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Short-term variability and nocturnal decline in ambulatory blood pressure in normotension, white-coat hypertension, masked hypertension, and sustained hypertension: a population-based study of older individuals in Spain

Running title: Ambulatory blood pressure variability

Authors:

Teresa Gijón-Conde^{1,2} Auxiliadora Graciani¹, Esther López-García¹, Pilar Guallar-Castillón¹, Esther García-Esquinas¹, Fernando Rodríguez-Artalejo¹, José R. Banegas¹

Authors' affiliations:

¹Department of Preventive Medicine and Public Health, School of Medicine, Universidad Autónoma de Madrid/IdiPAZ – CIBER in Epidemiology and Public Health (CIBERESP), Madrid, Spain.

²Centro de Salud Universitario Cerro del Aire, Majadahonda, Madrid, Spain

Correspondence: José R. Banegas, MD or Teresa Gijon, MD, Department of Preventive Medicine and Public Health, Universidad Autónoma de Madrid, Arzobispo Morcillo 2, 28029 Madrid, Spain. E-mail: joseramon.banegas@uam.es

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ABSTRACT

Blood pressure (BP) variability and nocturnal decline in blood pressure are associated with cardiovascular outcomes. However, little is known about whether these indexes are associated with white-coat and masked hypertension. We performed a cross-sectional analysis of 1047 community-dwelling individuals aged ≥ 60 years in Spain in 2012. Three observer-measured home BPs and 24-hour ambulatory blood pressure monitoring (ABPM) were performed under standardized conditions. BP variability was defined as BP standard deviation and coefficient of variation. Differences in BP variability and nocturnal BP decrease between groups were adjusted for sociodemographic and clinical covariates using generalized linear models. Of the cohort, 21.7% had white-coat hypertension, 7.0% had masked hypertension, 21.4% had sustained hypertension, and 49.9% were normotensive. Twenty-four hour, daytime, and nighttime systolic BP standard deviations and coefficients of variation were significantly higher in subjects with white-coat hypertension than those with normotension ($p < 0.05$) and were similar to subjects with sustained hypertension. In untreated subjects, 24-hour but not daytime or nighttime BP variability indexes were significantly higher in subjects with white-coat hypertension than in those with normotension ($p < 0.05$). Percentage decrease in nocturnal systolic and diastolic BP was greatest in the white-coat hypertension group and lowest in the masked hypertension group in all patients and untreated patients ($p < 0.05$). Lack of nocturnal decline in systolic blood pressure was observed in 70.2% of subjects with normotension, 57.8% of subjects with white-coat hypertension, 78.1% of subjects with masked hypertension, and 72.2% of subjects with sustained hypertension ($p < 0.001$). In conclusion, 24-hour BP variability was higher in subjects with white-coat hypertension and blunted nocturnal BP decrease was observed more frequently in subjects with masked hypertension. These findings may help to explain the reports of increased cardiovascular risk in patients with white-coat hypertension and poor prognosis in those with masked hypertension, highlighting the importance of ABPM.

Key words: aged, blood pressure variability, masked hypertension, population studies, white coat hypertension

INTRODUCTION

Conventional measurement of blood pressure (BP) in a medical office is the standard method for the diagnosis and management of hypertension. However, there are several limitations to this approach, including apparently innocent elevations of BP that only occur in the clinic (white-coat hypertension) or the observation of normal readings when, in fact, the patient is hypertensive (masked hypertension).^{1, 2} Numerous reports of a wide variety of conditions and populations have demonstrated that ambulatory BP monitoring (ABPM) is superior to office-based measurement with respect to cardiovascular risk assessment.^{3,4}

BP not only exhibits large circadian variations in terms of changes between day and night but also changes from minute-to-minute and hour-to-hour in both hypertensive and normotensive patients.⁵ Thus, non-invasive 24-hour ABPM is a robust method to assess short-term BP variability within 24 hours.⁶

Most studies have found that high 24-hour BP variability is associated with organ damage and may contribute to cardiovascular risk prediction, over and beyond mean BP.⁷⁻¹⁷ However, the degree to which variability improves the prediction of cardiovascular risk is controversial.¹⁸⁻²⁰ Previous studies have shown that nighttime BP is generally a better predictor of cardiovascular outcomes than daytime BP in patients with hypertension, and diminished nocturnal decline in BP is associated with or predictive of organ damage and cardiovascular events.²¹⁻²⁶

