

Can nocturnal hypertension predict cardiovascular risk?

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Abstract: Nocturnal hypertension and non-dipping of blood pressure during sleep are distinct entities that often occur together and are regarded as important harbingers of poor cardiovascular prognosis. This review addresses several aspects related to these blood pressure abnormalities including definitions, diagnostic limitations, pathogenesis and associated patient profiles, prognostic significance, and therapeutic strategies. Taken together, persistent nocturnal hypertension and non-dipping blood pressure pattern, perhaps secondary to abnormal renal sodium handling and/or altered nocturnal sympathovagal balance, are strongly associated with deaths, cardiovascular events, and progressive loss of renal function, independent of daytime and 24-hour blood pressure. Several pharmacological and non-pharmacological approaches may restore nocturnal blood pressure and circadian blood pressure rhythm to normal; however, whether this translates to a clinically meaningful reduction in unfavorable cardiovascular and renal consequences remains to be seen.

Keywords: blood pressure, sleep, nocturnal hypertension

Introduction

An appreciation of the normal sleep-wake cycle of blood pressure (BP) in humans, characterized by a nocturnal fall and diurnal rise, has been well established for several decades.¹ Consequently, this has resulted in an increased awareness of nocturnal hypertension as well as various sleep BP pattern disturbances, gleaned non-invasively from the recordings provided by 24-hour ambulatory BP monitoring (ABPM).

Definitions

Nocturnal hypertension has been defined using various absolute nocturnal BP cut-offs. According to the American Heart Association Council on High Blood Pressure Research, nocturnal BP < 115/65 is deemed optimal, <120/70 is deemed normal and >125/75 is deemed abnormal.² Non-dipping is commonly defined as a <10% fall in nocturnal BP relative to diurnal BP (ie, [daytime BP – night-time BP]/daytime BP × 100%),² arithmetically equivalent to a night-to-day BP ratio >0.9. Non-dippers have been further subdivided into either attenuated dippers (≥0% but <10% fall) or risers (<0% fall). There is also a patient subset, situated at the opposite end of the dipping spectrum, referred to as extreme dippers (≥20% fall) that has been linked in some, although not all, studies with increased cardiovascular risk and mortality, perhaps related to nocturnal hypoperfusion and/or an exaggerated morning BP surge;³⁻⁶ however, this entity is not further discussed herein. Of note, although high nocturnal

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BP may be accompanied by a non-dipping pattern, both are not always concomitantly present and the pathophysiologic and clinical significance of each may differ.⁷

Diagnostic limitations

Over the years, a number of diagnostic limitations categorizing nocturnal BP and dipping status have been identified. First, there is no universal agreement on the definition of non-dipping. For example, in some reports, it is defined as higher sleep BP level than awake BP level, rather than the more commonly used definition of a $<10\%$ fall in night-time BP.^{8,9} Second, studies of repeated ABPM have questioned the reproducibility of dipping status and diagnosing nocturnal hypertension using cut-off values, given the well-described phenomenon of regression to the mean. On repeated ABPM, expressing the decline in BP during sleep as a continuous variable (eg, percentage fall in nocturnal BP) was shown to be far more reproducible than its expression as a categorical variable (ie, using the traditionally adopted 10% cut-off), given a loss of information.¹⁰ This is particularly an issue for defining abnormalities of dipping status as definitions rest on a difference score of individual daytime and night-time BP levels.^{10–13} In a study of repeated ABPM, agreement in diagnosing nocturnal hypertension on the basis of two measurements was greater using an absolute nocturnal BP threshold value (Cohen's kappa = 0.485 systolic BP) rather than the percentage nocturnal BP fall (Cohen's kappa = 0.378 systolic BP).¹⁴ Because of better metrics, nocturnal hypertension using threshold values was also a better predictor of left ventricular hypertrophy than non-dipping BP pattern.¹⁵ Third, the dipping pattern of systolic BP has been shown to be more reproducible than that of diastolic BP in several,^{12,16,17} although not all,^{18,19} studies. Fourth, the methods used to define the night-time period have varied from arbitrarily fixed clock times to self-reported sleep times using diary entries or even, polysomnographically verified sleep times. With respect to the arbitrarily fixed clock time method, one improvement has involved the use of narrow clock intervals to exclude the transition period from 0600 to 1000 h²⁰ or 0700 to 1000 h²¹ in the morning and from 2000 to 0000 h²⁰ or 2300 to 0100 h in the evening.²¹ Recently, it was shown that different definitions significantly affect the classification of nocturnal BP dipping and its relation to left ventricular mass index and urinary albumin excretion as indices of hypertensive target organ damage.^{12,22} Fifth, failing to account for night-time awakenings²³ and daytime naps²⁴ has been associated with misclassification of nocturnal hypertension. Additionally, variations in nocturnal body

position and diurnal physical activity affect night-time and daytime BP.^{25,26} On balance, BP dipping status appears to be more influenced by night-time factors than by daytime physical activity.²⁷ Sixth, nocturnal BP may be unreliable as a prognostic marker for cardiovascular events and deaths among subjects with perceived sleep deprivation ≥ 2 hours during ABPM related to repeated cuff inflations.²⁸ Finally, antihypertensive drug treatment and the timing of their administration can influence circadian BP profile.^{29,30}

