Curr Hypertens Rep (2010) 12:474–479
DOI 10.1007/s11906-010-0152-0

Nighttime Blood Pressure: A Target for Therapy?

Bernard Waeber · Jean-Jacques Mourad · Eoin O'Brien

Published online: 23 September 2010

Abstract Ambulatory blood pressure (BP) monitoring is increasingly used in the evaluation of hypertensive patients. The ability to monitor BP throughout the day and night allows the detection of abnormal nocturnal BP patterns, the most common being a "nondipping" pattern, which is associated with increased cardiovascular risk; its correction appears to have a positive impact on cardiovascular outcome. Antihypertensive treatment should be individually adjusted to control BP during both daytime and nighttime. However, drug-induced lowering of nocturnal BP, if excessive, could amplify the morning BP surge in patients with daytime BP elevation, increasing the risk of developing a cardiovascular event. Ambulatory BP monitoring therefore represents a unique tool to establish the most appropriate antihypertensive drug regimen for the individual patient.

Keywords Ambulatory blood pressure · Morning surge · Nighttime blood pressure · Cardiovascular risk · Dipper pattern · Nondipping pattern

B. Waeber (✉)
Division of Clinical Pathophysiology,
Centre Hospitalier Universitaire Vaudois,
PPA-MP 14/204,
CH-1011 Lausanne, Switzerland
e-mail: Bernard.Waeber@chuv.ch

J.-J. Mourad
Hôpital Avicenne,
Rue de Stalingrad 125,
93000 Bobigny, Cedex, France
e-mail: jean-jacques.mourad@avc.aphp.fr

E. O'Brien
The Conway Institute of Biomolecular and Biomedical Research,
IE- Belfield,
Dublin 4, Ireland
e-mail: eobrien@iol.ie

Introduction

The superiority of noninvasive ambulatory blood pressure monitoring (ABPM) over clinic blood pressure (BP) in predicting cardiovascular morbidity and mortality has been demonstrated repeatedly in the general population [1, 2] as well as in patients with hypertension, both treated [3–5] and untreated [4, 6, 7].

A main advantage of ABPM is that it can provide multiple BP measurements taken away from the medical environment, thereby allowing the identification of normotensive individuals (with normal clinic BP and normal mean 24-hour or daytime ABPM), patients with true hypertension (high clinic BP and high mean 24-hour or daytime ABPM), patients with white-coat hypertension (high clinic BP but normal mean 24-hour or daytime ABPM), and patients with masked hypertension (normal clinic BP but high mean 24-hour or daytime ABPM). These different patterns of clinic BP and ABPM behaviors are associated with clinically relevant differences in cardiovascular outcome, which explains why ABPM is becoming more and more indispensable to good clinical practice [8, 9]. Overall, the severity of target organ damage and the incidence of cardiovascular events is greater in patients with masked hypertension than in those with white-coat hypertension [10].

ABPM has major advantages over conventional BP measurement. One is that it gives a view of the BP profile over a 24-hour period rather than an isolated BP value at a single time. This is an important advantage because BP is subject to diurnal BP phenomena (mainly nighttime dipping) as well as shorter-term BP changes related to physical and mental activities. Notably, there is strong evidence that cardiovascular prognosis is worsened in the presence of enhanced short-term BP variability [1, 11, 12].

Another key issue is the day-night BP pattern. Nighttime BP is known to better reflect cardiovascular risk than daytime BP, and a blunted nocturnal BP decrease has been shown to confer an increased risk of cardiovascular events [13–15]. There are therefore good reasons to wonder whether BP-lowering drugs can correct abnormal nocturnal BP patterns and thus may have a positive impact on cardiovascular outcome. This paper reviews the evidence suggesting that BP control should target not only daytime BP, but also nighttime BP.

Determination and Clinical Significance of Nighttime Blood Pressure

Nighttime BP is generally regarded as reflecting basal BP. It is defined as the average of BP readings recorded during the period most likely coinciding with sleep. One common method is to ask the patient the time of retiring and rising. Another way is to analyze the BP profiles according to a fixed time schedule, with the daytime period extending from 9 AM to 21 PM, for example, and nocturnal period that starts at 1 AM and ends at 6 AM [16].

