Integrated Blood Pressure Control

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REVIEW

# Isolated Nocturnal Hypertension: What Do We Know and What Can We Do?

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**Abstract:** Nocturnal hypertension has been recognized as a significant risk factor for cardio- and cerebrovascular diseases. Blood pressure (BP) monitoring significantly increased our awareness of nocturnal hypertension and studies revealed its influence on target organ damage. Nocturnal hypertension is associated with nonphysiological 24-h BP patterns, which consider inadequate drop or even increment of nighttime BP in comparison with daytime BP (nondipping and reverse dipping). Nevertheless, investigations showed that nocturnal hypertension was a predictor of adverse outcome independently of circadian BP pattern. There are still many uncertainties regarding diagnosis, mechanisms and treatment of nocturnal hypertension. There is a small difference between American and European guidelines in cutoff values defining nocturnal hypertension. Pathophysiology is also not clear because many conditions such as diabetes, metabolic syndrome, obesity, sleep apnea syndrome, and renal diseases are related to nocturnal hypertension and nonphysiological circadian BP pattern, but mechanisms of nocturnal hypertension still remain speculative. Therapeutic approach is another important issue and chronotherapy provided the best results so far. There are studies which showed that some groups of antihypertensive medications are more effective in regulation of nocturnal BP, but it seems that the timing of drug administration has a crucial role in the reduction of nighttime BP and conversion of circadian patterns from nonphysiologic to physiologic. Follow-up studies are necessary to define clinical benefits of nocturnal BP reduction and restoring unfavorable 24-h BP variations to physiological variant.

**Keywords:** nocturnal hypertension, nondipping, target organ damage, therapy

## Introduction

The growing amount of evidence is showing that 24-h ambulatory blood pressure monitoring (ABPM) provides clinically useful information that could be used not only for diagnosis, but also for control and prognosis of hypertensive patients.[1–3] Circadian blood pressure (BP) rhythm has been unrecognized for a long time. O'Brien et al first classified hypertensive patients into two large groups—dippers and nondippers, depending on the percentage of BP drop during the night.[4] Later studies showed that patients with a lack or insufficient nighttime BP drop (nondippers) had a significantly worse outcome than those with normal BP circadian pattern (dippers).[3] Dichotomous classification of circadian BP patterns was not specific enough to describe patients with extreme nighttime BP changes and therefore a new four-tiled classification was proposed and nowadays accepted.[5] It includes patients with extreme reduction of nighttime BP (>20% in comparison with daytime values)—extreme dippers and those with increment of nighttime BP—reverse dipping or raisers (nighttime BP is higher than daytime BP).

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The majority of studies are consistent with regard to negative impact of nondipping BP pattern on cardiovascular outcome.[6,7] Investigations showed that a nondipping pattern was allied with increased risk of stroke, myocardial infarction, heart failure, coronary events and cardiovascular mortality.[6–8] The prognostic impact of a reverse dipping pattern has not been well established due to limited amount of long-term data. Recent studies showed that this pattern was related to adverse cardiac remodeling[9,10] and unfavorable cardiovascular outcome.[11,12] The most controversial effect is the impact of extreme dipping BP pattern on cardiac changes and cardiovascular outcome.[13]

Nocturnal hypertension represents an interesting entity that is usually connected with nondipping and reverse dipping patterns. However, it could not be excluded in dippers, whereas it is very rare among extreme dippers. The main question is which of two entities—nocturnal hypertension or nondipping status is more responsible for target organ damage and outcome. Many authors gave advantage to nocturnal hypertension over nondipping BP pattern.[14–16] However, there are also investigations that showed that nondipping and reverse BP patterns were independent of nocturnal BP associated with target organ damage and outcome.[9,10,12]

Our study group showed that nocturnal hypertension was associated with left and right ventricular remodeling,[17–19] whereas other authors demonstrated its negative effect on cardiovascular outcome in hypertensive patients.[20] There are still differences in definition between guidelines regarding cutoff values that define nocturnal hypertension and this could represent one of the major obstacles in the assessment of its influence on target organ damage and prognosis. The other important question is therapeutic approach to the patients with nocturnal hypertension, which depends on age, comorbidities, BP values, race, gender, etc.

The aim of this review is to summarize the current knowledge about the mechanisms that could be responsible for nocturnal hypertension development, diagnostic dilemma, epidemiology, reported target organ damage, prognosis, and treatment of this condition.

