A BLUNTED NOCTURNAL BLOOD PRESSURE DECLINE IS ASSOCIATED WITH ALL-CAUSE AND CARDIOVASCULAR MORTALITY

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ABSTRACT

Objective: It has been suggested that a blunted nocturnal blood pressure (BP) decline is associated with a poor prognosis. Nevertheless, it remains unclear if an abnormal dipping is deleterious *per se* or it merely reflects an elevated BP during sleep. We aimed to assess the prognostic value of nocturnal BP decline, with or without concomitant elevated nocturnal BP.

Methods: Vital status and cause of death were obtained from death certificates in 59124 patients, enrolled in the Spanish ABPM Registry between 2004 and 2014 (median follow-up: 10 years). The association between night-to-day ratio and dipping patterns (extreme dippers, dippers, reduced dippers and risers) with all-cause and cardiovascular mortality were evaluated by Cox-proportional models adjusted for clinical confounders and 24-hour blood pressure.

Results: Night-to-day ratio was associated with all-cause mortality (hazard ratio for 1 SD change: 1.15; 95% CI: 1.13-1.17). Reduced dippers (1.13; 1.06-1.20) and risers (1.41; 1.32-1.51) were associated with an increased risk of all-cause death, whereas extreme dippers (0.90; 0.79-1.02) were not. Elevated night-to-day ratio (≥ 0.9) in the absence of elevated night systolic BP (< 120 mmHg) was associated with an increased risk of death (1.13; 1.04-1.22), as well as elevated night systolic BP but normal night-to-day ratio (1.38; 1.26-1.50), and the combination of both abnormalities (1.56; 1.46-1.66). Similar results were obtained for cardiovascular mortality.

Conclusion: Abnormalities in the circadian pattern are associated with an increased risk of all-cause and cardiovascular mortality. This is maintained even in the absence of nocturnal BP elevation.

Keywords: ambulatory blood pressure monitoring; nocturnal blood pressure dipping; mortality; cardiovascular mortality

INTRODUCTION

Blood pressure (BP) indices obtained through 24-hour ambulatory BP monitoring (ABPM) are better predictors of mortality and cardiovascular events than office or clinic BP [1-3]. Among such indices, nocturnal BP has emerged as the best prognostic indicator [2-9].

In addition to the absolute BP levels, ABPM provides information about circadian BP variability, especially the natural nocturnal BP decline occurring during sleep [1]. A blunted nocturnal BP decline (or an increased night-to-day ratio of BP) is associated with other cardiovascular risk indicators, with hypertension-mediated organ damage, and possibly, with a worse cardiovascular prognosis [10-16]. Nevertheless, patients with a reduced BP dip usually have higher levels of nighttime BP [10], being both parameters clearly related. Thus, it is unclear if an abnormal dipping is deleterious *per se* or it merely reflects an elevated BP during sleep.

Therefore, the aim of the present study was to assess the association of nocturnal BP decline, i.e, the dipping status, with all-cause and cardiovascular mortality. In addition, we specifically looked at the risks derived from an abnormal dipping in the absence of nocturnal BP elevation, as well as nocturnal hypertension in patients with a normal dipping pattern.

PATIENTS AND METHODS

Study Design

The Spanish ABPM Registry was developed to promote the use of ABPM in clinical practice. Details about recruitment characteristics have been previously reported [3,10,11]. Briefly, physicians and nurses received specific training in the technique of ABPM and used the internet-based platform that receives ABPM registries together with their corresponding medical records. Physicians then obtained a report in real time and these registries were stored in the database of an external clinical research organization. Patients were required to be aged ≥18 years and to meet guideline-recommended indications for ABPM, which included suspected white-coat hypertension, refractory or resistant hypertension, assessment of drug treatment efficacy, high-risk hypertension, labile or borderline hypertension, and the study of circadian BP pattern. The study was approved by the local institutional ethics committees, and informed consent was obtained from the participants. The present study is an analysis of mortality that includes 59 124 individuals aged ≥18 years who were enrolled in the registry between March 2004 and December 2014.

