOD PRESSURE IN NORMAL AND HYPERTENSIVE PATIENTS

The circadian rhythm of BP was ultimately established by Millar-Craig et al.[5] using continuous intra-arterial monitoring. In persons with normal BP or uncomplicated hypertension, BP declines to lowest levels during nighttime sleep (nocturnal dip), rises abruptly with morning awakening (morning surge), and attains near peak or peak values during the first hours of diurnal activity. In the normal dippers, the sleep-time BP mean is lower by 10% to 20% compared to the daytime mean. The timing and amplitude of the natural rhythm of BP is influenced by intrinsic factors (neurohumoral regulation) and the extrinsic factors (physical activity, sleep deprivation or quality, and dietary sodium). Furthermore, behavioral factors (mental activity and emotional status) and lifestyle factors (alcohol drinking and smoking) can also affect the natural rhythm of BP.[6]

When hypertension first develops, the normal circadian BP rhythm is preserved. Later, as target-organ damage compromises the regulation of systemic BP, the circadian rhythm becomes distorted, with a tendency towards greater variability and excessive morning BP surge. Finally, sleep-time BP may increase to produce a non-dipper pattern.[5] Diabetes, post-stroke, congestive heart failure, sleep apnea syndrome, orthostatic hypotension, or medicated hypertension are frequently associated conditions in non-dipper or riser pattern. Otherwise, smoking, alcohol drinking, over 60 years of age, cold weather, increased arterial stiffness, impaired baroreflex, or orthostatic hypertension is associated with a morning BP surge pattern.[7]

CLINICAL IMPLICATIONS OF BLOOD PRESSURE VARIABILITY IN HYPERTENSION

Blood pressure variability (BPV), standard deviation of mean daytime and sleep-time BP, has emerged as a complex phenomenon that includes both short-term (within minutes or hours) and long-term (daily or monthly) BP changes. In individuals with higher than normal BP, the amplitude of BPV is greater than normal and increases progressively with increasing levels of hypertension.[8] The prevalence of non-dipper and riser patterns reached 39% and 14%, respectively and high-risk hypertensive patients showed a remarkably high prevalence of circadian BPV abnormalities in a large cohort of treated hypertensive patients from the Spanish ambulatory blood pressure monitoring registry.[9]

The timing of onset of cardiovascular events strongly parallels the circadian rhythm of BP. Meta-analyses indicate that there is a 40% higher relative risk of acute myocardial infarction, a 29% increased risk of sudden cardiac death, and a 49% higher relative risk of stroke between 6:00 AM and 12:00 PM compared with the rest of the day though only limited data directly link the early morning surge and the incidence of cardiovascular events.[10,11] In one prospective study, for each 10 mm Hg increase in baseline early morning systolic BP, the risk of stroke increased by 24% and the change in BP on rising predicted cardiovascular events independently of age and 24-hour systolic BP mean.[12] However, so far, no clinical trial has been derived to address the relationship between a reduction in the early morning BP and a possible reduction in cardiovascular events.

The non-dipper pattern has been associated with increased risk of cardiac, renal, and vascular target-organ damage compared with the dipper pattern[13] and can be independent of the clinic and 24-hour mean BP values.[14,15] Additionally, patients with hypertension who exhibit a sleep-time BP increase compared with daytime BP have the worst prognosis for stroke and cardiac events.[14] Recently, the MAPEC study[4] found that a 13% decrease in cardiovascular risk was observed for every 5 mm Hg decline in sleep-time BP, and this risk reduction was independent of changes in other aspects of the circadian BP pattern. Also, reduction in the level of BP during sleep and the difference in sleep-waking BP were the most potent predictors of future events.