Only a few studies have analyzed whether different phenotypes on the hypertension spectrum such as normotension, white-coat hypertension, masked hypertension, and sustained hypertension are associated with BP variability independent of mean BP.^{27,28} As far as we know, there are no reports about circadian variability and BP variability in daytime and nighttime periods across the various BP phenotypes. It is possible that the reported increases in cardiovascular risk in patients with white-coat hypertension or masked hypertension² could be attributed, at least in part, to BP variability and nocturnal decline in BP. The objective of this study was to describe the relationships between mean daytime and nighttime ambulatory BP, BP variability, and nocturnal decline in BP with subjects with normotension and white-coat, masked, and sustained hypertension in a cross-sectional analysis of older adults in Spain.²⁹

METHODS

Study Design and Population

Data are taken from the Seniors-ENRICA cohort, and the methods have been previously reported.^{29,30} In brief, this cohort was established in 2008-2010 with 2614 individuals selected through stratified random sampling from the population of individuals in Spain aged ≥ 60 years.²⁹ Baseline information on sociodemographic variables, lifestyle, health status, and morbidity was collected by telephone interview. In addition, a home visit was conducted to collect blood samples, and another home visit was conducted to perform a physical examination and to record dietary habits and prescribed medications. Participants were followed until 2012, when a second wave of data collection was performed. At this time point, of the 2519 surviving subjects, 2037 provided updated information for the telephone interview, physical examination, diet, and medication. ABPM was offered to 1698 individuals in this second wave for cost and logistical reasons, and the analysis was performed in 1328 subjects (response rate, 78.2%). The subjects who underwent ABPM had similar characteristics to those who did not in terms of age, sex, education level, obesity, diabetes, current smoking, and previous history of cardiovascular disease.

Personnel involved in data collection received specific training in the study procedures. Study participants gave written informed consent. The study was approved by the Clinical Research Ethics Committee of the “La Paz” University Hospital in Madrid.

Study Variables

Study participants reported their age, sex, and smoking status. Weight and height were measured in each subject under standardized conditions. Body mass index (BMI) was calculated as weight in kilograms divided by the square of the height in meters. Study subjects reported whether they had been previously diagnosed with hypercholesterolemia or cardiovascular disease (myocardial infarction, stroke, heart failure). Diabetes mellitus was identified as fasting serum glucose ≥ 126 mg/dL or treatment with oral antidiabetic drugs or insulin. Medication use was assessed by a face-to-face interview and verified against drug packaging during the home visits.

Blood pressure measurement

BP was measured using standardized procedures and conditions, with validated automatic devices (Omron M6) and appropriate-sized cuffs. Trained observers measured each participant's BP during a home visit: three measurements were taken at two-minute intervals after resting for five minutes in a seated position. In the analyses, BP was calculated as the mean of the last two of the three readings. Thereafter, 24-hour ABPM was performed using a validated automated non-invasive oscillometric device (Microlife® WatchBPO3 monitor),³¹ programmed to measure BP at 20-min intervals during the day and at 30-min intervals during the night for a 24-hour period. Appropriate cuff sizes were used. The majority of measurements were performed on working days, and the patients were instructed to maintain their usual activities but keep the arm extended and immobile at the time of cuff inflation. Valid ABPM measurements had to fulfill several pre-established criteria, including 24-hour duration and at least 70% of systolic BP (SBP) and diastolic BP (DBP) successful recordings during the daytime and nighttime periods.^{1,2,32} Daytime and nighttime periods were defined individually according to the patient's self-reported time of going to bed and waking up. Based on international guidelines,^{1,2,32} white-coat hypertension was defined as conventional BP $\geq 140/90$ mm Hg and 24-hour ABPM $< 130/80$ mm Hg; masked hypertension was defined as conventional BP $< 140/90$ mm Hg and 24-hour ABPM $\geq 130/80$ mm Hg; sustained hypertension was defined as conventional BP $\geq 140/90$ mm Hg and 24-hour ABPM $\geq 130/80$ mm Hg; normotension was defined as conventional BP $< 140/90$ mmHg and 24-hour ABPM $< 130/80$ mmHg. We have used these terms for the sake of simplicity. However, among untreated patients, the terms normotension, white-coat hypertension, masked hypertension, and sustained hypertension would be more correct, and among treated patients, the terms controlled hypertension, white-coat uncontrolled hypertension, masked uncontrolled hypertension, and uncontrolled hypertension would be appropriate. Short-term variability was assessed by the standard deviation (SD) and the coefficient of variation (CV) [standard deviation/mean $\times 100\%$] of SBP and DBP in 24 hour, daytime, and nighttime periods. Nocturnal decrease in SBP and DBP was measured in both absolute terms (mmHg) and relative terms and as BP dipping (nondipping was defined as nocturnal BP decrease $< 10\%$ of daytime BP).^{1,2,32}