BP Measurements

BP was measured at the office with a validated upper-arm cuff oscillometric device, after a 5-minute rest in a sitting position. BP values were estimated as the mean of 2 readings. Thereafter, 24-hour ABPM was performed using the SpaceLabs 90207 automated oscillometric device (Snoqualmie, WA), programmed to register BP at 20-minute intervals for the day and at 30-min intervals for the night. Valid registries had to fulfil a series of pre-established criteria, including ≥70% of SBP and DBP successful readings during the daytime and nighttime periods, 24-hour 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.

The nocturnal decline in BP was calculated using the night-to-day ratio (NDR), i.e. nighttime BP / daytime BP[1]. For both systolic and diastolic BP, groups were classified as extreme dipping (NDR < 0.80) normal dipping (NDR ≥ 0.8 and < 0.9), reduced dipping (NDR ≥ 0.9 and < 1) and risers (NDR ≥1).

Study Variables

Variables collected for each patient based on the interviews and physical examination at the time of visit and on data drawn from clinical records were defined and measured in accordance with contemporary European guidelines [17-19]. These included age, sex, weight, height, cardiovascular risk factors, such as smoking, diabetes mellitus, and dyslipidemia, and history of cardiovascular disease (coronary heart disease, congestive heart failure, symptomatic peripheral artery disease, or cerebrovascular disease).

Mortality data

The date and cause of death were ascertained by a computerized search of the vital registry of the Spanish National Institute of Statistics (contract 20535 between the University of Barcelona and the National Institute of Statistics). Cause of death was determined by a nosologist from the death certificate and was coded according to the *International Statistical Classification of Diseases*, *Tenth Revision* (I00-I99 code for those of cardiovascular origin). For each study participant, follow-up was from the date of their recruitment visit in the blood pressure registry to the date of death or December 31, 2019, whichever occurred first.

Statistical Analysis

Data are presented as percentages for categorical variables and as mean ± SD or median (interquartile range), for continuous variables. Differences in study variables among groups were assessed with the Pearson χ^2 for categorical variables and ANOVA for continuous variables. Spearman's Rho coefficient was used to evaluate the correlation between nighttime BP and NDR.

Associations between NDR or groups regarding the dipping status and all-cause and cardiovascular mortality were summarized with hazard ratios and their 95% CI for 1 SD change (NDR), or with respect to normal dipping (the reference group), estimated by Cox models, adjusted for clinical confounders (age, sex, body mass index, smoking, diabetes, dyslipidemia, antihypertensive treatment, and previous cardiovascular disease) and additionally adjusted for the corresponding 24-hour systolic or diastolic BP.

In order to better evaluate the role of abnormal dipping on all-cause and cardiovascular mortality independently on nighttime BP elevation, patients were classified in 4 groups depending on the combination of nighttime BP and dipping status. Group 1 included patients with normal nighttime SBP (<120 mmHg) and normal or extreme dipping (NDR <0.9), group 2 included patients with normal nighttime SBP, but a blunted nocturnal dipping (reduced dipping and risers; NDR ≥ 0.9), group 3 included patients with elevated nocturnal SBP (≥ 120 mmHg), but normal or extreme dipping patterns (NDR < 0.9), and Group 4 included patients with abnormal both nighttime SBP and dipping pattern. Again, hazard ratios were calculated by using Cox regression models (adjusted for clinical confounders). Group 1 (normal night BP and normal dipping) was used as the reference group).

We assessed consistency in the results according to age (<65 and ≥65 years), sex (men and women), antihypertensive medication (yes and no), diabetes mellitus (yes and no) and overt cardiovascular disease at entry (yes and no).

The SPSS for Windows version 25.0 software (IBM, Armonk, New York) was used for statistical analysis.

RESULTS

During follow-up (median, 9.7 years), 7174 deaths occurred, of which 2361 were cardiovascular. Details of patients included as well as differences between those who were alive or dead at the end of the study have been previously reported [3] and are condensed in Table S1. In Table 1, we summarize clinical characteristics of patients grouped on the basis of their dipping status as derived from systolic NDR (extreme dippers, dippers, reduced dippers, and risers). Patients with a blunted nocturnal BP decline (reduced dippers and risers) were older, more frequently women, and with a higher prevalence of diabetes, dyslipidemia, and previous cardiovascular disease. They also had significantly increased values of 24-hour SBP and nighttime both systolic and diastolic BP (Table 1).

