Evaluation of tolerance to ambulatory blood pressure monitoring

Analysis of dipping profile in a large cohort of hypertensive patients

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Abstract

Ambulatory blood pressure monitoring (ABPM) is a helpful tool to comprehensively identify and diagnose arterial hypertension. Moreover, it allows to better identify alterations in the circadian BP profile, as the nocturnal "nondipping" status, characterized by a lack of the physiological 10% night BP reduction and associated with a greater risk of target organ damage. However, ABPM has some limitations such as restricted availability, discomfort, particularly at night, cost implications, and reproducibility.

Aim of the study was evaluate if the "nondipping" phenomenon may be related to low degree of tolerance to ABPM. Additionally, to determine whether self-reported events of sleep disorders and nighttime urinations may affect the "nondipping" status.

From January 2013 to December 2015, we consecutively evaluated 1046 patients with arterial hypertension, performing ABPM, considering a tolerance index calculated on the basis of the patients' responses to a questionnaire.

Thirty-eight out of 1046 patients showed complete lack of tolerance to the instrument during the day, whilst 126 during the night. There were no statistically significant differences in daytime and nighttime values of tolerance to the instrument between "dippers" and "nondippers," between "extreme-dippers" and the remaining patients or between "reverse-dippers" and the remaining patients. There were no statistically significant differences in the number of nocturnal awakenings between the groups. However, we found that the number of awakenings followed by urination was higher in "nondipping" patients and in "reverse-dipping" patients compared to the other groups.

We found that the poor tolerance to the instrument does not seem to influence the BP "dipping" phenomenon among hypertensive individuals. Moreover, we think that in the evaluation of the ABPM data, factors, such as nocturnal urination and sleep disorders, need to be carefully taken into account, since may lead to a higher incidence of "nondipping" pattern.

Abbreviations: ABPM = ambulatory blood pressure monitoring, BMI = body mass index, BP = blood pressure, CI = confidence interval, CV = cardiovascular, DBP = diastolic BP, OR = odds ratio, SBP = systolic BP, SD = standard deviation, WC = waist circumference.

Keywords: ambulatory blood pressure monitoring, device, dipper, hypertension, nondipper, sleep disorders, tolerance

1. Introduction

Ambulatory blood pressure monitoring (ABPM) is a useful tool that can comprehensively identify and diagnose arterial hypertension. The use of ABPM gives a larger number of data than office BP measurement providing a complete profile of BP behaviors during the patient's usual daily habits.[1] Furthermore, ABPM assesses BP variability and the antihypertensive medication efficacy over the 24-h period and it is recognized as a stronger predictor of cardiovascular (CV) morbidity and mortality than office measurements.[2] The use of ABPM has highlighted that the BP values usually obtained in the office settings could be artificial; in fact, the comparison of the office BP values with those obtained with ABPM permits to identify not only normotension and hypertension, but also the white coat hypertension and the masked hypertension.[3] In addition, Lovibond et al[4] demonstrated that ABPM is the most cost-effective strategy for the diagnosis of hypertension for men and women at all ages, mainly thanks to its ability to reduce misdiagnosis and to direct toward more targeted treatments. On the other hand, despite all the previously mentioned advantages, ABPM has some limitations such as restricted availability, discomfort, particularly at night, cost implications, reproducibility, and possible inaccurate readings during physical activity.[5]

One of the most important features of ABPM is the ability to define the circadian BP profile with a focus on nocturnal behavior. Usually BP values suffer oscillations during the 24 hours showing lower average values during the night.[6]

Depending on the BP profile, it is possible to identify subjects whose nocturnal average BP undergoes a physiological reduction

comprised between 10% and 20%, defined as "dippers"; subjects who do not reach the 10% reduction called "nondippers"; subjects that show a reduction of ≥20% defined as "extreme-dippers", and subjects who show a nocturnal increase in BP defined "reverse-dippers".[7]

In literature, different definitions of "nondipping" status are described, depending on whether one considers the systolic BP (SBP), diastolic BP (DBP), or both,[8] recent reports give a more relevant prognostic significance to the SBP.[9] However, some authors attribute importance not only to the "dipping profile" in itself, but also to the systolic or diastolic component, or both.[10] Importantly, there is a growing body of evidence suggesting that a "nondipping" BP pattern is associated with a greater risk of target organ damage among hypertensive patients.[11] It should be mentioned that some authors point out that ABPM could affect the quality of sleep, causing, per se, the "nondipping" phenomenon.[12] Thus, it becomes of great clinical importance to distinguish a real "nondipping" status from a false one due to the discomfort or lack of tolerance to ABPM.

