REVIEW

Nocturnal blood pressure and cardiovascular disease: a review of recent advances

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The accurate measurement, prediction and treatment of high blood pressure (BP) are essential issues in the management of hypertension. Ambulatory blood pressure monitoring (ABPM) has been shown to be superior to clinic BP measurements as ABPM can provide the following important information: (i) the mean BP levels, (ii) the diurnal variation in BP and (iii) the short-term BP variability. Among these parameters, there is increasing evidence that the mean nocturnal BP level is the most sensitive predictor of cardiovascular morbidity and mortality. Furthermore, several studies have shown that less nocturnal BP dipping, defined as less nocturnal BP decline relative to daytime BP, or a high night–day BP ratio was associated with poor prognosis irrespective of the 24-hour BP levels. These findings can be interpreted in at least two ways: namely, high nocturnal BP or less nocturnal BP dipping might be not only a potent risk factor for cardiovascular disease (CVD), but also a marker of pre-existing or concurrent diseases that can lead to nocturnal BP elevation. In this review, we consider the clinical utility of ABPM and in particular focus on the nocturnal BP levels or nocturnal BP dipping as a potent risk factor for CVD. In addition, the clinical management of high nocturnal BP and blunted nocturnal BP dipping with antihypertensive medications is discussed. *Hypertension Research* (2012) 35, 695–701; doi:10.1038/hr.2012.26; published online 1 March 2012

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INTRODUCTION

The accurate measurement, prediction and treatment of high blood pressure (BP) are essential issues in the management of hypertension. It has already been established that out-of-office BP monitoring by modalities such as ambulatory blood pressure monitoring (ABPM) and home BP monitoring is superior to clinic BP monitoring.^{1–4} In one type of ABPM (Figure 1), the 24-hour BP profile is characterized by considerable variability and marked diurnal BP rhythm. ABPM can provide the following information: (i) the mean BP levels, (ii) the diurnal variation in BP and (iii) the short-term BP variability.⁴ Such information can be assessed separately at specific times (for example, daytime, nighttime, morning hours and while working). This review considers the clinical utility of ABPM. In particular, we focus on nocturnal BP levels and nocturnal BP dipping as a risk factor for cardiovascular disease (CVD).

HOW TO EVALUATE NOCTURNAL BP

Evaluation of nocturnal BP can be achieved only by ABPM. There are a few newly developed, programmed home BP measurement devices (HEM-5041 and HEM-7471C-N, OMRON, Kyoto, Japan) that can measure nocturnal BP automatically,^{5,6} but their predictive power for CVD remains undetermined.

The time frame of nocturnal BP can be determined but with ambiguities. One simple and popular method of determining the

times of waking and sleeping is to assess this information using a sleep diary that includes information about whether the patient had taken daytime naps, which otherwise might contribute to a misclassification of the nocturnal BP dipping status. Another method of defining nocturnal BP is to use either wide (from 2200 to 0600 hours) or narrow (from midnight to 0600 hours), arbitrarily defined, clock-time intervals. The use of narrow-fixed intervals, excluding the transition periods in the morning and nighttime, is an accurate estimate of nocturnal BP.^{7,8}

According to the American Heart Association Council on High Blood Pressure Research, the European Society of Hypertension and the Japanese Society of Hypertension, nocturnal BP is considered within the normal range if the average of nighttime values is lower than 120/70 mmHg, whereas values higher than 125/75 mmHg are deemed abnormal.^{9–11} Currently available ABPM devices are much smaller and easier to use than previous devices;¹² however, compliant use of the devices is not always possible for patients, because it may disturb both their daytime activities and sleep quality. ABPM devices produce tactile and sonorous stimuli during BP measurements, which can cause sleep disturbances in some patients.^{13,14} As sleep deprivation resulting from the repeated cuff-inflate during overnight BP monitoring leads to BP elevation, the clinical implications of high nocturnal BP levels obtained in such cases should be interpreted with caution. In fact, Verdecchia *et al.*¹⁵ suggested that the nocturnal

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Figure 1 Twenty-four-hour blood pressure tracing in a patient with hypertension. The monitors are typically programmed to take readings every 30 min throughout the day and night. BP, blood pressure. A full color version of this figure is available at the *Hypertension Research* journal online.