The classification of a patient as a "dipper" or a "non-dipper" markedly depends on how reliably daytime BP and nighttime BP are measured [17]. In particular, dipping or nondipping status is greatly influenced by awake activities, the quality of sleep, and the position of the arm relative to the heart during both daytime and nighttime [18–20]. These interfering factors probably account for the rather poor reproducibility of the nocturnal BP decline [21–24]. The reproducibility of nocturnal BP changes may be improved using strict criteria to define the daytime and nighttime periods [25, 26].

A popular way to stratify patients according to their dipping status is based on the calculation of percentage changes in BP between daytime and nighttime. According to arbitrary criteria, "normal dippers" lower their BP by 10%–20% during sleep, "nondippers" by less than 10%, and "extreme dippers" by more than 20% [6, 27, 28]. An alternative to this dipper/nondipper classification is to assess whether nighttime BP is normal or elevated in a given patient. ABPM has been used to evaluate the nocturnal status of hypertensive patients by these two methods [29]. Figure 1 shows the percentage of dippers (defined as patients who demonstrated a decrease of 10% or more in nighttime systolic and diastolic BP relative to corresponding daytime BP) and the percentage of patients with nocturnal normotension (defined as a nighttime systolic BP of 125 mm Hg or less and nighttime diastolic BP of 80 mm Hg or less). A larger fraction of patients were considered normal based on their dipping status rather than on the actual level of nocturnal BP. It is unfortunately still unclear which of the two approaches is the best to evaluate cardiovascular risk. It may be more appropriate to characterize patients using nocturnal normotensive/hypertensive status rather than the dipper/nondipper classification when evaluating the effects of antihypertensive therapy in an individual. Attempting to achieve a target BP does seem more meaningful than trying only to correct an abnormal nighttime BP pattern. According to the Practice Guidelines of the European Society of Hypertension, awake BP should be less than 135/85 mm Hg and asleep BP should be less than 120/70 mm Hg [16]. BP readings should be obtained at intervals of 20–30 min, both during the day and at night.

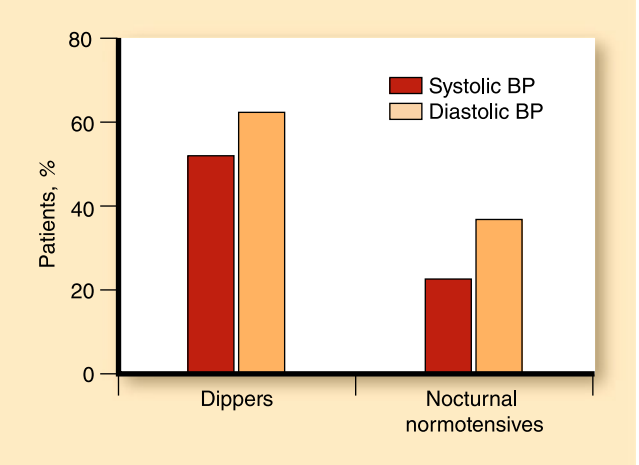

Fig. 1 Percentage of patients (n=129) considered as "dippers" (nighttime blood pressure [BP] lower than daytime BP by ≥10%) or nocturnal normotensives (nighttime BP≤125/80 mm Hg) during ambulatory BP monitoring. (*Data from* White and Larocca [29])

Conditions Associated With a Nondipping Profile

Daytime inactivity and poor sleep may contribute to the nondipping phenomenon, but there are also nondippers among patients with good subjective sleep quality [30]. The nondipping pattern may be encountered in a number of clinical conditions, as reviewed recently and summarized in Table 1 [31].The pathophysiologic mechanisms are complex; they may involve an insufficient decrease in cardiac output, abnormal autonomic function, or excessive renal fluid retention during sleep. Notably, patients with salt-sensitive forms of hypertension are likely to be nondippers, as illustrated by patients with essential hypertension in whom the normal nighttime BP rhythm could be restored by sodium restriction [32, 33].