Statistical analyses

For descriptive analysis, we used the mean and standard deviation for continuous variables and the percentage distribution of frequencies for categorical variables. To

compare means between groups, we used Student's t-test and analysis of variance. For comparison of percentages, the chi-square test was used.

Mean ambulatory BPs, BP variability indexes, and nocturnal decrease in BP were compared between BP phenotypes using generalized linear model analyses, adjusting for age, sex, BMI, smoking, diabetes, dyslipidemia, previous cardiovascular diseases, antihypertensive treatment (yes/no), and mean ambulatory SBP or DBP according to the time period, as appropriate. We also performed a separate analysis of mean ambulatory BPs and BP variability indexes in untreated subjects. Lastly, we analyzed the percentage reduction of nocturnal BP according to treatment status and adjusted for the covariates listed above. The Bonferroni correction was used for post hoc multiple comparisons. Statistical significance was established at $p < 0.05$. The Statistical Package for Social Sciences (SPSS) for Windows version 19.0 software (SPSS Inc., IBM, Armonk, NY) was used for statistical analysis.

RESULTS

A total of 1047 individuals (mean age 71.7 years, 50.8% men) with $\geq 70\%$ valid ABPM readings and complete information on the study variables were used for analysis (80% of all individuals with available ABPM). The mean conventional SBP/DBP was 137.8/74.0 mmHg, and the mean BMI was 27.8 kg/m²; 49.5% of subjects had hypercholesterolemia, 14.9% had diabetes, 5.7% had cardiovascular disease, and 42.9% were treated with an antihypertensive medication (**Table 1**). After ABPM, the global distribution of subjects was as follows: 49.9% had normotension (or controlled hypertension in treated subjects), 21.7% had white-coat hypertension (or white-coat uncontrolled hypertension in treated subjects), 7.0% had masked hypertension (or masked uncontrolled hypertension in treated subjects), and 21.4% had sustained hypertension (or uncontrolled hypertension in treated subjects) (**Table 1**).

After adjusting for demographic and clinical covariates (including mean ambulatory BP and antihypertensive treatment), systolic and diastolic 24-hour BP variability indexes were significantly higher in individuals with white-coat hypertension than in those with normotension (**Table 2**). As expected, mean systolic and diastolic 24-hour BPs were higher in subjects with masked hypertension relative to subjects with white-coat hypertension. We did not observe any differences between 24-hour BP variability indexes in subjects with masked vs. white-coat hypertension or between subjects with sustained vs. masked hypertension. During the daytime, systolic BP

variability indexes were higher in individuals with white-coat hypertension than in those with normotension. No differences between diurnal BP variability indexes were observed between subjects with masked vs. white-coat hypertension or sustained vs. masked hypertension. During the night, systolic BP variability indexes were higher in individuals with white-coat hypertension relative to those with normotension. We observed no differences in systolic and diastolic BP variability indexes in subjects with sustained vs. masked hypertension or masked vs. white-coat hypertension. Furthermore, no differences were observed in nighttime mean systolic and diastolic BP in subjects with sustained vs. masked hypertension. **Table 3** shows mean systolic and diastolic 24-hour pressures, day and night mean BPs, and BP variability indexes in untreated subjects. Notably, we observed a significant difference in mean 24-hour BPs and 24-hour variability indexes in subjects with white-coat hypertension vs. normotension, similar to our observations in the cohort as a whole. However, we did not observe any differences in day and night BP variability indexes between subjects with different hypertension phenotypes.

