

Original Research

Circadian Variation of Blood Pressure and Heart Rate in Normotensives, White-Coat, Masked, Treated and Untreated Hypertensives

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Introduction: Ambulatory blood pressure monitoring (ABPM) forms the basis for the diagnosis of masked hypertension, a condition associated with increased target organ damage, and of white-coat hypertension, a common condition among subjects referred to hypertensive centers. The aim of this study was to compare the circadian blood pressure (BP) and heart rate (HR) profiles in 1676 Greek subjects in order to identify the circadian patterns in these two categories of patient.

Methods: A total of 1676 subjects underwent 24-hour ABPM. The study population was divided into 5 subgroups in terms of the clinic and ambulatory BP levels: normotensives (224 subjects), white-coat hypertensives (353 subjects), masked hypertensives (42 subjects), treated (653 subjects) and untreated (404 subjects) hypertensives.

Results: The patterns of circadian BP and HR profiles were identical in the 5 groups. A clear nocturnal fall (23:00-04:00), an afternoon nadir (16:00), two daytime peaks (one between 09:00 and 14:00 and the other in the evening at 20:00), and a morning surge in systolic BP, diastolic BP, and HR were observed.

Conclusions: The circadian profiles of BP and HR in white-coat and masked hypertension show the same pattern as in normotensive and hypertensive patients (treated and untreated). These findings indicate that factors other than disturbances in BP and HR circadian pattern are likely to be responsible for the pathogenesis of white-coat and masked hypertension. A direct influence of autonomic nervous system activity on the circadian pattern of BP and HR could explain the persistence of a basic circadian profile in normotension, white-coat, masked, and sustained hypertension, independently of 24-hour BP and HR levels.

Circadian rhythms are a basic quality of human physiology. It is commonly known that, in healthy humans, heart rate (HR) and blood pressure (BP) increase during the day and decrease during the night, as a result of sleep-wake or rest-exercise changes.^{8,9} Many studies have reported that autonomic neural function shows a distinct circadian rhythm, with sympathetic activity being significantly increased during the day and decreased during the night. In addition, BP, HR, cardiac output, and serum catecholamine levels rise during the day and fall during

the night.⁴⁻⁹ According to Guo et al,⁶ these changes enable the organism to adapt to the need for higher activity levels while awake. However, the exact relationships of endogenous and exogenous factors to the circadian rhythms of the autonomic neural system are not yet clear.

The invention of tools for continuous monitoring has permitted more extensive observation of circadian rhythms.⁹⁻¹⁴ Ambulatory BP monitoring (ABPM) has provided detailed information about the circadian rhythm of BP.⁴⁻⁸ It is characterized by an increase in the early morning hours,

known as morning surge, high levels during the daytime, with peak values between 10 am and noon, an afternoon fall (siesta), and clear nocturnal dipping. This circadian pattern originates in the suprachiasmatic nuclei of the anterior hypothalamus, and is mediated either through the release of hormones from the hypothalamus or through efferent neural pathways. The autonomic nervous system plays a critical role.⁸

BP variability as evaluated by ABPM¹⁻³ seems to correlate with target organ damage better than office measurements do.¹²⁻¹⁴ However, little is known about the circadian variability of BP in masked and white-coat hypertension, two conditions that have been attracting increased interest, mostly with regard to their investigation and clinical impact.¹⁶ The aim of this study was to use ABPM to compare the circadian BP and HR profiles in masked and white-coat hypertensives with those in normotensives and diagnosed hypertensives, treated and untreated. Our purpose was to describe similarities and differences among the circadian patterns and to identify any abnormalities in these patterns in white-coat and masked hypertension in order to elucidate possible mechanisms underlying those two conditions.

Methods

Subjects

The study population consisted of 1676 individuals, aged 18-87 years old (mean \pm standard deviation 56 ± 13 years), who were referred to the Hypertension Center of the Department of Clinical Therapeutics (Athens University, Greece). All participants were ambulatory and fulfilled the following inclusion criteria: 1) absence of clinical evidence of hypertension-related complications (coronary artery disease, heart failure, cerebrovascular disease, renal insufficiency or peripheral artery disease); 2) no clinical signs or laboratory evidence of secondary causes of arterial hypertension; 3) at least three valid BP measurements per hour on 24-hour ABPM (75% successful measurements).