A large survey performed recently by the Spanish Society of Hypertension is particularly interesting in this context, as it gives information on circadian blood pressure patterns in everyday practice [34•]. In this study, 24-hour ABPM was performed in 42,947 hypertensive patients

Table 1 Clinical conditions associated with the "nondipping" blood pressure pattern

Endocrine conditions
Aldosteronism
Hyercortisolism
Pheochromocytoma
Acromegaly
Hyperthyroidism
Hyperparathyroidism
Renal dysfunction
Chronic renal disease
Renal transplantation
Unilateral nephrectomy
Disturbances of the autonomic nervous system
Pure autonomic failure
Diabetic neuropathy
Uremic neuropathy
Obstructive sleep apnea syndrome
Miscellaneous
Salt-sensitive hypertension
Pre-eclamptic toxemia
Malignant hypertension
Cardiac transplantation
Ethnicity (Africans and African Americans > Caucasians)

Data from Birkenhager and van den Meiracker [31]

observed by 1,126 physicians. The patients were men or women at least 18 years of age who had documented high BP (≥140 and/or ≥90 mm Hg) in the absence of antihypertensive treatment on two or more visits (n= 8,384) or who were under treatment with one or more BP-lowering drugs for at least 2 months (n=34,563). Daytime and nighttime periods were defined individually based on the reported time at which the patient went to bed. A normal dipping pattern was defined as a nocturnal reduction of more than 10% in the average systolic BP relative to the average daytime systolic BP. Patients were classified as "extreme dippers" when the nighttime systolic BP decrease was greater than 20%. When the mean night systolic BP was higher than the daytime BP, the patients were called "risers." Figure 2 illustrates the prevalence of the various circadian patterns in treated and untreated patients. The prevalence of nondipping status was high in both groups of patients, but it was even higher in treated patients (39.4%) than in untreated patients (35.0%). There were also a nonnegligible fractions of patients in the "extreme dippers" and "risers" categories. Abnormal nocturnal BP decline was seen more often in older patients, in women, and in patients with additional cardiovascular risk factors (including obesity or diabetes) or overt cardiovascular or renal disease. In treated patients, no relationship was found between a blunted nocturnal BP dip and the time of drug intake, but patients taking more than one drug were more likely to be nondippers. These observations do not allow conclusions about causal relationships, but they do point out the importance of performing ABPM in hypertensive patients with high cardiovascular risk, as they are also at high risk of being nondippers.

Effects of Antihypertensive Drugs on Nighttime Blood Pressure

ABPM is now considered mandatory during the developmental phase of antihypertensive drugs in order to establish the magnitude and duration of their BP-lowering effect. ABPM allows the characterization of the daytime and nighttime BP responses to a given drug, the detection of eventual excessive peak effects, and the calculation of indices reflecting the smoothness of its action. The results of such trials are usually provided by illustrating the 24-hour BP profiles before and after treatment and by showing the effect of the drug on the average daytime and nighttime BP. It is unfortunate, however, that more attention has not been given to the drug-induced BP normalization rate. This information would be very helpful, for example, in determining whether a drug is equally effective in normalizing BP during everyday activities and during sleep, and in assessing the fraction of patients in whom daytime BP and nighttime BP are normalized when the target clinic BP is achieved.

There is a growing interest in chronotherapy as a means of optimizing BP control in hypertensive patients [35•] by demonstrating not only normalization of daytime and nighttime BP but also the conversion of an abnormal dipping pattern to a normal pattern, with the use of doses that minimize the incidence of adverse effects. This approach allows selection of the most suitable dose and the best time for administering the drug. As an example, the dihydropyridine calcium antagonist nifedipine (the gastrointestinal therapeutic system [GITS] formulation) has been reported to be significantly more effective in lowering BP and is better tolerated when given at bedtime rather than in the morning [36]. In fact, a number of antihypertensive drugs—various calcium antagonists, angiotensin-converting enzyme (ACE) inhibitors and AT1-receptor antagonists—have been shown to have different effects on nocturnal BP dipping (as reflected by the so-called diurnal/nocturnal BP ratio) with changes in the time of administration [35•].