BP of patients who perceived sleep deprivation of at least 2 h of lost sleep lost its prognostic significance with at least 7 years of follow-up for mortality and also in terms of composite cardiovascular risk. Moreover, Hensken *et al.*¹⁶ also reported that the association between nocturnal BP levels and cardiac hypertrophy tended to be weaker when sleep was subjectively disturbed during overnight BP monitoring. Nevertheless, increasing evidence suggests that nocturnal BP is the more sensitive predictor of CVD outcomes than either daytime or 24-hour BP, and thus nocturnal BP measurement is becoming an important part of clinical practice.^{1–4,17–20}

NOCTURNAL BP AND CARDIOVASCULAR RISK

A recent systematic review of 23 856 hypertensive patients and 9641 subjects from population cohorts from Asia, Europe and South America by Hansen *et al.*²⁰ revealed that nocturnal BP is a significant risk factor for mortality and cardiovascular morbidity in both hypertensive patients and the general population, even when adjustments were made for daytime BP. The hazard ratios associated with each 10-mm Hg increase in nocturnal systolic BP were 1.16 or 1.14 for total mortality and 1.19 or 1.15 for cardiovascular morbidity in hypertensive patients or the general population, respectively (both $P < 0.001$). In contrast, the risk associated with daytime BP was no longer significant after adjustment for nocturnal BP, with the exception of cardiovascular events in the general population. Such differences in the clinical implications of nocturnal BP vs. daytime BP were more prominent in treated hypertensive patients, as shown by another meta-analysis of an International Database on Ambulatory BP in relation to Cardiovascular Outcome (IDACO; $n=7458$, mean age, 57 years), indicating that daytime BP was no longer a significant predictor of cardiovascular events after adjustment for nighttime BP in treated hypertensive patients.¹⁸ Surprisingly, the lower daytime BP was associated with increased risk of total mortality in treated hypertensive patients. These findings indicate that during treatment with antihypertensive medications, it may be necessary to assess nocturnal BP levels rather than daytime BP in order to identify individuals most likely to develop CVD.

Isolated nocturnal hypertension, characterized by BP elevation at night ($\geq 120/70$ mm Hg) and an absence of BP elevation at daytime ($< 135/85$ mm Hg), has attracted recent attention.^{21–23} The prevalence of isolated nocturnal hypertension was 6–10% in the general population, and a relatively higher prevalence was found in South Americans and Japanese than in Europeans. The following characteristics of

patients with isolated nocturnal hypertension were observed, when the patients were compared with normotensives: older, male, obese, higher pulse rate at night, and glucose and lipid abnormalities. Despite the fact that it cannot be detected by office and home BP measurements, this novel clinical entity was associated with target-organ damage and increased total mortality, as well as with all cardiovascular events, when patients were compared with normotensive cases.^{21–23} Further studies are needed to address the benefits of specifically lowering nocturnal BP in patients with isolated nocturnal hypertension.