The aim of our study was to evaluate if the "nondipping" phenomenon may be related to the degree of tolerance to the instrument reported by hypertensive patients that underwent ABPM. Additionally, it was assessed whether self-reported events of sleep disorders[13] and nighttime urinations may affect the "dipping" status evaluation.

2. Materials and methods

2.1. Study population

From January 2013 to December 2015, we consecutively evaluated 1046 patients with arterial hypertension. All the hypertensive patients underwent ABPM during their treatment-monitoring follow-up at the Internal Medicine Day Hospital, Department of Internal Medicine and Medical Specialties, "Sapienza" University of Rome.

The patients underwent the assessment of anthropometric data: weight (kg), height (cm), body mass index (BMI, expressed in kg/m^2), waist circumference (WC, cm: measured at the midpoint of the line joining the last rib and the iliac crest during minimal inspiration).

2.2. Ambulatory blood pressure monitoring

ABPM was performed on the nondominant arm for 24 hours using the TM-2430 device (A&D Company Ltd, Kitamoto, Japan), an oscillometric equipment validated by AAMI (Association for the Advancement of Medical Instrumentation) and BHS (British Hypertension Society). The size of the cuff used was tailored to the *circumference* of the patient's arm, with 3 available options (small, medium, and large). Appropriate cuff size is essential for an accurate measurement.[11] The procedures were considered reliable if at least 70% of the measurements resulted valid, both during day and night.[1]

A tolerance index was calculated on the basis of the patients' responses to a questionnaire, filled after ABPM.

The questionnaire included:

1. A "subjective" rating of tolerance to the instrument, both during day and night monitoring; in particular, it was asked to describe the degree of tolerance to the instrument, using 4 grades: "excellent," "good," "sufficient", and "not sufficient."
2. The nocturnal sleep quality perceived during the monitoring, as summarized by the parameters listed in the diary (hours of sleep, number of nocturnal awakenings, number of nocturnal

urinations, snoring (reported by a cohabitant), and insomnia), as compared to the quality of the usual nighttime sleep.
3. Personal lifestyle habits that could be considered as risk factors for hypertension and CV disease, for example, dietary sodium and potassium intake, levels of physical activity, weight gain, alcohol and tobacco consumption.
4. Anthropometric data, familiarity for hypertension, awakening-sleeping time, physical-rest activity, meal timing schedule, eating, drinking and smoking habits and office BP.

All patients were divided into 4 groups depending on the nocturnal BP behavior: "dippers," "extreme-dippers," "non-dippers," and "reverse-dippers." Patients were defined "dippers" if the nocturnal BP fall was more than 10% and less than 20% and "extreme-dippers" if the pressure fall was greater than 20%. Conversely, patients were defined "nondippers" when the overnight decrease in BP was lower than 10% but still greater than 0%, whereas they were identified as "reverse-dippers" if the above values increased compared to the daytime readings.

The following aspects were evaluated among the 4 groups:

1. Tolerance to the instrument, expressed as inadequate (a complete lack of tolerance to the instrument) or sufficient (this included tolerances that were defined as sufficient, good, and excellent).
2. The quality of sleep, expressed by the absence or presence of one or more awakenings.
3. The number of nocturnal urinations.
4. The presence or absence of sleep disorders, as stated by the patients or their cohabitants.

During the ABPM, patients were asked to follow their own lifestyle, paying attention to sexual activity, excessive efforts, stressful situations, and environmental thermal excursions.

Each patient was also instructed to keep a diary and record the time of his/her main daily activities (e.g., meals, sleep), and unusual events.

In addition, they were asked to observe the *following schedule* to prevent biases in the ABPM:

- sleeping and awakening time (wake time: 06:30–08:30; sleep time: 21:00–23:00);
- meal time (breakfast: 07:00–08:30; lunch: 12:00–14:00; dinner: 19:30–21:30).

The ABPM procedure started at 09:00 hours of a working day and stopped after 24 hours.

The overall compliance of the studied population was assessed by an interview about the accuracy of the diary filling, before performing the analysis of the ABPM data.