All modern antihypertensive drugs have been developed as once-a-day medications in order to facilitate long-term adherence with therapy. To achieve this goal, some agents are delivered in chronotherapeutically designed drug formulations, such as controlled-onset or extended-release preparations. One

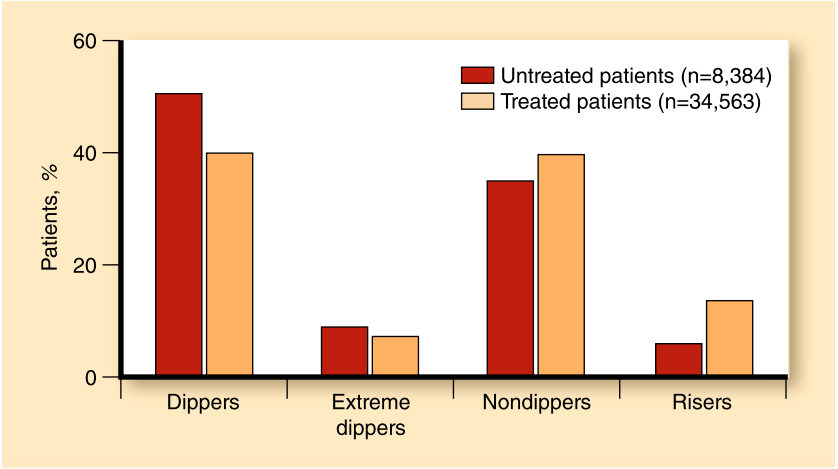

Fig. 2 Percentage of patients with treated or untreated hypertension in different blood pressure "dipping" categories. (*Data from* de la Sierra et al. [34•])

possible explanation for the nondipping pattern is insufficient 24-hour therapeutic coverage. The time at which a single daily dose is administered may greatly influence the 24-hour BP profile. For example, in a substudy of the Heart Outcomes Prevention Evaluation (HOPE) trial, patients with peripheral arterial disease underwent 24-hour ABPM at randomization and again after 1 year of treatment with ramipril, 10 mg once daily at bedtime (n=20), or placebo [37]. The ACE inhibitor lowered 24-hour BP and nighttime BP significantly more than did the placebo, but there was no such result for either daytime or clinic BP. The decreased cardiovascular morbidity and mortality observed in the ramipril group of the whole HOPE population, in the presence of only a modest mean difference in clinic BP (3/2 mm Hg in favor of ramipril-treated patients) may therefore be partly related to the better nocturnal BP control obtained by giving ramipril at the evening.

The importance of nighttime BP control in treated hypertensive patients is also supported by observations in a substudy of the Anglo-Scandinavian Cardiac Outcomes Trial (ASCOT-BPLA) [38]. In this substudy, 1,905 hypertensive patients with high cardiovascular risk were randomized to amlodipine or atenolol for a median follow-up of 5.5 years, with the possibility of adding perindopril or thiazide, respectively, to achieve a target clinic BP of less than 140/90 mm Hg. There was a direct relationship between the rate of cardiovascular events and both clinic and ambulatory BP, with the best predictive value provided by nighttime BP.

A recent cross-sectional study was performed in 1,794 patients with resistant hypertension (mean awake ambulatory BP≥135/85 mm Hg, nighttime ambulatory BP≥120/70 mm Hg, or the current intake of four or more drugs) [39]. Table 2 depicts daytime and nighttime ambulatory BP of patients taking all antihypertensive drugs on awakening (n=733), compared with BP measurements in patients who took at least 1 antihypertensive drug at bedtime (n=573). There was no significant difference between the two groups in terms of daytime BP, but nocturnal BP was significantly lower when the drug regimen included an evening dose of at least 1 antihypertensive agent. This finding has important implications, because resistant hypertension is a widely accepted indication for ABPM [16], which therefore may be useful not only to assess whether patients with high clinic BP also exhibit high BP values during everyday activities, but also to guide treatment, including the time of drug administration.