Both systolic and diastolic NDR were significantly higher in patients who died compared to those who remained alive at the end of the study (Table 2). Likewise, the distribution of dipping pattern categories was also significantly different between dead and alive patients, with increased proportions of patients with either reduced dipping or a riser pattern and reduced proportion of patients with either a normal dipping or an extreme dipping pattern among those who subsequently died (Table 2).

Compared with patients who died from other causes, those who died from cardiovascular causes also showed significantly higher values of NDR, as well as differences in the dipping pattern distribution with an increased proportion of risers (Table S2).

Table 3 shows the association of night-to-day ratio, both systolic and diastolic with all-cause and cardiovascular mortality. In fully adjusted models (clinical confounders plus 24-hour BP), hazard ratios for 1 SD increase in systolic NDR were 1.15 (95% CI: 1.13-1.17) and 1.17 (1.13-1.21) for all-cause and cardiovascular

mortality, respectively. Corresponding values for diastolic NDR were 1.16 (1.14-1.19) and 1.19 (1.14-1.23), respectively.

The association of the nocturnal BP dip and mortality was also evaluated by comparing dipping pattern categories. Concerning systolic BP, and relative to normal dipping, there was a higher all-cause mortality risk in the group with reduced dipping (hazard ratio: 1.13; 95% CI 1.06-1.20) and the group with a riser pattern (1.41; 95% CI 1.32-1.51) (Table 4). The extreme dipping pattern was not associated with a higher all-cause mortality risk (0.90; 95% CI 0.79-1.02). Similar results were observed for cardiovascular mortality and for diastolic dipping patterns (Table 4).

Nighttime BP and night-to-day ratio were moderately correlated (Spearman's Rho: 0.56; $p<0.001$ for systolic and 0.45; $p<0.001$ for diastolic). In order to separate the risk of abnormal nocturnal dipping from that of nighttime BP, we classified patients in 4 groups depending on normal or abnormal nighttime SBP and systolic night-to-day ratio. Results are shown in Table 5. In models adjusted for clinical confounders, an abnormal nocturnal BP decline (reduced dippers and risers) in the absence of nocturnal hypertension was associated with a slightly increased risk of all-cause mortality (hazard ratio: 1.13; 95% CI: 1.04-1.22) and of cardiovascular mortality (1.17; 95% CI: 1.00-1.35). There was a higher risk of all-cause and cardiovascular mortality associated with nocturnal hypertension with normal dipping (hazard ratio: 1.38; 95% CI: 1.25-1.50 and 1.62; 95% CI: 1.39-1.90, respectively), with the highest risk being observed in patients with both nocturnal hypertension and abnormal dipping (hazard ratio: 1.56; 95% CI: 1.46-1.66 and 1.90; 95% CI: 1.68-2.14) respectively, for all-cause and cardiovascular mortality.

Associations were consistent across subgroups of age, sex, antihypertensive treatment, diabetes status and previous cardiovascular disease (Table S3).

DISCUSSION

This study shows that the dipping pattern is associated with all-cause and cardiovascular mortality. A blunted nocturnal BP decline is associated with an increased risk of death and of cardiovascular death. Both systolic and diastolic NDR are associated with higher risk of mortality (13% - 20% higher risk per 1 SD higher NDR) and groups with a reduced dipping or a riser pattern have higher risk of mortality, with the latter group having the poorest prognosis. A blunted nocturnal BP fall is associated with an adverse outcome even in the absence of nocturnal BP elevation (≥ 120 mmHg), with increased risks of 13% and 17% for all-cause and cardiovascular mortality, respectively. This blunted nocturnal BP fall combined with nocturnal hypertension (another independent factor for cardiovascular risk) is associated with the highest risk of death (56% increase) and of cardiovascular death (risk almost doubled with respect to patients with both normal nighttime BP and normal dipping).

In 1988, O'Brien and colleagues [12] suggested that a nondipping status was associated with a poor cardiovascular prognosis. Since then, several population and clinical studies have examined the prognostic value of the nocturnal BP fall [10-16]. Absolute nocturnal dipping or night-to-day ratio is generally associated with both mortality and cardiovascular event development. However, when patients are classified into 4 categories (extreme dipping, normal dipping, reduced dipping and reverse dipping, or riser), the association of each category with prognosis is more controversial. Subjects with a riser pattern (sleep BP > awake BP) have been consistently found to be those at highest risk [14-16]. Patients with a reduced dipping (NDR ≥ 0.9 and < 1) have been found to be at increased risk in one study [16] and at similar risk as normal dippers in another [15].

