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REVIEW SERIES

Diurnal blood pressure variation, risk categories and antihypertensive treatment

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Ambulatory blood pressure (BP) monitoring is a useful tool aiding diagnostic and management decisions in patients with hypertension. Diurnal BP variation or circadian rhythm adds prognostic value to the absolute BP elevation. The Spanish ABPM Registry has collected information from >30 000 treated hypertensive patients attended by either primary care physicians or referral specialists. The analysis of BP diurnal variation has allowed the conclusion that nocturnal BP decline is related to the level of risk. Patients with blunted nocturnal dip frequently belong to high- or very high-risk categories and specifically are often older, obese, diabetics or with overt cardiovascular or renal disease. With respect to treatment, the non-dipper profile is more often observed in patients receiving several antihypertensive drug agents, but it does not correlate with the time of drug administration. Among patients receiving only one drug, non-dihydropyridine calcium channel blockers and α-blockers are associated with less nocturnal BP decline than other antihypertensive drug classes, even after adjusting for the level of risk.
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INTRODUCTION

Hypertension is one of the most important challenges for public health systems. This relevance is determined by its high prevalence and its association with the risk of cardiovascular and renal diseases.[1–3] In 2000, approximately a quarter of the worldwide adult population had hypertension, and this proportion is expected to rise to 29% in 2025.[4]

The current management of hypertensive patients often does not consider or gives little importance to the biological rhythms inherent to the disease process. The development of techniques for ambulatory blood pressure (BP) measurement has generated a series of questions directly related to the biological rhythms of the cardiovascular system.[5] In recent years, several evidences highlight the influence of nocturnal BP values and, more specifically, the absence of nocturnal dipping and increased morning surge of BP on the development of target organ damage and increased cardiovascular risk.[5]

Ambulatory BP monitoring techniques have expanded the knowledge regarding the circadian rhythm of BP. Several evidences suggest a relationship between cardiovascular complications such as acute myocardial infarction and cerebrovascular disease with circadian BP changes.[6] In fact, many studies suggest that patients who do not show an appropriate nocturnal dip in BP can suffer from a variety of disorders associated with increased rates of cardiovascular morbidity and mortality.[7–9] Ohkubo *et al.*[10] have shown that a blunted nocturnal decline in BP was a risk factor for cardiovascular mortality in the general population. In this regard, Cuspidi *et al.*[7] have shown that the persistence of a non-dipper pattern is associated with an increased left ventricular mass index, a thicker interventricular septum and a larger diameter of both the left atrium and the aortic root, in a group of 375 previously untreated hypertensive patients. Similarly, non-dipper hypertensives show a greater degree of insulin resistance and lower levels of adiponectin, compared with those showing a normal dipping pattern.[8] These non-dipper hypertensive patients have a more severe impairment of endothelial function as manifested by a reduced ability of endothelium-dependent vasodilation, mediated by a decrease in nitric oxide release.[9] In fact, reverse dippers show wider pulse pressure at night than any other groups, suggesting the potential role of arterial stiffness as an underlying mechanism of impaired cardiovascular risk.[11] All these changes determine a worse long-term prognosis of those hypertensives with absence of nocturnal dip in BP. In a meta-analysis including data of 3468 patients from four prospective studies, the dipping pattern and the night–day BP ratio significantly and independently predict mortality and cardiovascular events in hypertensive patients without history of major cardiovascular disease.[12] In diabetic patients, the loss of the physiological circadian pattern was associated with increased mortality in both type 1 and type 2.[13]

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Moreover, there is growing evidence linking early morning rise in BP and increased cardiovascular risk.[14] Although the mechanisms responsible for this relationship are not well known, several factors contribute to hemodynamic and neurohumoral changes.[6,14,15] In patients with coronary disease, transiently myocardial ischemia may appear in the first 2 h after waking.[16] Similarly, the observation of a group of 1167 patients with ischemic stroke revealed that the onset of the stroke occurred in the early morning hours more frequently than at other times of the day[17] and that the incidence of stroke is directly related to the magnitude of the morning rise in BP.[18] Similarly, several meta-analyses confirmed the relationship between higher rates of cardiovascular complications (myocardial infarction[19] and stroke[20]) and the early hours of the morning.

Definitely, the availability of techniques for ambulatory BP measurement has shown other aspects of circadian variability of BP (absence of physiological nocturnal dipping, early morning surge) that must be considered as a decisive factor influencing the development and progression of target organ damage and long-term prognosis. Proper management of these factors could positively contribute to the cardiovascular prognosis of hypertensive patients.