The Risk of the Morning Blood Pressure Surge

An excessive increase in morning BP upon awakening (morning surge) appears to be associated with an increased risk of fatal and nonfatal CV events [40•]. The risk appears particularly important in elderly hypertensive patients, especially with regard to cerebrovascular complications

Table 2 Chronotherapy in patients with resistant hypertension: The effect of taking antihypertensive medications on awakening or at bedtime

	Ambulatory blood pressure, *mm Hg*[a]		*P* (between groups)
	All drugs on awakening (n=733)	≥1 drug at bedtime (n=573)	
Awake SBP	137±16	135±15	0.053
Awake DBP	80±12	80±12	0.913
Asleep SBP	133±19	123±15	<0.001
Asleep DBP	73±11	69±10	<0.001
Nondippers	83.1%	40%	<0.001

[a] Mean±SD

DBP—diastolic blood pressure; SBP—systolic blood pressure

Data from Hermida et al. [39]

[41]. Growing attention has therefore been directed to the morning surge during the past few years [42]. A study performed in 1,430 Japanese patients at least 40 years of age, with a mean follow-up of 10.4 years, assessed whether the nocturnal BP decline and the BP surge influenced the risk of stroke [43]. It showed an increased risk of intracerebral hemorrhage in extreme dippers (≥20% mm Hg nocturnal BP decline) versus normal dippers (10%–19% decline), as well as in patients with a morning BP surge of 25 mm Hg or more.

The magnitude of the morning BP surge appears to be independent of the 24-hour ambulatory BP and the nocturnal dipping status, however [41, 44]. In a recent study in 5,645 individuals from 8 countries with a median follow-up of 11.4 years, the morning BP surge was evaluated using two approaches: 1) *Sleep-through morning surge*: the difference between the morning systolic BP (average of BP 2 h after awakening) and the lowest nighttime systolic BP (average of the lowest BP and the two readings immediately before and after the lowest value); and 2) *Preawakening morning surge*: the difference between the morning systolic BP (average of BP 2 h after awakening) and the preawakening systolic BP (average of BP during the 2 h before awakening) [40•]. The risk of cardiac and coronary events (but not cerebrovascular events), was significantly increased in patients with a sleep-through morning surge of 37 mm Hg or greater, or with a preawakening surge of at least 28 mm Hg. The evidence suggests that attempts to correct a nondipping pattern in hypertensive patients are fully justified, but in so doing, daytime BP also must be controlled to avoid inducing a large morning surge.

Conclusions

The current evidence shows that it is essential to control both daytime and nighttime BP to maximize the beneficial effects on clinical outcome of antihypertensive therapy. The individualization of BP-lowering treatment therefore requires ABPM in most hypertensive patients. Chronotherapy could greatly influence nocturnal BP profiles and should be considered in increasing populations such as patients with obstructive sleep apnea. Further studies are needed to establish whether certain classes of antihypertensive drugs (or certain drugs within a class) are particularly effective in correcting abnormalities of nocturnal BP.

Disclosure Conflicts of Interest: B. Waeber: consultant for Novartis and Menarini; honoraria from Novartis, AstraZeneca, Servier, and Menarini; J-J. Mourad: none; E. O'Brien: none.

References

Papers of particular interest, published recently, have been highlighted as:
• Of importance