Subjects gave their informed consent before entering the study, the study was approved by the institutional review committee of the hospital, and the procedures followed were in accordance with the institutional guidelines.

Clinic blood pressure measurements

Clinic BP measurements were obtained using a mercury sphygmomanometer in all subjects. Three con-

secutive measurements were made: the first at the beginning of the visit, 5 minutes after sitting down; the second 10 minutes later; and the third immediately before the fitting of the ambulatory BP monitoring equipment. The mean of the three systolic values and the mean of the three diastolic values of the same patient were recorded as the clinic systolic blood pressure (SBP) and the clinic diastolic blood pressure (DBP), respectively. Study participants remained seated with their arm placed comfortably at heart level. All measurements were obtained by the same doctor.

Ambulatory blood pressure monitoring

ABPM for 24 hours was performed using a Spacelabs 90207 ABP monitor (Spacelabs Inc., Redmond WA, USA). All subjects were measured on a working day and were instructed to carry out their usual daily activities. The cuff was fixed to the non-dominant arm and three BP readings were taken concurrently with a sphygmomanometer to ensure that the average of the two sets of values did not differ by more than 5 mmHg. Automatic BP readings were taken at 15-min intervals.

Risk factors and definitions

Each individual was questioned about factors such as age, time from first diagnosis of hypertension, family history of hypertension, pharmaceutical treatment used, and evidence of other risk factors for cardiovascular disease. Anthropometric measurements were expressed by body mass index. Smokers were defined as those reporting daily or occasional smoking. Normotensives were considered to be those with clinic BP < 140/90 mmHg and daytime ambulatory BP < 135/85 mmHg. White-coat hypertensives were defined as those with office readings of SBP \geq 140 mmHg or DBP \geq 90 mmHg and daytime ambulatory BP < 135/85 mmHg. Masked hypertensives were defined as those with clinic BP < 140/90 mmHg and daytime ambulatory SBP \geq 135 mmHg or daytime DBP \geq 85 mmHg. Untreated hypertensives were defined as those with clinic SBP \geq 140 mmHg or clinic DBP \geq 90 mmHg and daytime ambulatory SBP \geq 135 mmHg or daytime ambulatory DBP \geq 85 mmHg, who were not under any antihypertensive treatment.¹⁻³ Treated hypertensives were the only subjects who were using any kind of antihypertensive pharmaceutical treatment, regardless of whether the hypertension was eventually controlled or not. Nocturnal BP

dipping was computed as $100 \times (1 - \text{nighttime BP/day-time BP})$ for both systolic and diastolic BP. The day-time period was defined as the time between 06:00 to 21:59, and the nighttime period as the time between 22:00 and 05:59.

Statistical analyses

The SPSS statistical package (SPSS Inc., version 10.0 for windows, Chicago IL, USA) was used to store and analyze data. Values were expressed as mean \pm standard deviation. A p-value of 0.05 was used as the level of statistical significance. Statistical comparisons were performed among the five subgroups in terms of baseline characteristics, office and ambulatory BP measurements. Dichotomous variables were compared using the χ^2 test. Time-trend tables were constructed for SBP, DBP and heart rate, averaged every one hour by computer for each disease group. The significance of variations between the groups was calculated by analysis of covariance (ANOVA, Scheffe's test). Circadian patterns for each of the above variables were constructed.

Results

Based on the above definitions, participants were divided into five categories: normotensives (n=224, 13.4%), white-coat hypertension (n=353, 21%), masked hypertension (n=42, 2.5%), treated hypertensives (n=653, 39%) and untreated hypertensives (n=404, 24.1%). Table 1 presents the baseline characteristics of the subjects in the five groups. In the present sample, white-coat hypertension was more common in females than in males; masked hypertensives had a lower prevalence of smoking, and treated hypertensives were the oldest.