Pathophysiology

Although there have been several theories as to the pathogenesis of non-dipping including systemic and vascular inflammation and endothelial dysfunction,³¹ perhaps the two most cited explanations rest on abnormal renal sodium handling and disturbances in nocturnal autonomic or sympathovagal balance. Further, the association of nocturnal hypertension and non-dipping pattern with patient profiles provides further insights into mechanisms. Specifically, several patient characteristics have been associated with nocturnal hypertension and non-dipping BP pattern; not surprisingly, many of these states are associated with impaired renal capacity to excrete sodium and/or relative sympathoactivation.

Abnormal renal sodium handling

Many studies have shown an association between abnormal renal sodium handling and nocturnal hypertension and non-dipping pattern of BP during sleep. In a recent study of a large group of African subjects, those with the lowest day-to-night ratios of urinary sodium excretion had significantly higher night-time systolic BP and lower systolic BP dipping in both unadjusted and adjusted analyses.¹⁶ The 'low daytime sodium excretors' excreted three times less sodium during the day than during the night, whereas the 'high daytime sodium excretors' had a sodium excretion rate that was 46% higher during the day than during the night, although total daily sodium excretion was equivalent in both groups. These findings are in accord with earlier, smaller studies conducted in hospitalized subjects.^{32–34} In a study of Japanese patients with essential hypertension, non-dippers on a high sodium diet had a significantly higher night-time systolic BP and mean arterial pressure (MAP) and showed no nocturnal decrease in BP compared to the dippers.³² Furthermore, night-time urinary sodium excretion was significantly greater in non-dippers than dippers and there was a strong positive relationship between night-to-day ratios of urinary sodium excretion and MAP. When the non-dippers were placed on a sodium-restricted diet, there was a significant fall in systolic

BP and MAP in the non-dippers and there was no longer a significant difference in the night-to-day ratios of urinary sodium excretion between non-dippers and dippers. Given a greater antinatriuresis during the day in the non-dippers, higher nocturnal BP, as a result of pressure-natriuresis with near infinite gain over a wide range of urinary sodium excretion, may account for the greater proportion of urine sodium excreted at night to maintain total body sodium balance.³⁵

Enhanced salt sensitivity of BP is often found in non-dippers³⁵ and has been suggested as mediating nocturnal hypertension.^{33,34} Among black normotensive adolescents, a significantly greater proportion of non-dipping for MAP at 50% was identified in those deemed salt sensitive (defined as a ≥ 5 mmHg BP difference between the high and low dietary salt states) as compared to 18.9% in those deemed salt resistant.³⁶ Further, a Japanese study revealed that the nocturnal fall of BP from daytime to night-time was only significant among salt resistant hypertensives (defined as a $< 10\%$ BP difference between the high and low dietary salt states) compared to their salt sensitive hypertensive counterparts.³² This has been attributed, in part, to a disturbed antinatriuretic response to postural change. Specifically, among hypertensive subjects, although the urinary sodium excretion rate was found to be significantly less in the upright than the supine position in both non-dippers and dippers, the difference was magnified in the non-dippers (despite no difference in postural BPs) because of an exaggerated reduction in upright sodium excretion.³⁷ Exaggerated antinatriuretic effects of postural change may also contribute to the high prevalence of supine nocturnal hypertension in patients with autonomic failure, possibly related to increased sensitivity to changes in plasma volume with re-entry into the circulation of peripheral interstitial fluid accumulated during the day.^{38,39}

The renal sodium regulatory mechanisms that give rise to nocturnal hypertension and non-dipping BP pattern remain unclear. In the case of chronic kidney disease, reduced ultrafiltration capacity likely accounts for the blunting of the nocturnal fall in BP along with enhanced natriuresis at night.⁴⁰ However, many individuals with disturbed diurnal renal sodium excretion have normal glomerular function;¹⁶ in these instances, augmented tubular reabsorption of sodium during the day likely contributes to the genesis of the nocturnal BP and natriuretic abnormalities.³⁵ In salt sensitive forms of hypertension such as primary aldosteronism, or patients with diabetes mellitus or metabolic syndrome, there is evidence of enhanced tubular sodium reabsorption that may account for non-dipping.^{34,40} Further evidence supporting a role for renal tubular sodium handling comes from studies of patients

with essential hypertension showing a differential effect of hydrochlorothiazide, which inhibits sodium transport in the distal nephron, on nocturnal fall in BP in non-dippers compared to dippers;^{41,42} diuretic therapy restored the dipping BP pattern in non-dippers but had no effect in dippers.⁴¹