## Mechanisms

Circadian BP changes are conditioned by diurnal hormonal changes that include autonomic nervous system (sympathetic and parasympathetic nervous system, vasopressin, acetylcholine, adrenocorticotropic hormone, cortisol, insulin and ghrelin, adiponectin and leptin, and partly renin-angiotensin-aldosterone system. These fluctuations in levels of hormones are responsible for higher daytime and lower nighttime BP.

There are several potential mechanisms responsible for nocturnal hypertension: increased sympathetic nervous system activity, hyperactivity of renin-angiotensin-aldosterone system, sodium retention, renal function impairment, obstructive sleep apnea syndrome and other sleeping disorders, obesity, aging, stress, and diabetes.[21]

Nocturnal hypertension could be the first manifestation of hypertension, as a consequence of sympathetic overdrive, and in this case is usually related to adverse cardiovascular events (stroke, coronary artery disease, heart failure) or with other target organ damage (renal failure, cognitive dysfunction and peripheral artery disease) because it remains undetected for a long time.[22] This particularly refers to isolated nocturnal hypertension.

Alternatively, nocturnal hypertension could be the advanced stage of arterial hypertension. However, the supine position during sleep increases venous returns and results in elevation in the left ventricular preload and increased left ventricular wall stress according to the law of Laplace. The circulating volume is additionally increased by the movement of interstitial fluid from the soft tissue of the lower body, which further increases preload. The combination of elevated nocturnal intravascular volume and increased BP could induce the worsening of renal function due to increased intraglomerular pressure and hyperfiltration.

## Diagnosis According to the Different Guidelines

It is clear that nocturnal hypertension could be diagnosed only by BP monitoring. There are two possibilities: home and ambulatory BP monitoring. Even though ambulatory BP monitoring provides more measurements and therefore should be more accurate than home BP monitoring, Kario et al showed systolic BP obtained by home BP monitoring was a good predictor of cardiovascular events, independent of in-office and morning in-home SBP measurement.[23] Home BP monitoring in this study included three nocturnal BP measurements at one-hour intervals (02:00, 03:00 and 04:00).[23] Using ambulatory BP monitoring the number of nocturnal BP measurements (from going to bed to rising) should be ≥6.

There are small disparities between American and European guidelines regarding the definition of nocturnal hypertension. In the latest ACC/AHA guidelines nocturnal hypertension was defined as mean asleep SBP ≥110 mmHg and/or mean asleep DBP ≥65 mmHg measured by ambulatory BP monitoring, which corresponds to clinic BP ≥130/80

mmHg.[24] This definition for nocturnal hypertension is more restrictive in comparison with the European guidelines (SBP ≥120 mmHg and/or DBP ≥70 mmHg).[25] Isolated nocturnal hypertension considers that daytime BP is normal (<135/85 mmHg).[24,25]

Circadian BP pattern is determined by the percentage of BP drop during the night in comparison with diurnal BP. Four BP patterns could be defined: extreme dipping (>20% BP drop), dipping (10% <BP drop ≤20%), nondipping (0% <BP drop ≤10%), and inverse dipping or rising (BP drop ≤0%).

## Epidemiology

The prevalence of nocturnal hypertension varies between different populations because it largely depends on demographic, clinical, and ethnical factors. Additionally, the small differences in definition between American and European guidelines contribute to the various results regarding the prevalence of nocturnal hypertension. The Pressioni Monitorate E Loro Associazioni (PAMELA) study showed that nocturnal hypertension, diagnosed with ABPM, was present in 30% of participants (607 out of 2021 subjects).[26] Androulakis et al included 319 newly diagnosed hypertensive patients and found nocturnal hypertension in almost 50% of cases.[27] The Jackson Heart Study, which included African-Americans with a high prevalence of obesity and type 2 diabetes, showed that nocturnal hypertension was diagnosed in 39% of untreated participants.[28] Wang et al, in a Chinese population of 1322 patients with chronic kidney disease (56% with chronic glomerulonephritis), reported nocturnal hypertension in 60% of participants.[29] Patients with nocturnal hypertension were characterized by older age, presence of diabetes, higher levels of serum creatinine, cystatin C, calcium, uric acid, and homocysteine than nocturnal normotensive patients.