We took into account the classifications of the Joint National Committee on Prevention, Detection, Evaluation and Treatment of High Blood Pressure, according to which, stage I hypertension is defined as SBP of 140 to 159 mm Hg, or DBP of 90 to 99 mm Hg, stage II hypertension as a SBP greater than 160 mm Hg or a DBP greater than 100 mm Hg.[14]

The following *exclusion criteria* were adopted:

- known secondary hypertension;
- chronic kidney disease;
- diabetes mellitus, thyroid dysfunctions, major CV diseases;
- major depression or anxiety disorders.

Moreover, the following *lifestyle-related exclusion criteria* were adopted:

- irregular time schedule of awaking-sleeping as well as of meals;
- abuse in smoking (also cannabis), drinking (especially alcohol, coffee, caffeinated beverages, tea);

Table 1

Summary of mean blood pressure (BP) values of the 1046 patients.

	Mean 24 h, mmHg	Mean day, mmHg	Mean night, mmHg	BP fall, mmHg
Systolic BP	133.65 ± 12.37	137.07 ± 12.6	120.78 ± 14.86	11.79 ± 8.05
Diastolic BP	79.87 ± 8.45	82.47 ± 8.78	70.36 ± 9.31	14.5 ± 8.52

- more than 5 g/day salt consumption;
- licorice consumption.

This study was performed according to the Declaration of Helsinki II. All participants provided and signed informed consent.

2.3. Statistical analysis

Statistical analysis was performed using Statistical Package for the Social Sciences (SPSS) 2015 Release 23.0. All results are expressed as mean ± standard deviation (SD) for continuous variables and as proportions and percentages for categorical variables.

Student t test was used to test differences between 2 groups for quantitative variables with normal distribution. The Chi-squared test was used to determine whether there is a significant difference between the expected frequencies and the observed frequencies between groups. A P value $<.05$ was considered statistically significant.

The multivariate analysis was performed using a multiple logistic regression model (stepwise approach with backward elimination), evaluating in the first step of the model the influence on the dependent variable "being dipper" of the following variables: age, gender, 24 hours mean SBP, maximum SBP, simple awakenings, night awakenings, snoring, day and night tolerance to the instrument. The results are presented as odds ratio (OR) and 95% confidence intervals (95% CIs).

3. Results

One thousand forty-six patients were enrolled: 537 (51.34% males) and 509 (48.66% females), mean age 57.75 ± 12.98 years.

One hundred fourteen (10.9%) of them showed optimal BP values, 480 (45.9%) showed normal BP values, 421 (40.2%) showed first degree hypertension, and 31 (3%) of them showed second and third degree hypertension evaluated during ABPM.

The patients were divided into 4 groups depending on the nocturnal BP behavior: 592 (56.6%) "dippers"; 129 (12.3%) "extreme-dippers"; 277 (26.5%) "nondippers"; 48 (4.6%) "reverse-dippers." Mean BP values are summarized in Table 1 and age stratification for night BP fall is summarized in Table 2.

Regard the tolerance to the instrument, 38 (3.63%) of 1046 patients showed complete lack of tolerance to the instrument during the day, whilst 126 (12%) during the night (Table 3). The comparison among groups showed that there were no statistically significant differences in daytime and nighttime values of tolerance to the instrument between "dippers" and "nondippers" (P: .78 daytime; P: .65 nighttime), between "extreme-dippers" and the remaining patients (P: .65 d; P: .75 n) or between "reverse-dippers" and the remaining patients (P: .88 d; P: .7 n).

The total hours of sleep during ABPM reported by patients was 6.36 ± 1.53 hours, while the habitual hours of sleep were 6.52 ± 1.16 hours. No differences were found regarding total hours of sleep between "dippers" (6.43 ± 1.5 hours) and "nondippers" (6.26 ± 1.58 hours) (P: .08); "extreme-dippers" (6.52 ± 1.25 hours) and the remaining patients (6.33 ± 1.57) (P: .11); "reverse-dippers" (5.93 ± 1.66 hours) and the remaining patients (6.38 ± 1.53 hours) (P: .09).