Nocturnal sympathovagal imbalance

Nocturnal sympathoexcitation has also been suggested as mediating nocturnal hypertension and non-dipping BP pattern.^{9,26} This is in contrast to the normal sleep-wake cycle of sympathetic neural activity characterized by sympathoinhibition during sleep (particularly non-rapid-eye-movement sleep).⁴³ In a cohort of normotensive and hypertensive subjects, non-dippers were observed to have a reduced night-time fall in urine catecholamine levels and heightened alpha-1-adrenergic receptor responsiveness to phenylephrine (but similar beta-adrenergic receptor responsiveness to isoproterenol), unlike dippers.⁴⁴ A recent study found a significant inverse relationship between the degree of sympathetic activation, measured by muscle sympathetic nerve activity in the daytime, and the magnitude of night-time fall in BP.⁴⁵ In that report, the increase in sympathetic activity was greatest in subjects demonstrating an increase in nocturnal BP (risers). The findings are in accord with results of earlier studies demonstrating a higher mean daytime plasma norepinephrine level in risers⁹ and a greater reduction of night-time BP following administration of the alpha-adrenergic blocker, doxazosin.⁴⁶ Several reports using power spectral analysis of heart rate variability suggest that a reduction in parasympathetic nervous system activity may also contribute to the non-dipping BP pattern in essential hypertension.^{47,48} The causal mechanism(s) leading to sustained nocturnal sympathetic augmentation is still poorly understood, but may include the insulin resistance state, which frequently accompanies sympathetic activation^{45,49} and innate or acquired susceptibility to the pressor effects of salt.^{50,51} However, changes in baroreflex sensitivity do not appear to account for abnormal dipping pattern as a study measuring it spontaneously or by the phenylephrine bolus technique found no significant difference between hypertensive dippers and non-dippers.⁵²

Associations

A variety of factors including patient characteristics, clinical conditions, and dietary patterns have been reported to be associated with nocturnal hypertension and non-dipping. These links often provide some pathophysiologic insights.

Patient characteristics

Multivariable assessment of a large cohort of untreated hypertensive men and women revealed a highly significant inverse linear correlation between the day-night systolic BP change and age in both sexes.⁵³ The prevalence of the non-dipping BP pattern increased progressively with age, reaching >40% in subjects ≥ 70 years. Several studies have also noted increasing salt sensitivity of BP with increasing age, particularly among hypertensive patients, using provocative maneuvers to either contract or expand extracellular fluid volume.^{54,55} In fact, the presence of hypertension has been suggested as conferring a lower nocturnal fall in BP,⁵⁶ although this has not been unanimously confirmed.⁵⁷ Blacks have been consistently shown to have a greater frequency of both reduced nocturnal fall in BP^{58–62} and salt sensitivity of BP^{63,64} than whites. Blacks also have higher ambulatory heart rates and lower heart rate variability than non-blacks, possibly reflecting greater impairment in sympathovagal balance in this racial group.⁶⁵ There does not appear to be a sex difference in the prevalence of non-dipping;⁵³ nonetheless, several studies have shown more adverse health effects in hypertensive women with blunted nocturnal fall in BP. In contrast to men, they have a greater left ventricular mass index^{66,67} and are more likely to develop a cardiovascular complication.⁶⁸

Clinical conditions

Several studies have shown that non-dipping is more commonly found in clinical conditions, including hypertension, diabetes mellitus, impaired glucose tolerance, renal disease, autonomic failure, disrupted sleep, and sleep apnea. Overall, it is estimated that approximately 22% of patients with essential hypertension have a non-dipping pattern.²⁶ Among treated hypertensive patients, non-dipping may also be partly related to the absence of uniform 24-hour therapeutic antihypertensive coverage, perhaps especially in those treated with single morning doses and/or short-acting antihypertensive medications.^{29,69} We recently showed a significantly greater prevalence of non-dippers (particularly risers) in patients with refractory hypertension as compared to those with controlled hypertension and normal BP, matched for age, sex and BMI,⁷⁰ with figures ranging from 66% to 79% reported by others.^{71,72} Previously, in a 3-month interventional trial of drug-resistant hypertension, patients randomized to receive antihypertensive treatment dictated by non-invasive hemodynamic measurements were found to have significantly lower BP and better BP control than those receiving specialist care alone and the differences were attributed to a significantly

higher final diuretic dosing.⁷³ Such data suggest that covert extracellular fluid volume expansion may be a dominant feature accounting for apparent treatment resistance in refractory hypertension and may also explain our parallel observation of greater attenuation of the nocturnal dipping pattern in such patients.