The prevalence of isolated nocturnal hypertension is lower, which is expected. The retrospective analyses showed that the prevalence of isolated nocturnal hypertension was higher among South Africans of black ancestry (10.2%) and Japanese (10.9%) than in Western (6.0%) and Eastern (7.9%) Europeans.[30] The prevalence of isolated nocturnal hypertension was higher (20.4%) in a Chinese population of patients with chronic kidney disease.[31] Salazar et al detected isolated nocturnal hypertension in 12.9% of the study population.[32] Its prevalence was lower in patients with office hypertension than in normotensive ones (7.4 vs 17.2%; $p<0.001$) and similar between nonhypertensive office blood pressure categories (optimal, normal, and high–normal blood pressure).[32]

The long-term and short-term reproducibility of isolated nocturnal hypertension is poor in the only two investigations exploring this issue.[33,34] Li et al reported the long-term reproducibility of isolated nocturnal hypertension over a 3.5-year follow-up in a small group of 30 subjects.[33] The persistence of isolated nocturnal hypertension pattern was found only in 10 subjects, while two-thirds of the patients changed their BP profile over time.[33] Short-term reproducibility of nocturnal hypertension is significantly better. The results from our group showed that reproducibility in the period of four weeks was 72.5%.[35]

## Target Organ Damage

The large body of evidence confirms the negative impact of nocturnal hypertension on target organ damage. Our study group showed that nocturnal hypertension was associated with impaired left and right ventricular structure, diastolic function and mechanics.[18,19] The PAMELA study showed that nocturnal BP level rather than the nocturnal BP decline represented a reliable parameter for prediction of LV hypertrophy in subjects with normal LV mass.[36] Similar findings were reported from other authors.[14]

Meta-analysis showed that nocturnal hypertension was related with LV hypertrophy and common carotid intima media thickness.[17] Li et al showed that isolated nocturnal hypertension was associated with increased arterial stiffness in the Chinese population.[33] The Jackson study reported significantly higher LV mass index in patients with isolated nocturnal hypertension.[28] However, there are also studies that did not find significant difference in central pulse pressure, aortic pulse wave velocity, or LV mass index.[28,37] In hypertensive patients with well-controlled self-measured BP, isolated nocturnal hypertension was associated with increased carotid intima-media thickness and relative wall thickness.[38]

Salazar et al reported that nocturnal, but not diurnal hypertension, was associated with insulin resistance in untreated normotensive and mildly hypertensive patients.[39] Yan et al showed that a reverse dipping BP pattern was independent predictor of lacunar infarction in hypertensive patients.[40] The authors did not separately investigate the effect of nocturnal BP, but only 24-h BP.

Kario et al showed that nocturnal systolic BP, measured by home BP monitoring, was associated with urinary albumin/creatinine ratio, LV mass index, brachial-ankle

pulse wave velocity, carotid intima media thickness, NTpro-BNP and high-sensitive cardiac troponin.[41]

## Outcome

Available data show the relationship between isolated nocturnal hypertension and increased risk of cardiovascular morbidity and mortality. In a large study that included 8000 subjects from three continents it was demonstrated that isolated nocturnal hypertension was associated with a higher risk of all cardiovascular events and total mortality compared with nocturnal normotension.[20] Subgroup analyses revealed that isolated nocturnal hypertension was particularly relevant in younger subjects for all-cause mortality (HR: 1.99, 95%CI: 1.14–3.47) and in nonsmokers (HR: 1.78, 95%CI: 1.25–2.55), less obese subjects (HR: 1.63, 95%CI: 1.08–2.46), and subjects with a history of cardiovascular disease (HR: 2.09, 95%CI: 1.00–4.36).[20]

In the Chinese patients with chronic renal disease was shown that isolated nocturnal hypertension was associated with an elevated risk for renal events (HR: 3.81, 95%CI: 1.74–8.36) and cardiovascular events (HR: 8.34, 95%CI: 1.98–35.07), even when adjusted for clinic BP, 24-h BP, or daytime BP.[42]

Presta et al showed that patients with masked hypertension and reverse BP pattern had a significantly higher risk of stroke, even after adjustment for age, gender, BMI, dyslipidemia, and diabetes.[43] Even though reverse dipping pattern does not always mean nocturnal hypertension, in this study the patients with reverse dipping also had nocturnal hypertension.