CIRCADIAN BP VARIATION AND RISK CATEGORIES

As mentioned above, there is a close relationship between circadian BP variation and cardiovascular risk. One of the analyses from the Spanish Society of Hypertension ABPM Registry was a comparison between high-risk and low-to-moderate-risk hypertensive patients.[21] We identified 6534 (37.9%) hypertensive subjects as having high or very high added cardiovascular risk and 10 885 (62.1%) with low-to-moderate added risk according to the 2003 ESH–ESC guidelines stratification score.[22] Prevalence of a non-dipping pattern was 58.7% in high-risk patients and 47.9% in hypertensives with a lower risk profile. The difference in the non-dipper prevalence between these subgroups of hypertensives was almost entirely caused by an increased prevalence of risers. These data have been updated for the five categories of risk and are exposed in Figure 1. Similarly, a high prevalence of either a non-dipper or a riser pattern of BP has been reproduced in further analyses from our database performed diabetics, patients with chronic kidney disease or hypertensives with coronary heart disease. Hypertensive diabetics were non-dippers in 64.2% of cases, being 21.0% risers. Corresponding data in renal and coronary heart disease patients were 72.1 and 25.8%, and 69.4 and 25.1%, respectively.[23]

A relationship between the level of BP and the non-dipper pattern has also been reported, according to data from our group[21] (Table 1). Patients showing most elevated ambulatory systolic BP (>155 mm Hg) showed a prevalence of non-dippers of ≈70%. However, patients in the lowest levels of ambulatory BP (<135 mm Hg), but with high-risk showed an increased prevalence of non-dipping compared with those at the same level of BP, but with a lower risk (56.0 *vs.* 45.7%).

Opportunities to compare our results regarding prevalence of circadian patterns with that from other studies are scarce. Cuspidi *et al.*[24] reported that the prevalence of non-dippers pattern were 28.5% in low-risk, 32.6% in medium-risk and 42.2% in high-risk hypertensives. These investigators evaluated a series of 580 untreated patients, but office grade 3 BP, diabetes or associated clinical conditions were excluded. This is obviously in contrast with our database, in which most of the patients were on treatment, and these specific clinical situations were not excluded.

In a recent study, Redon *et al.*[25] have shown that the prevalence of non-dippers in patients with stages 3 or 4 chronic kidney disease was 47%, far below our 72.1% observation. Possible explanations include an office BP considerably lower in the former study and differences in the methodology for diagnosing the dipping status with regard to the nighttime period definition.[21,25]

In summary, high-risk hypertensives show a remarkable high prevalence of abnormalities in circadian BP variation with a key influence in absolute levels of nighttime and 24-h BP. These observations support the recommendation of a wider use of ABPM in high-risk hypertensive patients.[21,26]

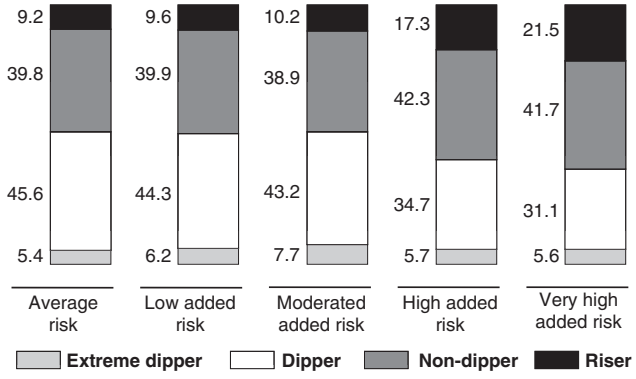

Figure 1 Prevalence of circadian patterns of BP according to cardiovascular risk stratification in 33 829 hypertensive patients.

INFLUENCE OF ANTIHYPERTENSIVE DRUG TREATMENT ON DIURNAL BP VARIATION

The Spanish National ABPM Registry has examined the presence of clinical factors associated with nocturnal BP decline in treated and non-treated hypertensive patients.[27] We present here the effects of treatment (number of antihypertensive drugs and time of administration) in nocturnal BP decline.

This analysis was performed in 34 563 hypertensive patients under antihypertensive treatment who were included in the Spanish National ABPM Registry between June 2004 and December 2006. General characteristics include male sex in 53%, and a mean age of 60.0 ± 13.8 years. Office systolic BP/diastolic BP was 149.5 ± 19.3/87.8 ± 11.7 mm Hg and 24-h ambulatory BP was 130.6 ± 14.6/77.0 ± 19.3 mm Hg. Mean body mass index was 29.0 ± 4.7 kg m^{-2}. Cardiovascular risk factors included dyslipidemia in 37.5% of cases, diabetes in 18.7% and current smoking in 17.2%. History of cardiovascular clinical conditions included coronary heart disease in 6.3%, stroke in 4.1%, congestive heart failure in 2.2% and chronic renal disease in 1.7%.