There is a higher prevalence of non-dipping among patients with diabetes mellitus,^{53,74} particularly among those with higher night-time than day-time readings.⁸ This finding does not appear to be a consequence of increased nocturnal awakenings from nocturia due to osmotic diuresis and/or neurogenic bladder. Among subjects reporting having taken an uninterrupted afternoon siesta, diabetics displayed a similar naptime BP decline to their night-time BP decline, which was blunted as compared to the non-diabetic controls.⁷⁵ Several small studies have shown that insulin resistance in non-diabetic hypertensive subjects is also associated with a reduced nocturnal fall in BP.^{76–78} Mancia et al, however, did not find an increase in non-dipping pattern in patients with the metabolic syndrome, although less than one-third of these individuals had impaired glucose intolerance.⁷⁹ Hermida et al recently reported a higher prevalence of non-dipping BP pattern in patients with the metabolic syndrome compared to those without this condition and they also had a higher BMI.⁸⁰ Increased BMI, however, is not a characteristic feature of the non-dipping BP pattern as it was not significantly different among subjects dichotomized into 4 categories of the night-to-day ratio of systolic BP (extreme, normal, decreased, reverse) in a meta-analysis of several prospective population studies of 24-hour BP monitoring.⁸¹

Abnormal diurnal BP variability is present in patients with chronic kidney disease such that they are more likely non-dippers.^{82,83} For example, the mean nocturnal systolic BP change among patients with essential hypertension was found to be a decrease of 12.7 mmHg compared to an increase of 2.7 mmHg among hypertensive patients with renal parenchymal disease, despite matching for age, sex and 24-hour BP.⁸⁴ Additionally, the decrease in unadjusted creatinine clearance following donor nephrectomy was found to correlate with the corresponding increase in the night-to-day BP ratio but not the 24-hour, daytime or night-time BP.⁸⁵ Non-dipping has also been linked to accelerated loss of renal function. In a retrospective cohort study of outpatients attending a hospital clinic, non-dipping was associated with subsequent deterioration in renal function that was independent of baseline renal function, systolic BP load and other risk factors for renal impairment.⁸⁶ Additionally, in a study of renal transplant recipients, non-dippers and risers had

lower glomerular filtration rates, measured by iothalamate clearance, than dippers one year after transplantation; there was no difference in iothalamate glomerular filtration rates at the three week time point post-transplantation.⁸⁷

Short habitual sleep duration may be associated with non-dipping of nocturnal BP. In two separate studies, untreated hypertensive patients who were non-dippers were found to have significantly shorter durations of sleep by 0.3 hours in men and 0.5 hours in women (according to self-report)⁵³ or by 81 minutes (according to wrist actigraphy),⁸⁸ compared to their dipper counterparts; further multivariable analysis in one of these studies showed a positive linear correlation between the day-night systolic BP change and sleep duration.⁵³ Moreover, poor sleep quality has also been suggested as being related to nocturnal hypertension. In a study of normotensive and hypertensive subjects with an apnea-hypopnea index (AHI) <10, the degree of nocturnal BP dipping was positively linked with the percentage of total sleep time occupied by stage 4 non-rapid eye movement sleep (reflecting depth of sleep) and negatively linked with the percentage of wake time following sleep onset (reflecting sleep fragmentation).⁸⁹ Similar findings of less time spent in stage 4 non-rapid eye movement sleep and sleep fragmentation with micro/arousals along with other qualitative disturbances have also been reported by others.⁹⁰⁻⁹² Notwithstanding the foregoing relations, sleep-disordered breathing, particularly obstructive sleep apnea-hypopnea (OSAH), has been strongly associated with non-dipping.⁹³⁻⁹⁶ Notably, the vast majority of mechanistic studies linking OSAH and hypertension are disproportionately represented by those implicating sympathoactivation (whether gauged by plasma or urine catecholamines or microneurography), independent of obesity. For example, a recent study involved normotensive subjects who were classified as lean or obese with or without OSAH (according to BMI, waist-to-hip ratio and AHI) and matched for age and sex. Relative to the non-OSAH lean group, muscle sympathetic nerve activity was significantly and similarly greater in both the OSAH lean group and in the non-OSAH obese group; the increase was even more pronounced in the OSAH obese group.⁹⁷

Dietary patterns

Several studies have recognized an increased prevalence of non-dipping status in obese patients, particularly in women.^{44,67,98} Salt sensitivity may underlie raised night-time BP in obese individuals. For example, in a study of obese and non-obese adolescents, when the obese group was changed from a high salt to a low salt diet there was a greater fall in their

BP compared to non-obese group.⁹⁹ This increased sensitivity to dietary salt intake may be a manifestation of the hyperadrenergic state that is a feature of abdominal obesity and often ascribed to the central sympathetic effects of hyperinsulinemia and hyperleptinemia.¹⁰⁰ The prevalence of OSAH, associated with increased likelihood of non-dipping pattern,⁹³⁻⁹⁶ also progressively increases as BMI and associated markers of obesity (eg, neck circumference, waist-to-hip ratio) increase.¹⁰¹

Dietary monovalent cation intake patterns, characterized by a high sodium or low potassium content, are also recognized as favoring a non-dipping BP pattern, particularly in salt sensitive individuals.¹⁰² The hypertensinogenic effects of a low potassium diet have been attributed, at least partly, to renal sodium retention.¹⁰³ In the Dietary Approaches to Stop Hypertension (DASH) Trial, the BP of individuals randomly assigned to the 'combination' (DASH) diet that emphasized low fat dairy products, fruits and vegetables, thus containing high amounts of calcium and potassium,¹⁰⁴ was significantly lower during the day and at night compared to the BP of those consuming the 'typical American' diet; however, the high quality (DASH) diet did not significantly affect dipping status.¹⁰⁵ This is a surprising finding in view of the evidence from the same group of investigators that the DASH diet increased, thus improving, the pressure-natriuresis slope (ie, reduced salt-sensitivity).¹⁰⁶ Possibly misclassification error from the use of a fixed clock method to determine dipping status might explain the negative result.