## Therapy

Nocturnal hypertension is closely connected with increased circulating volume and hyperactivation of sympathetic and renin-angiotensin-aldosterone systems. These are the main targets for therapeutic approach in the patients with nocturnal hypertension. Some authors showed that salt restriction and diuretics significantly reduced nocturnal BP and shifted BP pattern from nondipping to dipping.[44,45] Hermida et al reported a significant increase in the drop of nocturnal BP after evening administration of ACEI.[46] Due to mechanisms of action, it would be expected that angiotensin converting enzyme inhibitors (ACEIs)/angiotensin receptor II blockers (ARBs) in combination with diuretics would have a greater benefit than a combination of ACEI/ARB with calcium channel antagonists (CCBs). However, recently Kario et al showed that the ARB/CCB combination was superior to the ARB/diuretic combination in patients with uncontrolled nocturnal hypertension, independently of sodium intake, and despite the similar impact of both combinations in patients with higher salt sensitivity.[47]

Renin activity is increasing during the night and reaches its maximum in the morning, which is why long-acting direct renin inhibitor like aliskiren might be helpful. Giles et al showed that aliskiren and valsartan in combination reduced BP more significantly than valsartan alone, but only in nondippers and not in dippers.[48] The combination of aliskiren and valsartan induced conversion from nondippers to dippers in 32% and valsartan did the same in 22% of hypertensive patients. Even though there was no statistical significance in this study due to the limited number of participants, it was clear that the combination of aliskiren and valsartan might be more powerful in reduction of nocturnal BP.

Study that investigated the impact of CCB (cilnidipine) on circadian BP patterns in hypertensive patients reported significant changes in nocturnal systolic BP reduction rate only in reverse and extreme dippers, but not in dippers and extreme dippers.[49] Cilnidipine partially restored abnormal nocturnal BP pattern toward a normal dipping pattern in hypertensive patients. Effect of beta-blockers on circadian BP pattern has not been reported yet.

It is difficult to determine if antihypertensive group or timing of drug administration are responsible for the favourable effect on nocturnal BP reduction and modification from nondippers and reverse dippers to dippers and extreme dippers. The benefit of conversion in extreme dipping BP pattern is debatable because this circadian might be associated with nocturnal hypoxemia, coronary hypoperfusion, morning sympathetic activation, which could result with cerebro- and cardiovascular events, particularly in elderly patients.[50] Chronotherapy probably represents the best therapeutic approach in nocturnal hypertension. The MAPEC study compared the administration time between morning dose (taking all prescribed drugs in the morning) and bedtime doses (taking more than one drug at bedtime), and after a mean follow-up of 5.6 years in 2156 hypertensive patients reported that the bedtime dose provided better BP control.[51] Patients who were taking ≥1 drug at bedtime showed significantly lower relative risk of total cardiovascular disease events, compared to those taking all drugs in the morning. The prevalence of nondipping significantly reduced (62% vs 34%) and prevalence of well-controlled BP increased (62% vs 53%) in patients receiving medication at bedtime.[51]

Obstructive sleep apnea is likely one of the possible mechanisms for development of isolated nocturnal

hypertension. Several studies showed that obstructive sleep apnea is one of the major factors for development of nondipping BP pattern. However, to date there is no study that directly connects sleep apnea with isolated nocturnal hypertension and this should be more deeply investigated in future studies on isolated nocturnal hypertension.[52]

Interestingly, renal denervation showed significant reduction in nocturnal systolic BP in patients with obstructive sleep apnea and resistant hypertension.[53] This could be an interesting future direction in treatment of nighttime hypertension and conversion from nondipping and reverse dipping BP patterns to dipping BP pattern.

## Conclusion

A growing body of evidence is showing that nocturnal hypertension is associated with higher cardiovascular morbidity and mortality. There are several possible mechanisms that could explain an increase in nocturnal BP, but most of them are still in the domain of speculation. Uncertainties regarding pathophysiology determine the difficulties in therapeutic approach. It seems that chronotherapy represents the best treatment which provides appropriate reduction in nocturnal BP, as well as conversion from unfavorable BP patterns (nondipping and reverse dipping) to physiological BP pattern (dipping). However, longer follow-up studies are necessary to define clinical benefits of nocturnal BP reduction and restoring unfavorable circadian BP variations to physiological variant.

## Disclosure

Professor Giuseppe Mancia reports personal fees from Boehringer Ingelheim, Ferrer, Medtronic, Menarini, Merck, Novartis Pharma, Recordati, Sanofi, and Servier, outside the submitted work. The authors report no other conflicts of interest in this work.

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