NOCTURNAL BP DIPPING AND CARDIOVASCULAR RISK

The physiological decrease in nocturnal BP relative to daytime BP is referred to as 'nocturnal BP dipping'. Although arbitrary, a decrease of 10–20% in nocturnal BP relative to daytime BP is considered normal. In 1988, O'Brien *et al.*²⁴ provided the novel concept of 'nondippers' to describe a subgroup of hypertensive patients in whom the nocturnal BP decline was $< 10/5$ mm Hg and the stroke risk was high. Although subsequent investigators have used variable definitions for nondipping, several cross-sectional studies in general populations or hypertensive populations have revealed that cardiac hypertrophy, silent cerebral infarction and microalbuminuria were more common in nondippers than dippers.^{25–27} Furthermore, certain prospective studies have shown that each 5% attenuation in the nocturnal BP decline conferred a $\sim 20\%$ increase in the risk of cardiovascular mortality in the general or hypertensive population.^{18,19,28} Recently, Muxfeldt *et al.*²⁹ revealed that patients without nocturnal dipping in resistant hypertension had twofold higher risk of cardiovascular morbidity and mortality than those with dippers, in which association was independent from office and 24-hour BP level, and other cardiovascular risk factors. However, overall, the prognostic values of nondipping were inconsistent; the reasons may in part be explained by the arbitrary and varying definition of nondipping, poor reproducibility, differences in the study population or differences in the adjusted factors used in each study.^{8,20,30} A systematic review by Hansen *et al.*²⁰ revealed that nondipping was associated with higher total mortality and cardiovascular events in the general population, although it added only 0.1% prognostic value beyond that of the 24-hour BP levels.

The nondipping profile is frequently accompanied by high nocturnal BP. However, these two phenotypes are not always concomitantly present, and therefore the pathophysiological and clinical implications of each may differ. For example, an untreated man whose daytime BP

is 120/70 mmHg and nocturnal BP is 119/68 mmHg could be classified as a nondipper without nocturnal hypertension. One previous report considered this profile as not being associated with excess risk in terms of cardiovascular morbidity and mortality, as the daytime BP is normal.³⁰ In contrast, other reports have concluded that a patient with this profile would be at increased mortality risk, regardless of the patient's 24-hour BP levels.^{17–20,30} The clinical implications of nondipping in the absence of nocturnal hypertension may vary with age, smoking status, presence of antihypertensive drugs and co-morbidities such as diabetes, chronic kidney disease and pre-existing CVD. Nevertheless, the association of nondipping with excess mortality rather than cardiovascular morbidity^{17–21} raises the possibility that nondipping is a marker of pre-existing or concurrent diseases (Figure 2). In particular, reverse dipping (or a 'riser' pattern), that is, a night-to-day BP ratio of 1 or more, consistently shows the poorest outcomes among different types of dipping. Our previous data indicated that among older hypertensive patients ($n=575$, mean age 72 years), subjects with reverse dipping ($n=63$, 11%) had the highest incidence of stroke (22% during 41 months of follow-up), in particular fatal type stroke (Figure 3) and hemorrhagic stroke; the incidence of hemorrhagic stroke was more prominent in the reverse dipping group (29% of stroke events) than in other dipping groups (7.7% of stroke events, $P=0.04$).³¹ The patient characteristics associated with reverse dipping are older, male and lean. In another study of treated older hypertensive patients (mean age, 76 years; $n=148$), blunted nocturnal BP dipping was associated with poor physical function and cognitive dysfunction.³² These data indicate that reverse dipping in older hypertensive patients is an indication of frailty. According to the IDACO database, subjects with reverse dipping had the highest incidence of total mortality (27%), cardiovascular

mortality (11%) and cardiovascular morbidity (25%) during a median follow-up period of 9.6 years.¹⁸ Death due to reverse dipping occurred at an older age, raising the issue of reverse causality; that is, reverse dipping, an extremely unphysiological diurnal variation of BP, may be a marker of poor health rather than a cause of it. To determine whether nondipping or reverse dipping is a reversible risk factor or not, interventional studies will be needed, which may or may not demonstrate a clinical benefit of restoring normal BP in cases of disrupted diurnal BP variation.

Figure 3 Stroke and fatal stroke incidence for four dipping types. Shaded areas indicate nonfatal stroke incidence; solid areas, fatal stroke incidence.

Figure 2 Pathophysiology of altered diurnal BP variation and nocturnal hypertension. The pathophysiology of nocturnal blood pressure increase is multifactorial. A full color version of this figure is available at the *Hypertension Research* journal online.