Rothwell et al.[16] reported that visit-to-visit variability in systolic BP was a powerful predictor of stroke and coronary events independent of mean systolic BP in treated hypertensive patients. Also, they showed that residual variability in systolic BP on treatment had a poor prognosis and stable hypertension had a better prognosis than episodic hypertension. Cross-sectional and longitudinal studies have shown that BPV correlates with vascular events in the general population. The Ohasama study,[14] which examined the prognostic significance of increased BPV in a general population in rural Japan, found that increased systolic BPV and decreased heart rate variability were independent predictors of cardiovascular mortality. Similarly, higher levels of short-term visit-to-visit variability in systolic BP were associated with increased all-cause mortality in population based study of US adults.[17] All these results suggest that BPV has an important role in cardiovascular disease and a potentially important impact on the treatment of hypertension.

STRATEGIES TO REDUCE BLOOD PRESSURE VARIABILITY IN HYPERTENSIVE PATIENTS

Even small reductions in BP for short periods substantially improve cardiovascular outcomes. However, more recent evidence has emphasized the importance of optimal BP control, particularly on patients with high cardiovascular risk because the results are still unsatisfactory: 62% of cerebrovascular disease and 49% of ischemic heart disease can be attributed to suboptimal BP treatment.[18] BPV is not only associated with the severity of target-organ damage but also has a prognostic value for the subsequent target-organ damage in hypertensive patients.[19,20] These findings suggest that buffering the enhanced BPV commonly found in hypertensive patients may be an equally important target of antihypertensive treatment. Optimal BP control requires strategies that lower BP consistently and fully throughout a 24-hour period, maintain the normal circadian pattern of BP, do not increase BPV, and optimize the patient's compliance.[21]

The early morning surge in blood pressure is mediated in part by the sympathetic nervous system and through the renin-angiotensin-aldosterone system (RAAS). Otherwise, pathophysiology leading to a loss of decline in sleep-time BP is probably mediated by RAAS activation and volume excess. Therefore, the pathophysiology of the circadian BPV allows us to consider the potential for blockade of systems leading to this abnormal circadian BP profile.[6]

In 1987, Parati et al.[19] showed that for nearly any level of mean 24-hour BP assessed intra-arterially, subjects with high BP variability had more severe target-organ damage, an observation confirmed by long-term follow-up in the same patients. Moreover, evidence suggests that drug-induced BPV can also be deleterious. Short-acting antihypertensive agents can cause BPV over a 24-hour period due to the intrinsic fluctuation caused by multiple dosing.[21] In this regard, antihypertensive drugs with a short-lasting action or with an enhancing effect on BPV should be avoided. Instead, drugs with long action duration may be useful to this purpose. Control of sleep-time BP and BP during early morning may require agents that have a reasonably long-half life or are administered twice daily.

To produce its maximal effects, a drug must be present in appropriate concentration at its sites of action at the right moment. Modification of the administration timing of many antihypertensive agents may affect the extent of 24-hour BP control and modify circadian rhythm, including the conversion from a non-dipper to dipper profile. The chronotherapy of hypertension takes into account the BP pattern, potential administration-time determinants of the pharmacokinetics, and dynamics of antihypertensive medications, as a means of enhancing beneficial outcomes and reducing or preventing adverse effects.[18] Accordingly, chronotherapy is a cost-effective means of both individualizing and optimizing the treatment of hypertension and constitutes a new option to optimize BP control and reduce risk.

All therapeutic strategies have, in practice, one common element: the administration of antihypertensive medication in a single morning dose (either at the beginning of the diurnal activity or, more commonly, with breakfast), not only with a single prescribed drug, but also with combination therapy. Results from a recent study indicate that up to 89% of treated hypertensive patients take all their medication in a single morning dose.[22] However, this therapeutic approach is theoretically suitable only if all patients have an adequate dipper pattern of BPV and if all prescribed antihypertensive drugs have homogenous efficacy throughout 24-hour.[23] Some antihypertensive agents

recommended for once-daily administration are relatively short-acting, and may not provide efficient BP control for the entire time between doses intervals. This problem cannot be overcome simply by increasing the dose of a short-acting agent to prolong its action, because the patient would be exposed to the risk of an unacceptably low BP during the time of peak drug effect and the resulting BPV over 24-hour would be greatly amplified. In this regards, a hypertensive patient with dipper pattern should, at least a priori, probably be treated using a strategy consisting of a single morning dosing of an antihypertensive medication (alone or in combination) that is known to have a high therapeutic coverage. On the other hand, a hypertensive with non-dipper pattern will need to add a second dose or additional medication at bedtime, or even shift to evening dosing in order to control BP and to normalize the altered 24-hour BP pattern.