As shown in Table 2, mean clinic and ambulatory SBP and DBP values were significantly higher in white-coat hypertensives than in normotensives. Daytime SBP and DBP in white-coat hypertensives, as well as their nighttime values, differed when compared with the respective values found in normotensives, but remained well below the threshold of hypertension. Masked hypertensives did not differ in their mean clinic SBP and DBP from the normotensives, although ambulatory SBP and DBP in masked hypertensives were much higher than in normotensives, as expected. Daytime SBP and DBP in masked hypertensives, as well as their nighttime values, differed compared with the respective values found in white-coat hypertensives and normotensives. Daytime and nighttime pulse pressure measurements in normotensives were statistically significantly lower compared to all other groups. In white-coat hypertensives, daytime pulse pressure was significantly lower compared to masked, treated and untreated hypertensives, whereas nighttime pulse pressure was significantly lower compared to treated and untreated hypertensives. In untreated hypertensives the mean clinic and ambulatory SBP and DBP values were significantly higher compared to all other groups examined. Regarding daytime and nighttime heart rates, white-coat hypertensives were similar to normotensives, masked and untreated hypertensives, with the treated hypertensives having the lowest values among all the groups examined. Lastly, the percentages of SBP and DBP dipping were similar among the five groups, while all groups examined presented an afternoon fall, known as siesta.

Figures 1- 3 show the circadian patterns of SBP, DBP and heart rate, respectively, based on the average values recorded every 15 min over a 24-hour period in all five groups. The circadian profiles in the five

Table 1. Baseline characteristics of the participants in the five subgroups examined (normotensives, white-coat hypertensives, masked hypertensives, treated and untreated hypertensives).

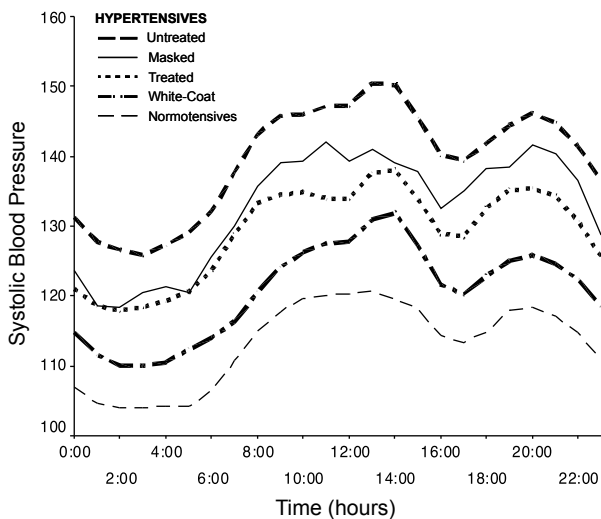
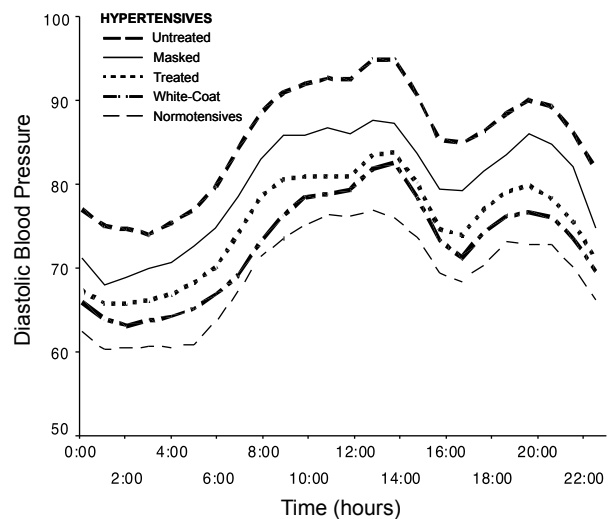
| Variables | Normotensives (n=224) | White-coat hypertensives (n=353) | Masked hypertensives (n=42) | Treated hypertensives (n=653) | Untreated hypertensives (n=404) |
|--------------------------------------|--------------------------|--|-----------------------------------|-------------------------------------|---------------------------------------|
| Age (years) | 50.3 \pm 15.9 | 53.3 \pm 13.3 ^{*,} | 51.2 \pm 15.8 | 60.7 \pm 11.2 | 53.8 \pm 11.9 |
| Male gender (%) | 50.9 | 39.7 ^{*,§} | 71.4 ^{*,} | 43.8 | 58.7 |
| Body mass index (kg/m ²) | 25.9 \pm 4.2 | 27.9 \pm 4.5 [*] | 26.4 \pm 3.7 | 28.4 \pm 4.6 | 27.8 \pm 4.3 |
| Smoking (%) | 38.9 | 34.1 | 26.3 | 26.5 | 38.2 |
| Diabetes mellitus (%) | 11.6 | 9.2 | 5.3 | 13.5 | 8.9 |
| Hyperlipidemia (%) | 32.9 | 38.7 [§] | 26.3 | 42.3 | 31.1 |