Extreme dipping is defined as a nocturnal BP decrease of $>20\%$ with respect to daytime BP; the prevalence of extreme dipping among Japanese older persons was found to be $\sim 30\%$.^{27,31,33–35} Extreme dipping is a complex phenomenon. Contrary to the established notion that subjects with low nocturnal BP are at low cardiovascular risk, extreme dippers have a higher prevalence of silent cerebral infarction, deep white matter lesions and silent myocardial ischemia during sleep than dippers.^{27,33,34,36,37} Nocturnal hypoperfusion at the brain and/or heart during extreme dipping may occur, leading to organ damage. This is particularly of concern in older hypertensive patients with impaired cerebral autoregulation.³⁸ However, it remains uncertain whether or not nocturnal extreme BP dipping itself could be a trigger for ischemic stroke onset or heart attack during sleep in older hypertensives.³¹ Recent studies have shown a close association between natural extreme dipping and mild cognitive impairment without reaching definitive dementia in community-dwelling older persons (mean age, 68 years),³⁹ indicating that extreme dipping may be associated with reduced quality of life in older persons. The pathophysiology of extreme BP decrease during sleep remained unclear, but care should be taken with interpreting extreme dipping in middle-aged or young persons, as the extent of dipping at a younger age was mainly determined by high daytime BP.⁴⁰ Our data indicated that extreme dipping in older hypertensive patients was concomitant with isolated systolic hypertension and excess BP variability, both of which are phenotypes of arterial stiffness. Intriguingly, when compared with dippers or nondippers, untreated older hypertensive patients with extreme dipping showed greater increases in plasma renin activity and vasopressin levels after a 70° head-up tilt test (10 min supine and 15 min tilting).⁴¹ These neurohumoral changes in extreme dippers might reflect a subclinical reduction in circulating blood volume or blood volume dysregulation by some physiological stressors, including orthostasis. Owing to such vasopressor increases after tilting, an orthostatic BP increase (that is, orthostatic hypertension) was observed in extreme dippers, but was seldom seen in dippers and nondippers;⁴² orthostatic hypertension in extreme dippers might contribute to morning BP elevation after awake. In fact, our previous data showed that about half of older hypertensive patients (mean, 72 years) with a morning BP surge (≥ 55 mm Hg; calculated as the mean systolic BP during the 2 h after awakening minus the mean systolic BP during the 1 h that included the lowest sleep BP) could be defined as extreme dippers.⁴³ Conversely, 24% of extreme dippers, but only 8.1% of dippers, 4.5% of nondippers and 2.3% of reverse dippers had an excess morning BP surge. In extreme dippers, 60% of the stroke events occurred during the morning period (0600 hours to noon), and 30% occurred during the nighttime period (midnight to 0600 hours). By contrast, in the other groups (dippers and nondippers), 46% of the 26 events occurred in the morning period, and 7.7% occurred during the night ($P=0.06$ by χ^2 -test). In that study, the increased stroke risk of extreme dippers largely depended on the concomitant excess morning BP surge; however, as mentioned above, the possibility of nocturnal hypoperfusion at the brain as well as brain damage during extreme dipping cannot be excluded. The pathophysiology of extreme dipping is heterogeneous, and thus the clinical implications of extreme dipping may differ according to the patient's clinical characteristics (for example, age, daytime physical activity and alcohol intake).

TREATMENT OF NOCTURNAL BP INCREASES

Although there is mounting evidence supporting the association of nocturnal hypertension and nondipping with increased mortality and cardiovascular morbidity, it is still unknown whether decreasing

nocturnal BP or restoring the abnormal diurnal BP variation to normal would improve prognosis. However, a few studies have indirectly demonstrated a benefit from nocturnal BP reduction.