1. Kikuya M, Ohkubo T, Asayama K, et al.: Ambulatory blood pressure and 10-year risk of cardiovascular and noncardiovascular mortality: the Ohasama study. Hypertension 2005, 45:240–245.
2. Sega R, Facchetti R, Bombelli M, et al.: Prognostic value of ambulatory and home blood pressures compared with office blood pressure in the general population: follow-up results from the Pressioni Arteriose Monitorate e Loro Associazioni (PAMELA) study. Circulation 2005, 111:1777–1783.
3. Clement DL, De Buyzere ML, De Bacquer DA, et al.: Prognostic value of ambulatory blood-pressure recordings in patients with treated hypertension. N Engl J Med 2003, 348:2407–2415.
4. Staessen JA, Thijs L, Fagard R, et al.: Predicting cardiovascular risk using conventional vs ambulatory blood pressure in older patients with systolic hypertension. Systolic Hypertension in Europe Trial Investigators. JAMA 1999, 282:539–546.
5. Redon J, Campos C, Narciso ML, et al.: Prognostic value of ambulatory blood pressure monitoring in refractory hypertension: a prospective study. Hypertension 1998, 31:712–718.
6. Verdecchia P, Porcellati C, Schillaci G, et al.: Ambulatory blood pressure. An independent predictor of prognosis in essential hypertension. Hypertension 1994, 24:793–801.
7. Dolan E, Stanton A, Thijs L, et al.: Superiority of ambulatory over clinic blood pressure measurement in predicting mortality: The Dublin Outcome Study. Hypertension 2005, 46:156–161.
8. O'Brien E: Ambulatory blood pressure measurement is indispensable to good clinical practice. J Hypertens 2003, 21:S11–S18.
9. Pickering TG, Shimbo D, Haas D: Ambulatory blood-pressure monitoring. N Engl J Med 2006, 354:2368–2374.
10. Verdecchia P, Angeli F, Gattobigio R, et al.: The clinical significance of white-coat and masked hypertension. Blood Press Monit 2007, 12:387–389.
11. Mancia G, Bombelli M, Facchetti R, et al.: Long-term prognostic value of blood pressure variability in the general population: results of the Pressioni Arteriose Monitorate e Loro Associazioni Study. Hypertension 2007, 49:1265–1270.
12. Dolan E, O'Brien E: Blood pressure variability: clarity for clinical practice. Hypertension 2010, 56:179–181.
13. Fagard RH, Celis H, Thijs L, et al.: Daytime and nighttime blood pressure as predictors of death and cause-specific cardiovascular events in hypertension. Hypertension 2008, 51:55–61.
14. Boggia J, Li Y, Thijs L, et al.: Prognostic accuracy of day versus night ambulatory blood pressure: a cohort study. Lancet 2007, 370:1219–1229.
15. Ohkubo T, Hozawa A, Yamaguchi J, et al.: Prognostic significance of the nocturnal decline in blood pressure in individuals with and without high 24-h blood pressure: the Ohasama study. J Hypertens 2002, 20:2183–2189.
16. O'Brien E, Asmar R, Beilin L, et al.: Practice guidelines of the European Society of Hypertension for clinic, ambulatory and self blood pressure measurement. J Hypertens 2005, 23:697–701.
17. Parati G: Blood pressure reduction at night: sleep and beyond. J Hypertens 2000, 18:1725–1729.
18. Kammila S, Campbell NR, Brant R, et al.: Systematic error in the determination of nocturnal blood pressure dipping status by ambulatory blood pressure monitoring. Blood Press Monit 2002, 7:131–134.
19. Hermida RC, Calvo C, Ayala DE, et al.: Relationship between physical activity and blood pressure in dipper and non-dipper hypertensive patients. J Hypertens 2002, 20:1097–1104.