Our results confirm the association between NDR and mortality, even after adjusting for the absolute value of 24-hour BP. With respect to dipping categories either a reduced dipping pattern or a reverse dipping (risers) was associated with an increased risk of death. Not surprisingly, while reduced dippers had a risk that was between 13% and 20% higher for all-cause mortality and between 22% and 23% higher for cardiovascular mortality, the excess risk in risers was greater (41%-49% for all-cause mortality and 54%-56% for cardiovascular mortality).

Controversy exists regarding the risk of individuals with a nocturnal BP fall greater than 20%, i.e. the extreme dipping pattern. Kario et al [13] first reported that extreme dipping was associated with an increased incidence of stroke in Japanese patients. However, a meta-analysis of four European studies found extreme dipping to be associated with a lower risk of all-cause mortality [15]. In a subsequent meta-analysis of studies from different countries, including Europe and Japan, it was found that extreme dipping was neutral in terms of cardiovascular prognosis [16]. It has also been proposed that the extreme dipping pattern might have a different prognostic value depending on age or on the presence or absence of antihypertensive treatment. In this view, Palatini et al [20] suggested that the extreme dipping pattern could be deleterious only in subjects older than 70 years. Moreover, in the aforementioned meta-analysis [16], the authors found the extreme dipping pattern deleterious in untreated patients, and slightly protective in the treated ones [16]. All these studies only considered the systolic dip for definition of circadian patterns [13,15,16, 20].

In the present study, we did not find that extreme dipping was associated with an increased risk of mortality or cardiovascular mortality. In addition, we did not find a different behavior of dipping patterns in patients depending on age or antihypertensive treatment. Hazard ratios for the extreme dipper group were higher in older patients, as

well as those receiving antihypertensive treatment. However, in all cases they were < 1 (tables S4 and S5). Differences among studies could be explained due the participation of an important proportion of the Asian population in the aforementioned reports [16,20]. It has been previously reported that individuals from Asian origin have a more pronounced both dipping and morning surge [21]. In addition, in the meta-analysis by Salles et al [16], the heterogeneity of the extreme dipping group according to antihypertensive treatment was concentrated on non-fatal events, but not with respect to mortality. Unfortunately, we did not assess non-fatal events.

The nocturnal dip is closely related to the night BP elevation. Patients with either a riser or a reduced dipping pattern have usually higher levels of nocturnal BP in comparison to those with normal dipping[10]. Considering that nighttime BP is the most powerful predictor of subsequent mortality and cardiovascular events [2-9], the impact of nondipping is usually lost when adjusted for nocturnal BP [2,7]. Nevertheless, as nighttime BP is obviously involved in the calculation of nocturnal dipping, this may cause an over adjustment. For this reason, we decided to classify patients in groups having one isolated abnormality, either abnormal dipping (reduced dippers or risers) or nighttime BP elevation. Using this approach, we were able to demonstrate that a blunted dipping was associated with an increased mortality risk even in the absence of nocturnal BP elevation. There was an increased risk in the group of nondipping alone (without nighttime hypertension) or in those with nocturnal hypertension alone (with adequate dipping). However, the risks were clearly higher for nocturnal hypertension (even with normal dipping) than for abnormal dipping in the absence of nocturnal hypertension. This latter group had increased risk of 13% and 17%, for all-cause and cardiovascular mortality, respectively, while risks for nocturnal hypertension were clearly higher (38% and 62%). Both alterations were additive in terms of mortality risk, with the group with

both nocturnal hypertension and nondipping having the highest rates of total and cardiovascular deaths.