*Statistically significant difference from normotensives; †statistically significant difference from white-coat hypertensives; ‡statistically significant difference from masked hypertensives; §statistically significant difference from untreated hypertensives; ||statistically significant difference from treated hypertensives.

Table 2. Blood pressure and heart rate variables of the participants in the five subgroups examined (mean \pm standard deviation).

| Variables | Normotensives (n=224) | White-coat hypertensives (n=353) | Masked hypertensives (n=42) | Treated hypertensives (n=653) | Untreated hypertensives (n=404) |
|-----------------------|--------------------------|--|------------------------------------|-------------------------------------|---------------------------------------|
| SBP _{CLINIC} | 117.2 \pm 10.6 | 146.2 \pm 16.9 ^{*,‡,§,} | 124.0 \pm 6.7 ^{†,§,} | 150.3 \pm 23.4 | 154.5 \pm 18.1 |
| DBP _{CLINIC} | 75.1 \pm 7.3 | 93.6 \pm 10.1 ^{*,‡,§} | 78.3 \pm 5.8 ^{†,§,} | 92.0 \pm 14.1 | 97.1 \pm 10.2 |
| PP _{CLINIC} | 42.1 \pm 8.8 | 52.6 \pm 16.2 ^{*,§,} | 45.8 \pm 6.7 ^{§,} | 58.3 \pm 18.6 | 57.4 \pm 17.0 |
| HR _{CLINIC} | 74.3 \pm 10.4 | 76.8 \pm 11.7 | 76.3 \pm 10.9 | 73.9 \pm 11.4 | 77.9 \pm 12.2 |
| SBP ₂₄ | 112.6 \pm 9.7 | 119.8 \pm 7.6 ^{*,‡,§,} | 132.7 \pm 7.9 ^{*,†,§} | 128.5 \pm 14.9 | 139.1 \pm 11.0 |
| DBP ₂₄ | 69.2 \pm 7.0 | 72.5 \pm 6.2 ^{*,‡,§,} | 80.4 \pm 7.6 ^{*,†,§,} | 75.1 \pm 10.3 | 85.3 \pm 9.0 |
| HR ₂₄ | 72.8 \pm 9.3 | 72.3 \pm 9.0 ^{§,} | 73.1 \pm 8.3 | 69.3 \pm 9.8 | 74.9 \pm 9.0 |
| SBP _{DAY} | 116.0 \pm 9.8 | 123.6 \pm 7.2 ^{*,‡,§,} | 137.4 \pm 7.9 ^{*,†,§} | 132.6 \pm 15.1 | 143.7 \pm 10.8 |
| DBP _{DAY} | 72.6 \pm 7.3 | 75.9 \pm 6.1 ^{*,‡,§,} | 84.2 \pm 7.5 ^{*,†,§,} | 78.7 \pm 10.6 | 89.2 \pm 9.0 |
| HR _{DAY} | 76.2 \pm 9.9 | 75.9 \pm 9.7 ^{§,} | 76.7 \pm 8.6 | 72.5 \pm 10.6 | 78.5 \pm 9.5 |
| SBP _{NIGHT} | 106.4 \pm 10.7 | 113.2 \pm 10.3 ^{*,‡,§,} | 124.1 \pm 10.7 ^{*,†} | 121.4 \pm 16.0 | 130.9 \pm 13.5 |
| DBP _{NIGHT} | 63.2 \pm 7.8 | 66.5 \pm 8.0 ^{*,‡,§,} | 73.4 \pm 9.1 ^{*,†} | 68.9 \pm 10.9 | 78.3 \pm 10.4 |
| HR _{NIGHT} | 66.6 \pm 9.0 | 66.0 \pm 9.1 ^{§,} | 66.5 \pm 9.1 | 63.7 \pm 9.3 | 68.5 \pm 9.1 |
| SBP dipping (%) | 8.2 \pm 5.5 | 8.4 \pm 6.5 | 9.6 \pm 6.6 | 8.3 \pm 6.5 | 8.9 \pm 6.1 |
| DBP dipping (%) | 12.9 \pm 6.9 | 12.4 \pm 7.8 | 12.9 \pm 6.9 | 12.4 \pm 7.2 | 12.3 \pm 7.1 |