Epidemiological studies

Numerous observational studies have emerged addressing the prognostic significance of nocturnal hypertension and non-dipping BP pattern on mortality and cardiovascular disease.

Considerations

The presence of nocturnal hypertension in one individual but not the other would be expected to connote a greater 24-hour BP load if daytime BP levels were otherwise equivalent in the two individuals. Certainly, then, one would not be surprised to find a larger burden of hypertensive target organ damage in the former individual. What remains less clear is whether night-time BP is able to predict such vascular insult independent of daytime or 24-hour BP and perhaps further, whether its predictive ability is superior to that provided by daytime BP. If such an association is truly not spurious, several explanations could be held accountable. First, a proper interpretation of any observational study must be tempered by the potential

for residual confounding. For example, if nocturnal hypertension were simply a marker for underlying illnesses linked to deaths and cardiovascular events,^{81,107} then any association identified with nocturnal hypertension may be inaccurately estimated if the given state and/or condition were either undefined or poorly defined. In addition, it may not be nocturnal hypertension per se but rather its underlying pathophysiologic state (eg, heightened sympathetic neural tone) that bestows vascular injury. Second, a cause-effect relation may indeed apply. The sleep state is typically associated with the minimum BP necessary to maintain organ perfusion; perhaps then, if also given a permissive hormonal milieu, susceptibility to vascular target organ damage may demonstrate circadian variability for a given BP load marked by an increase during sleep.^{108,109} Moreover, for the cerebrum, its vasculature may be less protected from hydrostatic (gravitational) forces when recumbent during sleep than when erect or sitting.¹¹⁰ Third, an effect-cause relation can be argued instead, particularly with cross-sectional and case-control studies. Specifically, nocturnal hypertension may simply reflect more extensive target organ damage placing the patient in a high-risk group, as opposed to having a direct effect. Fourth, in view of a narrower dispersion of nocturnal BP values compared to diurnal BP values, partly related to ambulatory physical activity,¹¹¹ night-time BP would be expected to perform

mathematically, but not necessarily biologically, better as a predictor than daytime BP.⁷

Summary of findings

On the basis of ABPM performed 1 to 5 years earlier, a case-control study of hypertensive subjects revealed a significantly lower nocturnal fall in BP among cases as compared to controls (based on the occurrence of a fatal or non-fatal cardiovascular event) but only in women, despite matching for several covariates including daytime BP.⁶⁸ However, the vast majority of more recent studies focusing on the prognostic implications of nocturnal hypertension have been prospective cohort in design. Of course, there is also a robust body of literature that speaks to the association between nocturnal hypertension and a multitude of unfavorable structural (eg, cardiac chamber dilatation, ventricular hypertrophy, carotid intima-media thickening, silent lacunae, leukoariosis, brain microbleeds) and functional (eg, diastolic dysfunction) cardiovascular consequences.^{112–120} Tables 1 to 3 summarize the varied patient populations enrolled in and the methodological aspects and accompanying results of larger studies (sample size >500) that examined the clinical endpoints of all-cause mortality, cardiovascular mortality and/or cardiovascular morbidity. As evident, additional adjustments for either daytime or 24-hour BP were not uniformly made in such studies to allow for a determination

Table 1 Studies addressing independent prognostic significance of nocturnal blood pressure on all-cause mortality and/or cardiovascular mortality/morbidity

Primary author	Year	Source of publication	Country of primary author's affiliation	Sample size	Study design
Ohkubo ^{5,145}	1997 ^a 2002	<i>Am J Hypertens</i> <i>J Hypertens</i>	Japan	1542	Prospective cohort
Staessen ⁶	1999	<i>JAMA</i>	Belgium	808	Prospective cohort
Dolan ¹²²	2005	<i>Hypertension</i>	Ireland	5292	Prospective cohort
Ben-Dov ¹²¹	2007	<i>Hypertension</i>	Israel	3957	Prospective cohort
Fagard ¹²³	2008	<i>Hypertension</i>	Belgium	3468	Meta-analysis
Bjorklund ¹⁴⁶	2004	<i>J Hypertens</i>	Sweden	872	Prospective cohort
Kikuya ¹²⁴	2005	<i>Hypertension</i>	Japan	1332	Prospective cohort
Ingelsson ¹⁴⁷	2006	<i>JAMA</i>	Sweden	951	Prospective cohort
Sega ¹⁴⁸	2005	<i>Circulation</i>	Italy	2051	Prospective cohort
Boggia ⁸¹	2007	<i>Lancet</i>	Uruguay	7458	Meta-analysis
Clement ¹⁴⁹	2003	<i>N Engl J Med</i>	Belgium	1963	Prospective cohort
Hansen ^{150,151}	2005 2006	<i>Hypertension</i> <i>Am J Hypertens</i>	Denmark	1700	Prospective cohort
Verdecchia ¹⁵²	1994	<i>Hypertension</i>	Italy	959	Prospective cohort
Brotman ¹⁵³	2008	<i>Am J Hypertens</i>	USA	621	Retrospective cohort

^aPilot analysis.