The proportion of systolic non-dipping was 70.2% (95% confidence interval (CI): 66.0% to 74.0%) in subjects with normotension, 57.8% (95% CI: 51.6% to 63.8%) in subjects with white-coat hypertension, 78.1% (95% CI: 66.6% to 86.5%) in subjects with masked hypertension, and 72.2% (95% CI: 66.1% to 77.6%) in subjects with sustained hypertension ($p < 0.001$). The proportion of diastolic non-dipping was 51.0% (95% CI: 46.6% to 55.4%) in subjects with normotension, 35.7% (95% CI: 30.0% to 41.8%) in subjects with white-coat hypertension, 64.1% (95% CI: 51.8% to 74.7%) in subjects with masked hypertension, and 50.0% (95% CI: 43.6% to 56.3%) in subjects with sustained hypertension ($p < 0.001$). These differences were maintained in untreated subjects but not in treated subjects (data not shown).

Table 4 shows the percentage decrease in nocturnal systolic and diastolic BP according to antihypertensive treatment status and adjusted for demographic and clinical covariates. In the whole cohort, as well as untreated patients, the relative reduction in systolic and diastolic BP was greatest in subjects with white-coat hypertension and lowest in those with masked hypertension. Significant differences were observed in subjects with white-coat hypertension vs. normotension, masked vs. white-coat hypertension, and sustained vs. masked hypertension ($p < 0.05$).

DISCUSSION

This study performed in a cohort of community-dwellers in Spain aged ≥ 60 years found the following: i) a higher ambulatory 24-hour BP variability in individuals with white-coat hypertension than in those with normotension (and similar to that in those with sustained hypertension), and (ii) diminished rates of nighttime BP dipping and a higher proportion of non-dipping in subjects with masked hypertension than those with normotension, independent of important sociodemographic and clinical covariates. These results were only maintained when untreated patients were considered. These findings may be pertinent to the reports that patients with white-coat hypertension have higher cardiovascular risk than those with normotension.³³⁻³⁵ Furthermore, the observation that those patients with masked hypertension have a worse prognosis than those with white-coat hypertension could be partly explained by both the higher mean ambulatory BPs at all time periods (including sleeping) and the diminished nocturnal BP dip. This reinforces the importance of ABPM as a helpful tool to establish the diagnosis and prognosis of BP phenotypes. To the best of our knowledge, no previous studies have focused on these relationships including overnight examination.

The reported frequency of white-coat and masked hypertension ranges from 10 to 50%³⁶ depending on the cut-offs used for normal ambulatory BP and the study population. Thus, the apparent low frequency of white-coat and masked hypertension in our study (21.7% and 7.0%, respectively) is noteworthy in comparison to other studies that included thresholds of 140/90 mmHg for clinic BP and 135/85 mmHg in daytime BP³⁶ but that ignored the nighttime period. Such an omission may lead to overestimation of the frequency of white-coat and masked hypertension. We have used 140/90 mmHg as a threshold for observer-measured home BP and 130/80 mmHg in 24-hour ambulatory BP that included nocturnal BP values and could thus be considered a relatively exigent scenario. Although any time interval suffices to diagnose masked hypertension, as proposed in current guidelines, full 24-hour recordings remain standard in clinical practice.³⁷ The higher 24-hour BP variability in subjects with white-coat hypertension may help to explain the higher rates of cardiovascular risk that have been reported in previous studies of these patients.³³⁻³⁵ BP variability depends on sympathetic vascular modulation and changes in arterial distensibility. Higher short-term BP variability in subjects with white-coat hypertension than in those with normotension has been reported in a few other studies^{38,39} and may be intrinsic or an enhanced stress response to external stimuli. Alternatively, it may reflect a diffuse atherosclerotic process induced by aging and hypertension that leads to increased

stiffness of the large elastic arteries and/or depressed baroreflex functions causing impaired cardiovascular control mechanisms.⁵ In addition, we postulate that mechanisms other than sympathetic activity are operating in white-coat hypertension, since this activity correlates with the level and standard deviation of BP, but not with the coefficient of variation, a measure of variability that is less dependent on the level of BP than the standard deviation.⁴⁰ It is noteworthy that in patients with antihypertensive treatment, we did not observe any differences in BP variability indexes. So, it is possible that antihypertensive treatment controls BP variability independent of mean BP. This may be a future target for controlling BP.