In this study, BP was measured at the office with a calibrated mercury sphygmomanometer or a validated semiautomatic

Table 1 Prevalence of non-dipper pattern according to four strata of 24-h systolic BP

24-h systolic BP stratum	*High added risk* n *6534 (37.9%)*	*Low-to-moderate added risk* n *10 685 (62.1%)*	P
>155 mm Hg	69.0%	70.0%	0.763
145–155 mm Hg	62.2%	56.7%	0.023
135–145 mm Hg	57.3%	49.9%	<0.001
<135 mm Hg	56.0%	45.7%	<0.001

Abbreviation: BP, blood pressure.
Comparison between high-risk and low-to-moderate-risk patients.

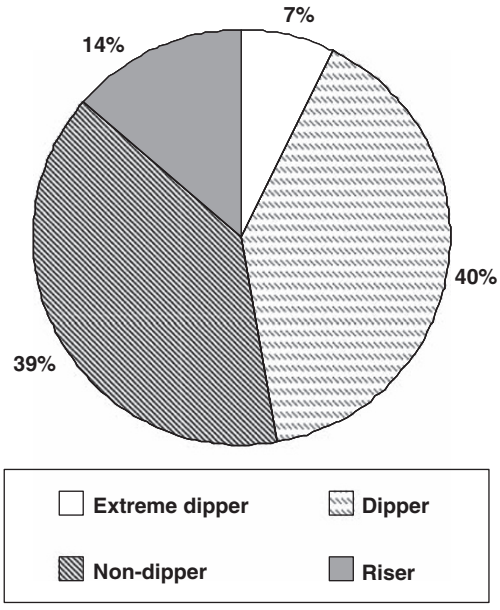

Figure 2 Circadian BP patterns distribution in treated patients from the Spanish ABPM Registry.

oscillometric device, after 5-min rest in a sitting position. BP values were estimated as the mean of two readings. Thereafter, 24-h ABPM was performed using the SpaceLabs 90207 automated non-invasive oscillometric device (Spacelabs Medical, model 90207; Space-Labs Inc., Redmond, WA, USA), programmed to register BP at 20-min intervals for the 24-h period. Patients were instructed to maintain their usual activities, return the following morning for device removal and keep the arm extended and immobile at the time of each cuff inflation. Valid registries had to fulfill a series of pre-established criteria, including $\geqslant$80% of systolic BPs and diastolic BPs successful recordings during the daytime and nighttime periods, 24-h duration, and at least one BP measurement per hour. Daytime and nighttime periods were defined individually according to the patient self-reported data of going-to-bed and getting-up times. Nocturnal BP decline and circadian patterns were defined by calculating the percent decline in both systolic BP and diastolic BP during the night, using the formula: (daytime BP—nighttime BP)/daytime BP. Normal dipping was diagnosed when BP nocturnal fall was $>$10% (10–20% dippers and $>$20% extreme dippers). Otherwise, patients were classified as non-dippers (0–10% non-dippers and $<$0% risers).

The distribution of patients among different nocturnal BP fall categories is depicted in Figure 2. Dippers accounted for 39.9% (n=13 800), extreme dippers for 7.2% (n=2499), non-dippers for 39.4% (n=13 594) and risers for 13.5% (n=4670). The prevalence of dipping (dippers/extreme dippers) and non-dipping (non-dippers/risers) patterns was 47.2 and 52.8%, respectively.

The main characteristics of the study sample according to dipping status are shown in Table 2. Dippers and non-dippers showed statistically significant differences in most of the study variables. Those with a non-dipping profile were older, more frequently women and obese, and had a longer duration of hypertension. They also had more frequently a previous diagnosis of dyslipidemia, type 2 diabetes or cardiovascular disease. Conversely, the proportion of smokers was slightly lower in those with a non-dipping pattern.