Table 2 Studies addressing independent prognostic significance of nocturnal blood pressure on all-cause mortality and/or cardiovascular mortality/morbidity

Primary author	Age (yrs)	Male (%)	BMI (kg/m ²)	Current/exsmoker (%)	DM (%)	Prevalent CVD (%)	Mean daytime BP (mmHg)	HTN (%)
Ohkubo ^{5,145}	61.6	36.6	NA	21.7	NA	4.5	128.6/76.1	30.7
Staessen ⁶	69.6	38.5	26.7	35.5	NA	26.6	151.4/84.1	100
Dolan ¹²²	53.3	46.3	27.4	23.8	5.2	10.6	146.1/89.0	100
Ben-Dov ¹²¹	55.0	47.0	27.2	NA	9.0	NA	NA	70.4
Fagard ¹²³	60.8	44.8	27.7	13.7	8.4	0	143.5/87.1	100
Bjorklund ¹⁴⁶	71.0	100	26.0	20.6	13.5	0	NA	30.1
Kikuya ¹²⁴	61.8	34.5	NA	20.4	17.4	5.6	128.9/76.1	30.4
Ingelsson ¹⁴⁷	50.0	100	26.2	20.4	10.0	13.9	140.0/79.0	49.2
Sega ¹⁴⁸	52.9	52.8	NA	28.4	2.3	4.8	129.0/81.4	44.2
Boggia ⁸¹	56.8	54.3	NA	29.3	7.5	8.3	132.4/80.1	46.1
Clement ¹⁴⁹	56.4	51.3	27.9	17.2	11.0	5.9	139.1/88.3	100
Hansen ^{150,151}	55.8	47.9	25.3	44.3	2.2	0	131.0/78.0	8.9
Verdecchia ¹⁵²	52.9	49.8	27.0	23.7	9.8	3.1	146.4/93.0	100
Brotman ¹⁵³	61.3	48.1	27.8	21.1	10.8	13.5	NA	74.4

Abbreviations: BMI, body mass index; BP, blood pressure; CVD, cardiovascular disease; DM, diabetes mellitus; HTN, hypertension; NA, not available.

of the independent prognostic significance of night-time BP. Regardless, the bulk of the existing data suggests that nocturnal hypertension, whether expressed as a categorical or continuous predictor, is strongly associated with deaths and/or cardiovascular events. For example, in the Japanese general population, a 5% attenuation in the nocturnal BP fall was associated with a 20% increase in cardiovascular mortality, even among individuals with a normal 24-hour BP (defined as <135/80).⁵ In fact, several studies have also found that night-time BP, independent of daytime BP, may predict death and/or adverse cardiovascular outcomes better than daytime BP.^{6,81,121–124} For instance, among untreated hypertensive patients, an increase of 10 mmHg in daytime or night-time BP was associated with hazard ratios (HRs) for cardiovascular mortality of 1.12 (daytime systolic) compared to 1.21 (night-time systolic) and 1.04 (daytime diastolic; not significant) compared to 1.19 (night-time diastolic), after adjustment for the other BP.¹²² In a substudy of the Systolic Hypertension in Europe (Syst-Eur) trial, a 10-mmHg increase in night-time systolic BP was more predictive for all-cause deaths (adjusted HR 1.21), cardiovascular deaths (adjusted HR 1.21) and fatal and non-fatal cardiovascular events (adjusted HR: 1.26) than a comparable increase in daytime systolic BP (adjusted HRs 0.93, 1.03 and 0.94, respectively; not significant).⁶

The non-dipping BP pattern also predicted total mortality and cardiovascular events compared to the normal or extreme dipping pattern, independent of cohort and confounding variables and after adjustment for 24-hour BP, in a large

meta-analysis of prospective studies from Europe, Asia and South America.⁸¹ Similarly the night-to-day BP ratio treated as a continuous variable predicted all-cause mortality, again independent of 24-hour BP and confounding variables, in a smaller meta-analysis of only European prospective studies.¹²³ Reverse dipping was the strongest predictor of total mortality and cardiovascular events in fully adjusted models.⁸¹ In this study, they were older, more frequently on antihypertensive medications and more likely to have a history of diabetes mellitus or previous cardiovascular disease, indicating that these individuals were at high risk. Compared to night-time BP, however, non-dipping BP pattern and night-to-day BP ratio were less consistent predictors of cardiovascular mortality and non-fatal events in fully adjusted analyses,^{81,123} thus making them less important targets for interventions than absolute nocturnal BP level.

Therapeutic strategies

Whether greater effort should be expended on achieving night-time BP control and reversal of the non-dipping pattern over and above the attainment of daytime and 24-hour BP control so as to reap a greater reduction in deaths and cardiovascular events remains uncertain. Nonetheless, several strategies have been suggested as preferentially reducing night-time BP with restoration of the normal circadian BP rhythm.