OUTCOMES OF NORMALIZATION OF CIRCADIAN BLOOD PRESSURE VARIABILITY

Indeed, normalization of the circadian BP pattern towards a more dipper pattern has already been associated with a significant decrease in plasma fibrinogen, decrease in urinary albumin excretion, better metabolic profile, and better BP control.[23] However, until recently, these strategies have not yet been shown to alter clinical outcomes. The MAPEC study[24] is the first prospective trial to show that bedtime dosing of BP medications lowers the risk of cardiovascular events and death. In this study, patients were enrolled if they had a diagnosis of either untreated hypertension (based on ambulatory BP monitoring criteria) or resistant hypertension (uncontrolled on 3 or more optimally dosed antihypertensive drugs). Patients were randomly assigned to one of 2 time-of-day dosing groups: morning dosing of all their BP medications (n = 1,109) or dosing of one more BP medications at bedtime (n = 1,092). Ambulatory BP monitoring was conducted once a year or more frequently when medication adjustment occurred. Patients were followed for a mean of 5.6 years for the endpoints of cardiovascular events and mortality. Throughout the study, patients in the bedtime dosing group had lower mean sleep-time systolic and diastolic BP, a lower prevalence of non-dipping pattern, and a higher prevalence of controlled ambulatory BP. The bedtime dosing group also had a lower risk of total cardiovascular events (relative risk [RR], 0.39; 95% confidence interval [CI], 0.29 to 0.51), major cardiovascular events (RR, 0.33; 95% CI, 0.19 to 0.55), and fewer overall deaths (4.16/1000 vs. 2.11/1000 patient-years; P = 0.008). A subgroup analysis of patients with type 2 diabetes (n = 448) and with chronic kidney disease (n = 661) had similar results.[25,26]

CHALLENGES TO IMPLEMENTATION

While ambulatory BP monitoring appears to be a better indicator of cardiovascular risk compared with clinic BP monitoring, most physicians still rely on clinic BP for diagnosing and managing hypertension. Furthermore, how ambulatory BP translates to clinic BP is somewhat unclear. Also, morning BP surge, sleep-time BP, and dipper or non-dipper patterns of BP profiles are usually assessed using ambulatory BP monitoring; however, there is no consensus on a single definition or on the threshold of pathological conditions.

Patients who have a long-standing routine of taking their medications in the morning may be resistant to change. Pharmacists and nurses, as well as some physicians, may continue recommending morning dosing, which could be confusing for patients. Despite the potential benefits of conversion of a non-dipper to a dipper pattern, the safety of bedtime drug administration must be clearly established. Bedtime drug administration raises the possibility of nocturnal hypotension, which has been reported to cause both cerebral and myocardial ischemia in susceptible patients. Thus, in the ideal situation, changes in administration time should be followed by repeated ambulatory BP monitoring to assess the effects of therapy and rule out an excessive BP fall during the night.

CONCLUSION

Although BPV is often unrecognized, BPV and BP instability have important roles in the progression of target-organ damage and in triggering of cardiovascular events. Patients with well controlled BP, but high residual variability in systolic BP also have a poor prognosis, despite greater use of add-on drugs. Diagnostic

strategies should take into account the effect of increased BPV and episodic hypertension on vascular risk. The goals of antihypertensive treatment should consider the reduction of both 24-hour mean BP and its variability. Antihypertensive drugs and dosing timing should be chosen to reduce BPV as well as mean BP. Bedtime dosing of BP medications is one way to decrease the prevalence of non-dipper patterns and lowers the risk of cardiovascular events and death in hypertensive patients with or without diabetes or chronic kidney disease. Thus reduction of BPV might represent a new strategy and target for the treatment of hypertension.

CONFLICT OF INTEREST

No potential conflict of interest relevant to this article was reported.

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