In the HOPE (Heart Outcomes Prevention Evaluation) study, including patients at high risk for cardiovascular events, the angiotensin-converting enzyme inhibitor ramipril markedly reduced cardiovascular morbidity and mortality (relative risk, 0.68–0.80; $P<0.001$) out of proportion to the modest changes observed in office BP ($-3/-2$ mm Hg).⁴⁴ This may partly be explained by a marked reduction in nocturnal BP ($-17/-8$ mm Hg), as shown in a small ABPM substudy of HOPE (mean age, 71 years; $n=38$),⁴⁵ as well as by data showing that bedtime administration of ramipril could reduce nocturnal BP more efficiently than morning administration of ramipril.⁴⁶ Other evidence provided by the BP-lowering arm of the ABPM substudy of the Anglo-Scandinavian cardiac outcomes trial (mean age, 63 years; $n=1905$) showed a more significant reduction of nocturnal BP with an amlodipine–perindopril regimen than with atenolol–thiazide, despite the fact that the daytime BP was higher in the former group, which might account for the lower cardiovascular events in the amlodipine–perindopril group.^{47,48} However, these data were derived from a substudy with a small sample size, and thus interpretations should be made with caution. Recently, the importance of nighttime BP control during the follow-up treatment of patients was strengthened by a report by Hermida *et al.*,⁴⁹ who prospectively treated 3344 subjects with or without hypertension (mean age, 53 years) for a median follow-up period of 5.6 years. Analysis of changes in ABPM during the follow-up period revealed that a 5-mm Hg reduction in nocturnal systolic BP was associated with a 17% reduction in cardiovascular events ($P<0.001$), independent of changes in any other ambulatory BP parameters. The study subjects were middle-aged, and half of them were defined as obese or as having metabolic syndrome. Therefore, it remained unclear whether these results also apply to older hypertensive patients or subjects who have pre-existing CVD.

While there is no evidence-based approach for the treatment of nocturnal hypertension or nondipping, it seems to be promising to treat the pathophysiology underlying the altered diurnal BP variation, including nocturnal hypertension. The etiology of nocturnal hypertension or nondipping is complex, and may be encountered together with a number of clinical backgrounds, such as autonomic dysfunction, volume overload secondary to salt sensitivity and CKD, poor quality of sleep, disruption of biological circadian rhythms and other factors (Figure 2).

It is difficult to alter autonomic dysfunction in patients who are nondippers or in those with nocturnal hypertension, as this phenomenon reflects, to some extent, underlying advanced poor health (for example, patients with diabetic neuropathy, pre-existing cerebrovascular disease and neurodegenerative disease). We previously reported that nighttime dosing with an α -blocker, doxazosin, markedly reduced nocturnal BP in nondippers and reverse dippers in uncomplicated hypertensive patients.⁵⁰ Recently, the dramatic usefulness of new strategies to manipulate autonomic function, such as baroreflex activation therapy or renal denervation in resistant hypertension, has been reported.^{51,52} New frontiers in the treatment of hypertension are therefore promising in terms of their potential for improving diurnal BP variation.

Salt restriction can force nondipping into dipping status, and alternatively, salt loading attenuates dipping.^{53,54} Thiazide diuretics that promote natriuresis can also restore nocturnal BP variation.⁵⁵ However, thiazide diuretics are not sufficient to reduce volume expansion in some cases (for example, resistant hypertension); one

possible reason for such insufficiency may be the excessive aldosterone production that follows thiazide diuretic use,^{56,57} and thus aldosterone antagonists may be effective in such cases.⁵⁸