Influence of antihypertensive therapy in non-dipping status was examined by comparing nocturnal BP decline and proportion of

Table 2 Characteristics of treated hypertensive patient according to dipping (dippers/extreme dippers) and non-dipping (non-dippers/risers) status

Variable	*Dipping* (n=*16 299*)	*Non-dipping* (n=*18 264*)	P-*value*
Sex (% women)	45.5	48.5	<0.001
Age, year	55.7 ± 13.5	61.9 ± 13.3	<0.001
SBP, mm Hg			
Clinic	149.1 ± 18.4	149.8 ± 20.0	0.003
24-h	129.3 ± 13.1	131.7 ± 15.7	<0.001
Daytime	134.7 ± 13.7	132.8 ± 15.7	<0.001
Nighttime	113.6 ± 12.3	128.6 ± 16.8	<0.001
% Nocturnal decline in BP, mm Hg	15.6 ± 4.2	3.1 ± 6.1	<0.001
DBP, mm Hg			
Clinic	89.0 ± 11.1	86.6 ± 12.1	<0.001
24-h	78.2 ± 9.7	76.2 ± 10.6	<0.001
Daytime	82.3 ± 10.1	77.8 ± 10.9	<0.001
Nighttime	65.7 ± 9.1	71.6 ± 10.7	<0.001
% Nocturnal decline in BP, mm Hg	20.2 ± 5.7	7.8 ± 7.1	<0.001
24 h BP < 130/80, %	42.5	41.5	0.057
Duration of hypertension, year	4.9 ± 6.4	6.9 ± 7.5	<0.001
BMI, kg m^{-2}	28.6 ± 4.5	29.3 ± 4.8	<0.001
Current smoking, %	19.5	15.1	<0.001
Dyslipidemia, %	35.2	39.5	<0.001
Diabetes, %	14.5	22.4	<0.001
History of cardiovascular disease, %			
Congestive heart failure	1.5	2.8	<0.001
Cerebrovascular disease	2.9	5.2	<0.001
Coronary heart disease	4.1	8.3	<0.001
Chronic renal disease	1.0	2.3	<0.001

Abbreviations: BMI: body mass index; BP, blood pressure; DBP, diastolic blood pressure; SBP, systolic blood pressure.

dippers in patients depending on the number of antihypertensive drugs used. Figure 3 (left) shows the proportion of dipping and non-dipping patterns in groups of patients treated with monotherapy, two antihypertensive drugs or three or more drugs. As observed, the proportion of dippers increased as the number of drugs was greater. Moreover, as also observed in Figure 3 (right), nocturnal BP decline was also less pronounced as the number of drugs increased. In multivariate models, the number of antihypertensive drugs was associated with both the amount of BP decrease during the night (β: $-$0.700; 95% confidence interval (CI): $-$0.812 to $-$0.588; $P<0.001$) and the classification into the non-dipper status (odds ratio: 1.22; 95% CI: 1.15–1.29; $P<0.001$).

The relationship of the time of the day when treatment was administered with diurnal BP variation was also examined. A majority of the patients (26 410) received antihypertensive treatment only in the morning, whereas less patients received antihypertensive treatment only at night (3646) or combined morning and night (3649). We did not find differences between dippers and non-dippers in the proportion of patients receiving all or part of their medication at bedtime (20.5 *vs.* 21.2%; P=0.352). Differences in nocturnal BP decline were minimal, but with statistical significance. The nocturnal BP decline (systolic/diastolic) was 8.2/12.8 in those treated only in the morning, 8.0/12.5 in those treated only at bedtime and 7.5/12.2 in those treated both in the morning and at bedtime (P=0.004 for systolic and P=0.012 for diastolic, respectively). However, the time

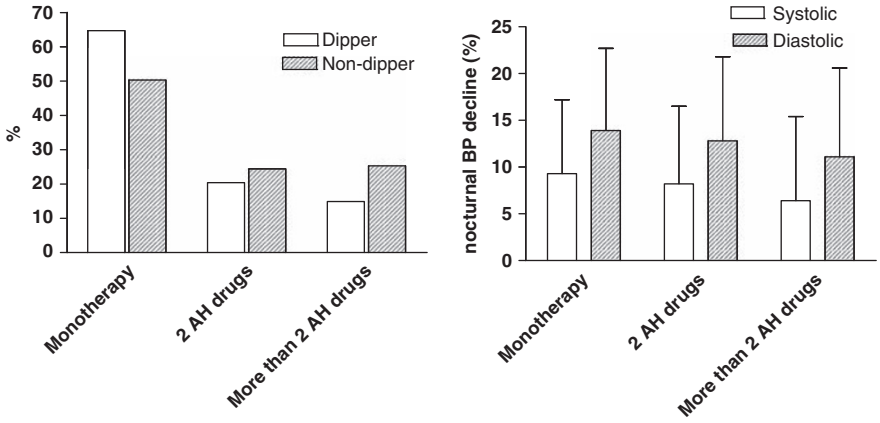

Figure 3 Left: proportion of dippers and non-dippers depending on the number of antihypertensive drugs used ($P<0.001$). Right: nocturnal BP fall (systolic and diastolic) in patients depending on the number of antihypertensive drugs used ($P<0.001$).

when treatment was administered was strongly influenced by the risk profile of the patient. Thus, patients who received all or part of their antihypertensive medication at bedtime were older, more frequently diabetics and had higher BP values. In the multivariate analyses, time of administration was not associated with either the dipping pattern or the amount of BP decline during the night.