20. Cavelaars M, Tulen JH, Man in 't Veld AJ, et al.: Assessment of body position to quantify its effect on nocturnal blood pressure under ambulatory conditions. J Hypertens 2000, 18:1737–1743.
21. James MA, Fotherby MD, Potter JF: Reproducibility of the circadian systolic blood pressure variation in the elderly. J Hypertens 1995, 13:1097–1103.
22. van der Steen MS, Lenders JW, Graafsma SJ, et al.: Reproducibility of ambulatory blood pressure monitoring in daily practice. J Hum Hypertens 1999, 13:303–308.
23. Mochizuki Y, Okutani M, Donfeng Y, et al.: Limited reproducibility of circadian variation in blood pressure dippers and nondippers. Am J Hypertens 1998, 11:403–409.
24. Omboni S, Parati G, Palatini P, et al.: Reproducibility and clinical value of nocturnal hypotension: prospective evidence from the SAMPLE study. Study on Ambulatory Monitoring of Pressure and Lisinopril Evaluation. J Hypertens 1998, 16:733–738.
25. Ben-Dov IZ, Ben-Arieh L, Mekler J, Bursztyn M: Blood pressure dipping is reproducible in clinical practice. Blood Press Monit 2005, 10:79–84.
26. Chaves H, Campello de Souza FM, Krieger EM: The reproducibility of dipping status: beyond the cutoff points. Blood Press Monit 2005, 10:201–205.
27. Pickering T: Recommendations for the use of home (self) and ambulatory blood pressure monitoring. American Society of Hypertension Ad Hoc Panel. Am J Hypertens 1996, 9:1–11.
28. Kuwajima I, Shimosawa R, Kanemaru A, et al.: Diminished nocturnal decline in blood pressure in elderly hypertensive patients with left ventricular hypertrophy. Am Heart J 1992, 123:1307–1311.
29. White WB, Larocca GM: Improving the utility of the nocturnal hypertension definition by using absolute sleep blood pressure rather than the "dipping" proportion. Am J Cardiol 2003, 92:1439–1441.
30. Cavelaars M, Tulen JH, van Bemmel JH, van den Meiracker AH: Physical activity, dipping and haemodynamics. J Hypertens 2004, 22:2303–2309.
31. Birkenhager AM, van den Meiracker AH: Causes and consequences of a non-dipping blood pressure profile. Neth J Med 2007, 65:127–131.
32. Uzu T, Ishikawa K, Fujii T, et al.: Sodium restriction shifts circadian rhythm of blood pressure from nondipper to dipper in essential hypertension. Circulation 1997, 96:1859–1862.
33. Uzu T, Kazembe FS, Ishikawa K, et al.: High sodium sensitivity implicates nocturnal hypertension in essential hypertension. Hypertension 1996, 28:139–142.
34. • de la Sierra A, Redon J, Banegas JR, et al.: Prevalence and factors associated with circadian blood pressure patterns in hypertensive patients. Hypertension 2009, 53:466–472. *A lot of knowledge has been accumulated owing to this large survey performed in Spain by doctors in everyday practice to compare ABPM and casual office blood pressure*.
35. • Hermida RC, Ayala DE, Calvo C, et al.: Chronotherapy of hypertension: administration-time-dependent effects of treatment on the circadian pattern of blood pressure. Adv Drug Deliv Rev 2007, 59:923–939. *This extensive review discusses in detail the current knowledge on chronotherapy.*
36. Hermida RC, Ayala DE, Mojon A, et al.: Reduction of morning blood pressure surge after treatment with nifedipine GITS at bedtime, but not upon awakening, in essential hypertension. Blood Press Monit 2009, 14:152–159.
37. Svensson P, de Faire U, Sleight P, et al.: Comparative effects of ramipril on ambulatory and office blood pressures: a HOPE substudy. Hypertension 2001, 38:E28–E32.
38. Dolan E, Stanton AV, Thom S, et al.: Ambulatory blood pressure monitoring predicts cardiovascular events in treated hypertensive patients—an Anglo-Scandinavian Cardiac Outcomes Trial substudy. J Hypertens 2009, 27:876–885.
39. Hermida RC, Ayala DE, Mojon A, Fernandez JR: Effects of time of antihypertensive treatment on ambulatory blood pressure and clinical characteristics of subjects with resistant hypertension. Am J Hypertens 2010, 23:432–439.
40. • Li Y, Thijs L, Hansen TW, et al.: Prognostic value of the morning blood pressure surge in 5645 subjects from 8 populations. Hypertension 2010, 55:1040–1048. *An International Database on Ambulatory Blood Pressure was used to assess the prognostic value of the morning blood pressure surge. This is a very appealing approach to accumulate data and gain new insight into ABPM*.
41. Kario K, Pickering TG, Umeda Y, et al.: Morning surge in blood pressure as a predictor of silent and clinical cerebrovascular disease in elderly hypertensives: a prospective study. Circulation 2003, 107:1401–1406.
42. Kario K: Time for focus on morning hypertension: pitfall of current antihypertensive medication. Am J Hypertens 2005, 18:149–151.
43. Metoki H, Ohkubo T, Kikuya M, et al.: Prognostic significance for stroke of a morning pressor surge and a nocturnal blood pressure decline: the Ohasama study. Hypertension 2006, 47:149–154.
44. Yano Y, Hoshide S, Inokuchi T, et al.: Association between morning blood pressure surge and cardiovascular remodeling in treated elderly hypertensive subjects. Am J Hypertens 2009, 22:1177–1182.