Associations between obstructive sleep apnea (OSA) and high BP have been confirmed, and nondipping was found in 48–84% of the patients with OSA.^{59–61} The mechanisms contributing to nondipping or nocturnal hypertension in OSA are multifactorial, including hypoxia- and hypercapnea-induced sympathetic nerve activation, renin–angiotensin–aldosterone activation, endothelial dysfunction and increased vascular stiffness.^{59–62} The effectiveness of OSA treatment with continuous positive airway pressure (CPAP) was modest and the results are conflicting.⁶² Haentjens *et al.*⁶³ examined the effects of CPAP on 24-hour BP with a meta-analysis of 572 patients from 12 randomized controlled trials. The CPAP treatment, compared with placebo, reduced the mean 24-hour systolic BP by 1.64 mm Hg (95% confidence interval, –2.67 to –0.60 mm Hg) and 24-hour diastolic BP by 1.48 mm Hg (95% confidence interval, –2.18 to –0.78 mm Hg; both, $P < 0.01$). The reasons for the modest effectiveness or lack thereof of CPAP therapy on BP may be derived from multiple variables, including differences in study design, degree of CPAP adherence and treatment duration. Furthermore, as precise BP changes caused by nocturnal hypoxia in OSA patients could not be assessed by conventional ABPM, the BP-lowering effect of CPAP therapy may have been underestimated. However, such assessment may be performed with our newly developed, non-invasive, hypoxia-triggered BP monitoring system.⁶⁴

Recent findings from human and animal studies have provided new insights showing a close association between circadian clock system abnormalities and high BP or abnormal circadian BP variation.⁶⁵ Indeed, ablation of the suprachiasmatic nucleus, a master clock to orchestrate the multitude of cellular clocks within the body, results in a loss of BP circadian rhythmicity.⁶⁶ Doi *et al.*⁶⁷ have reported that a deletion of *Cry* gene, a major transcriptional factor of the clock gene, causes a complete loss of circadian variation of BP and leads to salt-sensitive hypertension via excess aldosterone production. Recent advances in identifying novel clock-controlled genes using rodent and cellular models have also shed light on the molecular mechanisms, by which the circadian clock controls renal function, such as the regulation of certain types of water and electrolyte transportation and fluid balance. Much more work remains to be done in this emerging field.^{68,69} To modulate the circadian clock system becomes a potential target for establishing novel prevention or treatment strategies for hypertension and CVD. Perturbation of the circadian clock is associated with behavior aberrations; such perturbations include short sleep duration, shift work, hectic lifestyle and sleep apnea. Therefore, the improvement of daily routines is a fundamental component in avoiding a compromise of the circadian clock. A blunted nocturnal surge in melatonin excretion, which is secreted from the pineal body and acts to entrain the suprachiasmatic nucleus, has been reported in nondippers.⁶⁹ In addition, melatonin supplementation or supplementation with its receptor agonists has been shown to lower nocturnal BP in hypertensive patients.^{70,71} These may be novel complementary or alternative approaches to lowering nocturnal BP; however, the mechanisms and targets of circadian BP regulation by melatonin, that is, central or peripheral action, remain obscure.

Chronotherapy, the scheduled administration of pharmaceutical agents with respect to an individual's circadian rhythm, may increase the effectiveness of pharmacological agents. The potential benefit of chronotherapy in the treatment of hypertension includes restoration of the nondipping pattern. The administration of at least one antihypertensive drug at bedtime has been reported to be more effective

than morning administration, not only at lowering nocturnal BP and restoring circadian variability in BP, but also for reducing cardiovascular events and total mortality.^{46,49,72,73} The methods described here are promising, although larger and more comprehensive trials are needed to elucidate relevant mechanisms of action.

In conclusion, in this review, we discussed the clinical impact of nocturnal BP levels and nocturnal BP dipping status on mortality and cardiovascular risk during the clinical management of hypertensive patients and in the general population. Additional interventional studies are required to confirm whether the nocturnal BP level, or nocturnal BP dipping, is merely a useful parameter for identifying individuals with a poor prognosis or if it is a reversible risk factor to be linked with improved prognosis. Further investigation will also be needed to demonstrate any clinical benefits of lowering nocturnal BP and of restoring disrupted diurnal BP variations to normal.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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