Both therapeutic lifestyle changes and pharmacological approaches are associated with conversion from non-dipper to dipper status. Two Japanese studies revealed that therapeutic interventions, namely dietary salt restriction and

Table 3 Studies addressing independent prognostic significance of nocturnal blood pressure on all-cause mortality and/or cardiovascular mortality/morbidity

Primary author	F/U (yrs)	Ascertainment of nighttime period	Adjusted HR for all-cause mortality	Adjusted HR for cardiovascular mortality	Adjusted HR for cardiovascular morbidity ^a
Ohkubo ^{5,145}	5.1 9.2	Sleep diary	Riser: 2.12 Attenuated dipper: 1.35 (NS)	Riser: 4.97 ^b and 3.79 ^c Attenuated dipper: 2.88 ^b and 2.66 ^c Non-dipper and 24-hour BP \geq 135/80: 5.37 Non-dipper and 24-hour BP < 135/80: 2.35	NA
Staessen ⁶	4.4	0000–0600 h	10 mmHg \uparrow sBP: 1.21 ^b	10 mmHg \uparrow sBP: 1.21 ^b (NS)	10 mmHg \uparrow sBP: 1.26 ^b 10% \uparrow night-to-day sBP ratio: 1.41 ^c
Dolan ¹²²	7.9	0100–0600 h	10 mmHg \uparrow sBP: 1.18 ^b 10 mmHg \uparrow dBP: 1.23 ^b	10 mmHg \uparrow sBP: 1.21 ^b 10 mmHg \uparrow dBP: 1.19 ^b	NA
Ben-Dov ¹²¹	6.5	Sleep diary	Riser: 1.96 ^a Attenuated dipper: 1.30 ^b	NA	NA
Fagard ¹²³	6.7	0000–0600 h	I SD \uparrow sBP: 1.34 ^b I SD \uparrow dBP: 1.28 ^b	I SD \uparrow sBP: 1.34 ^b I SD \uparrow dBP: 1.40 ^b	I SD \uparrow sBP: 1.36 ^b I SD \uparrow dBP: 1.21 ^b
Bjorklund ¹⁴⁶	6.6	0000–0600 h	NA	NA	I SD \uparrow sBP: 1.18 I SD \uparrow dBP: 1.05 (NS)
Kikuya ¹²⁴	10.8	Sleep diary	NA	10 mmHg \uparrow sBP: 1.32 ^a	NA
Ingelsson ¹⁴⁷	9.1	0000–0600 h	NA	NA	I SD \uparrow sBP: 1.41 ^c (NS) I SD \uparrow dBP: 1.47 ^c (heart failure hospitalization)
Sega ¹⁴⁸	10.9	2300–0700 h	10 mmHg \uparrow sBP: 1.42 10 mmHg \uparrow dBP: 1.47	10 mmHg \uparrow sBP: 1.75 10 mmHg \uparrow dBP: 1.87	NA
Boggia ⁸¹	9.6	0000–0600 h (Europe, South America) 2200–0400 h (Asia)	I SD \uparrow sBP: 1.22 ^b I SD \uparrow dBP: 1.20 ^a Riser: 1.56 ^c Attenuated dipper: 1.19 ^c	I SD \uparrow sBP: 1.22 ^b I SD \uparrow dBP: 1.24 ^b Riser: 1.45 ^c Attenuated dipper: 1.08 ^c (NS)	I SD \uparrow sBP: 1.21 ^b I SD \uparrow dBP: 1.20 ^b Riser: 1.30 ^c Attenuated dipper: 1.05 ^c (NS)
Clement ¹⁴⁹	5.0	0000–0600 h	I SD \uparrow sBP: 1.06 (NS) I SD \uparrow dBP: 1.07 (NS)	NA	I SD \uparrow sBP: 1.27 I SD \uparrow dBP: 1.18 (NS)
Hansen ^{150,151}	9.5	Diary	10 mmHg \uparrow sBP: 1.19 10 mmHg \uparrow dBP: 1.35	10 mmHg \uparrow sBP: 1.41 10 mmHg \uparrow dBP: 1.85	10 mmHg \uparrow sBP: 1.27 10 mmHg \uparrow dBP: 1.54 Non-dipper and daytime BP \geq 135/85: 1.68 ^c Non-dipper and daytime BP < 135/85: 0.58 ^c (NS)
Verdecchia ¹⁵²	3.2	1000–0600 h	NA	NA	Non-dipper and male: 1.04 (NS) Non-dipper and female: 6.26
Brotman ¹⁵³	6.3	2300–0600 h	Non-dipper: 1.47 ^c	NA	NA

^aIncludes fatal and non-fatal cardiovascular events unless otherwise specified.^bIncludes adjustment for daytime blood pressure.^cIncludes adjustment for 24-hour blood pressure.**Abbreviations:** BP, blood pressure; dBP, diastolic blood pressure; F/U, follow-up; HR, hazard ratio; NA, not available; NS, not significant; sBP, systolic blood pressure; SD, standard deviation.