There were no statistically significant differences between the groups considering the number of nocturnal awakenings: "dippers" 1.69 ± 1.54 versus "nondippers" 1.83 ± 1.49 (P .13); "extreme-dippers" 1.65 ± 1.5 versus the remaining patients 1.76 ± 1.52 (P .45); "reverse-dippers" 2.03 ± 1.35 versus the remaining patients 1.73 ± 1.52 (P .19). Moreover, we did not find statistically significant differences of sleep quality in relation to the nocturnal awakenings (Table 4), whereas we found that the number of awakenings followed by urination was higher in nondipping patients and in "reverse-dipping" patients: "dippers" versus "nondippers": 0.79 ± 0.94 versus 1.09 ± 1.1 ($P < .01$); "reverse-dippers" versus the remaining patients: 1.54 ± 1.1 versus 0.89 ± 1 ($P < .01$).

Patients referring sleep disorders, such as snoring, were more often "nondippers": "dippers" (3.1% of the total) versus "nondippers" (7.48% of the total) (P .023).

Table 2

Age stratification for night blood pressure (BP) fall.

Age	Patients	Dipper/extreme-dippers, %	Nondippers/reverse-dippers, %
<30 years old	33	54.5	45.5
30–60 years old	566	62.4	37.6
>60 years old	447	49.4	50.6

Table 3

Daytime and nighttime tolerance to the instrument between dippers and nondippers, extreme-dippers, reverse-dippers and subjects with any other dipping pattern.

Tolerance to the instrument	Dippers	Nondippers	P	Extreme-dippers	Other groups	P	Reverse-dippers	Other groups	P
	Daytime			Daytime			Daytime		
No	23 (3.9%)	9 (3.2%)		7 (4.7%)	32 (3.5%)		2 (4.2%)	36 (3.6%)	
Yes	569 (96.1%)	268 (96.8%)	.78	123 (95.3%)	885 (96.5%)	.65	46 (95.8%)	962 (96.4%)	.88
	Nighttime			Nighttime			Nighttime		
No	73 (12.3%)	32 (11.6%)		13 (10.1%)	113 (12.3%)		7 (14.6%)	120 (12.1%)	
Yes	519 (87.7%)	245 (88.4%)	.65	116 (89.9%)	804 (87.7%)	.75	41 (85.4%)	878 (87.9%)	.7

Yes = tolerance defined as "sufficient", "good," or "excellent".

Comparison among groups regarding the quality of sleep, related to the presence or the absence of nocturnal awakenings.

Quality of sleep	Patients, N (%)	Dippers, N (%)	Extreme-dippers, N (%)	Nondippers, N (%)	Reverse-dippers, N (%)
0	187	87 (46.5%)	27 (14.43%)	66 (35.3%)	7 (3.74%)
≥1	859	376 (43.77%)	102 (11.87%)	340 (39.58%)	41 (4.77%)
	1046	0.492	0.132	0.275	0.541

0 = no night awakenings, ≥1 = one or more night awakenings.
P = ns.

As far as it concerns the multivariate analysis, the results of the logistic regression analysis are presented in Table 5. As expressed in the table, risk factors of being dipper are maximum SBP and simple awakenings (OR over 1), while protective factors of being dipper are age, nocturnal urination, snoring, and high values of 24 hours mean SBP (OR under 1).

4. Discussion

According to the most recent evidences, ABPM is the recommended procedure standard for the diagnosis of real hypertension and provides an appropriate assessment of CV risk in all subjects. Moreover, the evaluation of the nocturnal BP behavior currently is the approved protocol to distinguish different categories of hypertension and to predict CV event-free interval.[15] It has been described that the progressive reduction of BP values, which occur while asleep, rather than awake, or 24 hours SBP mean toward the normal dipper BP profile, reflects in a decreased CV morbidity and mortality risk.

The neuroendocrine regulation, integrating the monoaminergic and endocrine within the central nervous system (hypothalamic–pituitary–thyroid/adrenal gland axes, renin–angiotensin–aldosterone system) is the major determinant of the nocturnal BP profile, but during BP registration, it is fundamental to evaluate if the personal tolerance to the procedure could affect the BP profile.[16]

Our cross-sectional study on patients undergoing ABPM highlights that the different patterns of the BP night fall do not depend on the perceived stress caused by the device, deriving from the inflating procedure, thus seem independent from the tolerance to the instrument.

Furthermore our study found no significant differences among the groups when total hours of sleep and frequency of nocturnal awakenings were compared. This finding suggests that the nocturnal BP fall was not caused by any discomfort due to ABPM.