There is strong evidence that patients with masked hypertension are at increased risk of target organ damage and cardiovascular morbidity,^{2,41,42} with an overall cardiovascular risk approaching that of patients with sustained hypertension.⁴³ In our study, the higher level of mean nighttime BP in patients with masked hypertension (vs. those with white-coat hypertension or normotension and no difference when compared to those with sustained hypertension) may also explain the poorer prognosis of patients with masked hypertension in comparison with those with white-coat hypertension. This is in line with several observational and longitudinal analyses demonstrating the superior value of nocturnal BP compared with daytime BP in predicting cardiovascular events and all-cause mortality.^{19,24,43} Nocturnal BP at resting conditions is the minimum BP needed for adequate organ perfusion, and high BP at night could overload the cardiovascular system and lead to negative effects on the heart and vascular structures.⁴⁴ Mentally stressful situations have been associated with masked hypertension and high BP variability.⁴⁵

In this study, the high frequency of systolic and diastolic nondipping and the significant decrease in nocturnal BP decline in patients with masked hypertension after adjusting for ambulatory BP levels, antihypertensive drug treatment, and other covariates could help to explain why patients with masked hypertension have a poor prognosis. It has been reported that nondipping and diminished decline in nocturnal BP is associated with organ damage and poor cardiovascular outcomes both in population studies and in hypertensive patients.⁴⁶⁻⁴⁹ It is noteworthy that in patients with pharmacological treatment, we did not observe any differences in nocturnal BP declines between groups. So, it is possible that antihypertensive treatment may affect nocturnal BP decline independent of mean BP. This may be a target for future BP control.

Nighttime masked hypertension is observed in various conditions that produce non-dipping status, including high salt intake, renal dysfunction, obesity, sleep apnea, and autonomic failure.⁵⁰ In particular, investigation of nocturnal BP and decline in nocturnal BP using ABPM suggest that this process is salt sensitive, which is associated with increased sympathetic activity and increased cardiovascular risk.⁵¹ Nondipping could reflect an inadequacy of the mechanisms regulating BP; it could be the result of baroreflex or autonomic dysfunction, relative nocturnal volume overload, or abnormal sodium handling. ABPM can refine the prognostic assessment in hypertension not only by providing an accurate BP value that is the average of a large number of BP measurements but also by assessing circadian variability, a parameter which requires ABPM.⁴⁴

Given that this study was not strictly representative of the general older population of Spain, extrapolations should be interpreted with caution. Nevertheless, the baseline sociodemographic and clinical characteristics of the participants were similar to those who did not participate. It should be noted that in this study, conventional BP was not measured in the office or clinic but in subjects' homes as in other studies,⁵² thereby decreasing the effect of anxiety and giving more realistic estimates. Nevertheless, we used the 140/90 mmHg target for the primary analysis of conventional BP, since BP was measured on only one occasion and involved a technique similar to that used for office BP measurements. Furthermore, although white-coat and masked hypertension are not entirely accurate terms and "isolated home BP elevation" or "isolated ambulatory BP elevation," are more appropriate and descriptive terms, we have maintained the terms "white coat" and "masked" hypertension for the sake of clarity and comparison with other studies. Lastly, determination of antihypertensive therapy was based on the participant's self-report and may, therefore, be inaccurate; however, medications were checked against prescription containers. Lastly, the cross-sectional design prevents us from assessing causal relationships between the associations we report.

In conclusion, we found that 24-hour BP variability was higher in subjects with white-coat hypertension than in normotensive individuals and that non-dipping was higher, with diminished decline in nocturnal BPs, in subjects with masked hypertension. These findings may help to explain the reports of higher cardiovascular risk in patients with white-coat hypertension and the poor prognosis observed in patients with masked hypertension, highlighting the clinical diagnostic and prognostic utility of ABPM.

Future research should evaluate the causal relationship between ambulatory BP variability and white-coat hypertension and between diminished nocturnal decreases in BP and masked hypertension.

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Conflicts of interest. The authors declare no conflict of interest.

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