In summary, using a large cohort of patients from the ABPM Spanish database we have observed that the amount of nocturnal BP decline was closely related to the level of risk.[27] Non-dipping was associated with advanced age, obesity and diabetes, conditions that increase cardiovascular risk. Moreover, a history of previous cardiovascular or renal disease was more common in non-dippers than in dippers. With respect to antihypertensive treatment, we have previously reported that treated patients had a blunted nocturnal BP decline with respect to those untreated.[27] This has been attributed to the use of antihypertensive treatment, which is commonly administered in the morning and lowers BP especially during daytime.[28,29] With our data, it seems to be an inaccurate assumption. We observed that the proportion of patients receiving all or a part of their medication at night was not different between dippers and non-dippers. Moreover, although some differences in the nocturnal BP decline were observed depending on the time when antihypertensive treatment was administered, these differences can be explained by the level of risk of patients, and they disappeared in the multivariate analysis.[30,31] In support of this, the need for more antihypertensive drugs in the non-dipping group could also reflect the severity and the difficulty to treat elevated BP.

TYPE OF ANTIHYPERTENSIVE DRUG AND DIURNAL BP VARIATION

Table 3 shows the proportion of dippers and non-dippers, as well as the systolic and diastolic nocturnal BP dip in the cohort of 34 563 treated hypertensives depending on the antihypertensive drug class used for treatment in monotherapy. As observed, those who received either non-dihydropyridine calcium channel blockers or α-blockers presented a blunted nocturnal dip and higher proportion of non-dippers. This relationship was also present in the multiple linear regression analysis using nocturnal systolic (β: 0.035; 95% CI: 0.022–0.047) or diastolic (β: 0.039; 95% CI: 0.026–0.053) BP decline as dependent variable. Moreover, these results were also observed in the logistic regression analysis (odds ratio: 1.01; 95% CI: 1.00–1.02).

Table 3 Nocturnal BP fall (systolic and diastolic) and prevalence of non-dipping in hypertensives treated with specific drug classes in monotherapy

AH drug class	*Systolic BP fall*	*Diastolic BP fall*	*% of non-dippers*
Diuretics (3417)	9.3 ± 7.8	14.2 ± 8.6	52.0
β-Blockers (2626)	9.0 ± 8.1	13.6 ± 8.9	53.1
DHPCCB (1424)	7.9 ± 7.6	12.5 ± 8.6	60.2
NDHPCCB (240)	6.2 ± 8.6	10.3 ± 8.8	66.2
ACEI (3174)	9.4 ± 7.9	13.8 ± 8.8	52.1
ARB (2631)	9.1 ± 8.4	13.7 ± 8.9	52.1
α-Blockers (410)	6.2 ± 8.2	10.6 ± 8.4	70.1

Abbreviations: ACE, angiotensin-converting enzyme inhibitors; AH, antihypertensive; ARB, angiotensin receptor blocker; BP, blood pressure; DHPCCB, dihydropyridine calcium channel blockers; NDHPCCB, non-dihydropyridine calcium channel blockers.

These results need to be interpreted with caution, as they do not represent a prospective controlled trial, just only observational data. The use of specific drug classes is related to the clinical profile of the patients and this profile has great influence on the circadian pattern as described above. Moreover, grouping antihypertensive drug classes does not take into account particular pharmacokinetic and pharmacodynamic properties of the member belonging to the same class.

In summary, the Spanish ABPM Registry, the largest database on ABPM in the world, has provided evidence regarding the circadian patterns of the population of treated hypertensives. The non-dipping pattern is very common and closely related to the level of risk of the patient. In addition to this, and even understanding that this level of risk is a powerful determinant of treatment, it seems that a more intense antihypertensive treatment, with two or more drugs, and the use of some specific drug classes, such as non-dihydropyridine calcium channel blockers or α-blockers is associated with a non-dipping pattern, a finding that needs to be corroborated in specifically designed prospective trials.

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