The current study has some limitations. First ABPM was performed only once (with the exception of a small subset of patients in whom ABPM was repeated). In this view, the reproducibility of the circadian pattern categories is only moderate [22]. However, the relationship with mortality of both NDR and dipping categories adds consistency to the results obtained here. Second, both ABPM and clinical data collection were obtained at the time patients were recruited from the study. Thus, the impact of subsequent changes in treatment, lifestyle or other aspects which could potentially influence the outcome is unknown. Third, there were clear differences in clinical parameters, including cardiovascular risk factors and diseases, among patients with different dipping patterns; in particular, patients with a blunted nocturnal BP fall (reduced dippers and risers) had a worse clinical profile. Although, we tried to adjust for available confounders, these were only crudely measured. Thus, residual confounding based on this or on the presence of other clinical factors not collected in the present study is also possible. Fourth, this is an observational study, and no direct inference can be made regarding the potential benefit of antihypertensive treatment on the circadian dipping pattern.

In conclusion, this very large study performed in a single cohort of patients suggests that in addition to the risk derived from the level of BP elevation, and particularly, nocturnal BP, abnormalities in the circadian dipping pattern are associated with an increased risk of mortality, both all-cause and cardiovascular. Increased mortality rates are observed in patients with a reduced nocturnal dip and, even more intensively, in those with a riser pattern. This abnormal dipping is associated with a risk of mortality even in the absence of nocturnal BP elevation. In contrast, this study also

suggests that the extreme dipping pattern is not associated with an increased mortality risk.

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Table 1. Demographic and clinical characteristics in the four dipping categories based on systolic blood pressure night-to-day ratio

Parameter	**Extreme dippers (NDR< 0.8) N=4028**	**Dippers (NDR ≥ 0.8 and < 0.9) N=24165**	**Reduced dippers (NDR ≥ 0.9 and < 1) N=23399**	**Risers (NDR ≥ 1) N=7532**	**P value***
Male sex,%	52.6%	55.1%	52.1%	49.2%	<0.001
Age, y	55.6 ± 12.7	55.5 ± 13.7	59.8 ± 14.0	67.1 ± 12.5	<0.001
Obesity†, %	34.7%	36.8%	42.7%	46.3%	<0.001
Current smoker, %	22.1%	17.6%	14.3%	10.6%	<0.001
Diabetes, %	13.5%	15.4%	20.8%	30.2%	<0.001
Dyslipidemia, %	40.8%	38.5%	42.6%	50.2%	<0.001
Cardiovascular disease, %	5.5%	6.5%	10.3%	18.6%	<0.001
Blood pressure, mmHg					
Clinic systolic	150.1 ± 18.5	147.4 ± 17.9	147.9 ± 18.9	149.0 ± 21.2	<0.001
Clinic diastolic	88.8 ± 10.9	87.5 ± 10.9	86.1 ± 11.6	83.2 ± 12.5	<0.001
24-h systolic	127.7 ± 13.1	127.8 ± 12.6	129.1 ± 14.0	131.3 ± 15.7	<0.001
24-h diastolic	77.3 ± 9.8	77.2 ± 9.7	76.0 ± 10.3	73.2 ± 10.2	<0.001

Daytime systolic	135.9 ± 13.9	132.8 ± 13.0	131.2 ± 14.2	129.3 ± 15.6	<0.001
Daytime diastolic	83.3 ± 10.3	81.2 ± 10.1	78.1 ± 10.5	73.2 ± 10.3	<0.001
Nighttime systolic	104.4 ± 11.1	113.9 ± 11.6	123.6 ± 13.8	136.5 ± 17.1	<0.001
Nighttime diastolic	60.3 ± 8.4	66.0 ± 8.9	70.2 ± 10.1	73.1 ± 10.8	<0.001

Data expressed as mean ± SD or %. *Chi square or ANOVA tests. †Obesity defined as a body mass index ≥ 30 kg/m^2

Table 2. Mean values of night-to-day ratios of BP and distribution of dipping categories in the whole cohort of patients and differences between dead and alive patients.