*Statistically significant difference from normotensives; †statistically significant difference from white-coat hypertensives; ‡statistically significant difference from masked hypertensives; §statistically significant difference from untreated hypertensives; ||statistically significant difference from treated hypertensives. SBP – systolic blood pressure; DBP – diastolic blood pressure; PP – pulse pressure; HR – heart rate.

**Figure 1.** Circadian rhythm of ambulatory systolic blood pressure in the five subgroups.**Figure 2.** Circadian rhythm of ambulatory diastolic blood pressure in the five subgroups.

groups followed the same pattern, though with higher or lower values depending on the hypertensive status.

Discussion

To our knowledge, this is the first study that used ABPM to evaluate the circadian pattern of white-coat hypertension and masked hypertension, in comparison with normotension and hypertension, in a large group of individuals in Greece. In this hospital-based

cross-sectional study, the comparison of circadian BP and HR profiles showed that white-coat hypertensives and masked hypertensives present the same pattern as normotensives and hypertensives, treated or untreated.

ABPM allows the circadian pattern of blood pressure to be monitored and has enabled the diagnosis of hypertension subtypes, such as white-coat hypertension and masked hypertension.^{1-3,12} In addition, ABPM can be used for the evaluation of BP variabil-

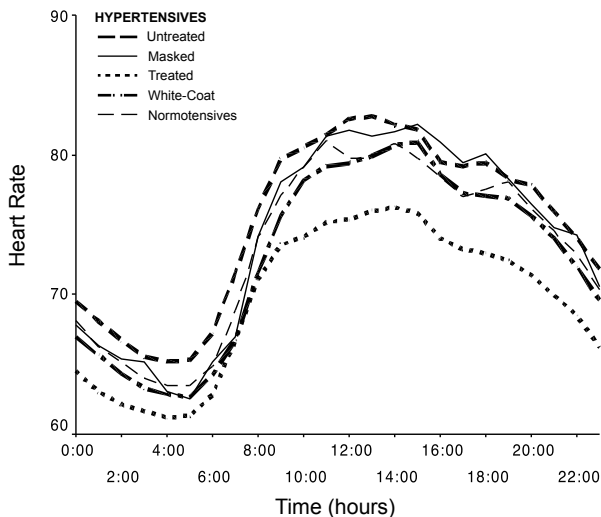


Figure 3. Circadian rhythm of ambulatory heart rate in the five subgroups.

ity and seems to correlate with target organ damage better than office measurements do.¹²⁻¹⁴ Thus, ABPM is superior to clinic BP in the prediction of cardiovascular morbidity and mortality.¹²