It is known that the "nondipping" circadian pattern of BP is a predictor of CV events.[17,18] Some evidence show that patients with "nondipping" BP pattern have more target organ damage and higher incidence of stroke than "dippers."[19]

Furthermore it was demonstrated that a therapeutic intervention able to reverse the "nondipping" pattern to "dipping" profile improves prognosis.[20]

Of note, even if "reverse-dipping" pattern has been reported to be closely related to CV mortality, chronic kidney disease, muscle sympathetic nerve activity, and lacunar infarctions,[21,22] sometimes this condition has been included in a generic "nondipping" group, without any distinction.

Thus, these findings suggest that a more precise and personalized BP management should be provided to patients with elevated nocturnal BP. For this reason, it is important to ensure that ABPM does not cause false elevations of nocturnal BP due to poor tolerance to the instrument or to a higher number of night awakenings.

A solution would be represented by the use the new cuffless devices, applied to wrist or finger, that track vital signs with optical sensors and use beat-to-beat variability to compute systolic and diastolic readings based on mathematical modeling. They could be helpful in the future for the assessment of sleep BP, in particular, in patients with sleep disordered breathing, but the accuracy of these BP measurements has yet to be confirmed.[23]

Interestingly, we did not find any significant difference between the perceived quality of nocturnal sleep, during the ABPM, compared with the usual habits, as described by the patients in the diary. This could be an additional proof that the diagnosis of "dipping"/ "nondipping"/"reverse-dipping"/"extreme-dipping" patterns are not linked to artifacts from discomfort caused by the device.

Our findings, if supported by future studies with the analysis of a larger sample size, may allow clinicians to make better risk assessment in patients with impaired circadian rhythm of BP and to obtain better prognosis through BP lowering therapy.

Nevertheless, some studies describe a correlation between the poor tolerance to the instrument and "nondipping" profile.[24] This result may be due to the absence of analysis of other factors that may impair the "dipping" profile, such as nocturnal urination and sleep disorders. In fact, another important finding of our study is that, while simple awakenings do not affect the "dipping profile," waking up to urinate and sleep disorders, such as snoring, might affect the "dipping" profile determining a higher "nondipping" occurrence. It is possible that physical activation during the night alters the "dipping" profile.

Thus, in accordance with Perk et al,[25] our work highlights the importance of taking into account the presence or absence of nocturnal urination and of sleep disorders to obtain a more precise BP "dipping" pattern. Our study confirms data showing that individuals with sleep disordered breathing have a higher incidence of blunted nighttime BP.[26]

Results of the logistic regression model—dependent variable: being dipper.

Variable	OR (95% CI)
Age	0.984 (0.973–0.994)
Nocturnal urination	
No (reference)	1
Yes	0.82 (0.71–0.93)
Simple awakenings	
No (reference)	1
Yes	1.25 (1.08–1.45)
Sleep disorders	
No (reference)	1
Yes	0.60 (0.35–1.00)
Mean systolic blood pressure, 24 h	0.988 (0.976–0.999)
Max systolic blood pressure	1.008 (1.001–1.014)

CI = confidence interval, OR = odds ratio.

Among the strengths of this manuscript is the robustness of the statistical analysis. In particular, the univariate analysis was followed by a multivariate approach in which several variables were taken into account simultaneously. Using this approach we found that some factors are to be considered independently as risk factors (maximum of SBP and simple awakenings), and protective factors for being dipper (age, nocturnal urination, and high values of mean SBP in the 24 hours). Moreover, the narrow 95% CIs reflects the power of the study.

Limitation of the study is the lack of more precise methods of investigation, due to the large enrolled group (more than 1.000 subjects), such as administration of questionnaire regarding quality of sleep or evaluation of other biochemical parameters, but the obtained results are of course of high relevance and interest, thus further investigations could improve the results of our study.

In this regard, the outcome and strength of the statistical analysis encourages us to believe that further correlations can be the subject of future work.

In conclusion, we found that the poor tolerance to ABPM does not seem to influence the occurrence of BP "dipping" phenomenon among hypertensive individuals. Thus, once again ABPM has been shown to be the gold standard in the clinical practice, to accurately classify hypertensive patients. Moreover, we suggest that for a correct, unbiased ABPM interpretation, factors that may lead to a higher incidence of "nondipping" pattern, such as nocturnal urination and sleep disorders, need to be carefully investigated. The knowledge of these factors associated with a blunted fall in nighttime BP will lay the foundation for interventions to treat alterations in nocturnal BP patterns.

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