diuretic therapy, which reduce total body sodium content were able to restore the normal dipping pattern of BP in salt sensitive hypertensive patients (defined as a $\geq 10\%$ BP difference between the high and low dietary salt states) unlike their salt resistant hypertensive counterparts.^{32,41} Similarly, intensified ultrafiltration in hemodialysis patients initially identified

as risers led to a conversion to either dipper or attenuated dipper status, in the majority of cases.¹²⁵ In addition to dietary sodium, among 58 black normotensive adolescents, a 3-week high potassium diet was able to revert salt sensitive (defined as a ≥ 5 mmHg BP difference between the high and low dietary salt states) individuals originally deemed non-dippers to

dippers, which was unlike both their salt resistant counterparts as well as the usual diet control group in which nearly all such individuals remained non-dippers.¹²⁶ Correspondingly, among normotensive men, potassium supplementation was found to dose-dependently suppress salt sensitivity (defined as an increase in mean BP ≥ 3 mmHg with salt loading), particularly in blacks who had a greater frequency and severity of salt sensitivity.⁶³ A significant reduction of night-time BP following a 1-year multidisciplinary weight loss program was observed among normotensive obese women.¹²⁷ Moreover, in morbidly obese (body mass index BMI > 35 kg/m²) hypertensive patients, bariatric surgery restored the normal circadian rhythm in non-dippers from a nocturnal systolic BP fall of 4% to 16.4%.¹²⁸ In parallel, following the institution of a 20-week weight loss program, a decreased salt sensitivity of BP was observed but only in those who had successfully lost more than 1 kg of body weight.⁹⁹

In the area of nocturnal sympathoexcitation, a significant reduction of nocturnal BP following night-time dosing of an alpha-1-adrenergic blocker in hypertensive patients was identified but in non-dippers only.¹²⁹ This differential effect, however, has been observed with other classes of antihypertensive agents, arguing against the specificity of the response.^{42,130} Pharmacokinetic and pharmacodynamic differences between various antihypertensive medications and their times of administration ('chronotherapy') may be important factors in determining nocturnal antihypertensive effects. For example, despite equivalent daytime BP control, differential antihypertensive effects on night-time BP were demonstrated between a long-acting calcium channel blocker and a similarly long-acting angiotensin converting enzyme inhibitor in a group of elderly hypertensive patients.¹³¹ Nocturnal dosing of antihypertensive agents has also been associated with conversion from attenuated dipper or riser to dipper status in both controlled and refractory hypertensive patient populations.^{130,132–135} Uncontrolled short-term studies have revealed reductions in night-time BP readings along with transition from non-dipper to dipper status among normotensive and hypertensive subjects following nocturnal application of therapeutic continuous positive airway pressure (CPAP),^{136–138} which has been associated with sympathoinhibition unlike nocturnal application of subtherapeutic CPAP or oxygen.¹³⁹ In patients with end-stage renal disease, renal transplantation has been associated with a significant lowering of the prevalence of non-dipping from 73% within the first year after transplantation to 27% following the first year after transplantation, independent of 24-hour BP and concomitant medication changes,¹⁴⁰ with the

nocturnal BP fall correlating with renal allograft function.⁸⁷ Finally, in randomized parallel and crossover trials, nocturnal administration of exogenous melatonin was associated with a significant reduction of night-time BP, especially among non-dippers, unlike daytime BP and in some cases, this could not be entirely explained on the basis of an improvement in sleep.^{141–143} Non-dipping in subjects with type 2 diabetes mellitus has been found to relate more closely to post-prandial glycemic excursions, rather than fasting hyperglycemia.¹⁴⁴ However, whether improvements in glycemic control as well as sleep quality and duration translate into normalization of the circadian BP rhythm remains to be seen.

Conclusions

Awareness of the normal sleep–wake cycle of BP has resulted in an increasing appreciation for the significance of non-dipping, a concept often used to construe nocturnal hypertension. Notwithstanding various limitations, principally related to its reproducibility, the identification of nocturnal hypertension has been shown to predict deaths and/or adverse cardiovascular events both independent of and often superior to daytime BP. Several patient profiles have been associated with its occurrence (eg, older age, black race, diabetes mellitus, obesity, chronic kidney disease, sleep-related disturbances); moreover, many of these states are associated with sympathoexcitation and/or augmented salt sensitivity suggesting a common pathophysiologic basis. Further, a number of therapeutic strategies (eg, dietary salt restriction, diuretic therapy, dietary potassium liberalization, weight loss, chronotherapy, nocturnal CPAP) have demonstrated restorative capacity for the normal circadian BP rhythm. Nevertheless, whether greater effort expended on achievement of night-time BP control above and beyond daytime BP results in a greater improvement in patient outcomes remains to be seen.

Acknowledgments

Funding from Grant-in-Aid #NA-5327 from the Heart and Stroke Foundation of Ontario.

Disclosures

The authors declare no conflicts of interest.

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