Parameter	All patients N=59124	Alive N=51952	Dead N=7174	P value
Systolic NDR	0.911 ± 0.082	0.905 ± 0.079	0.951 ± 0.096	<0.001
Diastolic NDR	0.865 ± 0.091	0.860 ± 0.088	0.903 ± 0.100	<0.001
Systolic dipping pattern				<0.001
Extreme dippers	6.8	7.2	3.8	
Dippers	40.9	42.8	26.7	
Reduced dipping	39.6	39.2	42.2	
Risers	12.7	10.7	27.4	
Diastolic dipping pattern				<0.001
Extreme dippers	23.7	24.9	14.8	
Dippers	43.7	44.8	35.8	
Reduced dipping	25.5	24.4	33.9	
Risers	7.1	6.0	15.4	

NDR means night-to-day ratio. Values are mean ± SD (NDR) or % (dipping categories)

Table 3. Hazard ratios for each 1 SD change in night-to-day ratio in relation to total and cardiovascular mortality

Parameter	Confounder adjusted*	Additionally adjusted for 24-hour BP
	All-cause mortality	
Systolic NDR	1.16 (1.13-1.18)	1.15 (1.13-1.17)
Diastolic NDR	1.16 (1.14-1.19)	1.16 (1.14-1.19)
	Cardiovascular mortality	
Systolic NDR	1.17 (1.14-1.21)	1.17 (1.13-1.21)
Diastolic NDR	1.19 (1.14-1.23)	1.19 (1.14-1.23)

NDR means night-to-day ratio. * Adjusted for age, sex, body mass index, smoking status, diabetes, dyslipidemia, antihypertensive treatment, and previous cardiovascular disease.

Table 4. Hazard ratios for groups classified on the basis of the dipping pattern in relation to total and cardiovascular mortality

Parameter	Confounder adjusted*	Additionally adjusted for 24-hour BP
All-cause mortality		
Systolic dipping pattern		
Dippers	Reference	Reference
Extreme dippers	0.90 (0.79-1.02)	0.90 (0.79-1.02)
Reduced dipping	1.14 (1.08-1.21)	1.13 (1.06-1.20)
Risers	1.46 (1.37-1.57)	1.41 (1.32-1.51)
Diastolic dipping pattern		
Dippers	Reference	Reference
Extreme dippers	0.94 (0.87-1.01)	0.93 (0.87-1.00)
Reduced dipping	1.20 (1.14-1.27)	1.20 (1.14-1.27)
Risers	1.49 (1.38-1.60)	1.49 (1.38-1.60)
Cardiovascular mortality		
Systolic dipping pattern		
Dippers	Reference	Reference
Extreme dippers	0.96 (0.76-1.21)	0.95 (0.76-1.20)
Reduced dipping	1.25 (1.12-1.38)	1.22 (1.10-1.35)
Risers	1.62 (1.44-1.82)	1.54 (1.37-1.74)
Diastolic dipping pattern		
Dippers	Reference	Reference
Extreme dippers	0.90 (0.79-1.03)	0.90 (0.79-1.03)
Reduced dipping	1.23 (1.12-1.36)	1.23 (1.11-1.35)
Risers	1.56 (1.38-1.76)	1.56 (1.38-1.76)

*Adjusted for age, sex, body mass index, smoking status, diabetes, dyslipidemia, antihypertensive treatment, and previous cardiovascular disease.

Table 5. Hazard ratios for groups combining systolic nocturnal hypertension and abnormal dipping pattern in relation to all-cause and cardiovascular mortality

Parameter	Number of patients	Nighttime SBP	Systolic NDR	All-cause mortality*	Cardiovascular mortality*
Normal nighttime SBP, normal dipping	21383	107.5 ± 8.0	0.84 ± 0.04	Reference	Reference
Normal nighttime SBP, abnormal dipping	10981	111.5 ± 6.5	0.95 ± 0.05	1.13 (1.04-1.22)	1.17 (1.00-1.35)
Abnormal nighttime SBP, normal dipping	6810	128.4 ± 7.6	0.86 ± 0.03	1.38 (1.26-1.50)	1.62 (1.39-1.90)
Abnormal nighttime SBP, abnormal dipping	19950	135.2 ± 12.6	0.98 ± 0.07	1.56 (1.46-1.66)	1.90 (1.68-2.14)

SBP means systolic blood pressure; NDR: night-to-day ratio of BP. *Adjusted for age, sex, body mass index, smoking status, diabetes, dyslipidemia, antihypertensive treatment, and previous cardiovascular disease. Normal nighttime SBP defined as <120 mmHg and abnormal nighttime SBP defined as ≥120 mmHg. Normal dipping defined as NDR <0.9 and abnormal dipping defined as NDR ≥ 0.9.