Previous studies have demonstrated a significant link between the circadian rhythm of BP and cardiovascular events,¹² namely that the absence of a nocturnal fall in BP, known as “non-dipping” status, is associated with more severe target organ damage and increased cardiovascular risk. Both genetic and environmental factors are implicated in a blunted nocturnal decline in blood pressure.¹³ ABPM plays a critical role in the detection of non-dippers, which is of great importance in the prevention of target organ damage and cardiovascular events in hypertensive patients. However, an impaired nocturnal decline can be observed even in normotensives.³² In our study, all the subjects examined presented the same circadian variation, with a clear nocturnal fall during the night between 23:00 and 4:00, regardless of their hypertensive status. Furthermore, the prevalence of a non-dipping pattern showed no significant differences among the five subgroups (Table 2). A previous study that investigated the prevalence of the dipping pattern in a large population in Spain³¹ reported different results. De la Siera et al found, in a population of both treated and untreated hypertensive patients, that about 50% of hypertensives presented a blunted nocturnal BP decline. The proportion was higher in treated hypertensives than in untreated patients. A possible limitation in our study is that the subgroups were not well matched concerning age, gender, body mass in-

dex, and the prevalence of diabetes mellitus, which are factors known to influence the dipping pattern.

Another feature of the circadian BP pattern determined by ABPM, the “morning surge”, has also been well described. This surge coincides with acute cardiovascular events, such as myocardial infarction, stroke, sudden cardiac death and ischemic episodes.¹² An explanation proposed for this link is the stimulation of sympathetic activity during awakening from sleep, resulting in increased plasma renin activity and angiotensin II levels, increased catecholamine production and cortisol levels, enhanced platelet aggregation, and thus an increased risk of thrombosis. In the present study, all the subgroups presented a distinct morning surge of SBP, DBP and HR between 4:00 and 6:00 am, with untreated hypertensives reaching the highest values of BP, as expected. A possible explanation for this observation is that factors other than the BP levels might be responsible for the increased incidence of cardiovascular events during awakening. Zakopoulos et al³⁴ found greater BP variability during the morning BP surge in patients with target organ damage, independently of the morning BP level, while Kario et al^{35,36} reported a possible risk of exaggerated morning surge and cardiovascular events independently of 24-hour BP level in hypertensives.

Another interesting finding of our study is that all subgroups demonstrated a clear afternoon fall, which could reflect the time of an afternoon nap, known as siesta. Individuals who take a siesta demonstrate a blood pressure dip during the afternoon nap, which reduces the average daytime blood pressure levels. Siesta is a common habit in Greece and other Mediterranean countries, probably as a result of climatic, social and cultural factors.³⁸ It has been estimated that roughly 70% of the general Greek population take a siesta.⁴⁰ Previous studies have shown a strong positive relationship between the evening blood pressure surge following siesta and cardiovascular events such as sudden cardiac death, myocardial infarction,³⁹ and stroke onset.³⁷

ABPM is a useful tool for the detection of white-coat hypertension, a condition with elevated clinic BP, but normal ambulatory BP levels. The circadian pattern of white-coat hypertension has been previously described by Pierdomenico et al,²¹ who showed similar circadian patterns in white-coat hypertension and in sustained hypertension. However, urinary norepinephrine excretion and vanillyl-mandelic acid excretion over the 24-hour period were significantly

higher in patients with sustained hypertension than in those with isolated office hypertension. These findings indicate sympathetic overactivity throughout the day in sustained hypertension but not in white-coat hypertension, suggesting that the two conditions show some differences in pathophysiological background. Moreover, Vyssoulis et al²² showed that patients with white-coat hypertension and a greater number of metabolic syndrome components presented elevated nighttime SBP levels, suggesting that those patients are at increased cardiovascular risk. However, a recent meta-analysis did not show a significantly different incidence of cardiovascular events between white-coat hypertension and true normotension.¹⁷ In our study, white-coat hypertensives presented the same circadian pattern as hypertensives and normotensives, with the same prevalence of a non-dipping pattern. Thus, we could hypothesize that other factors, such as sympathetic overactivity or concomitant diseases, rather than a disturbance in the circadian pattern, are responsible for the development of target organ damage in sustained hypertension but not in white-coat hypertension.

On the other hand, masked hypertension, the converse phenomenon, with high ambulatory blood pressure but normal office blood pressure, not only is associated with target organ damage, but also seems to be a predictor of cardiovascular morbidity, much like sustained hypertension.²³⁻²⁵ Thus, it is of great importance to diagnose and treat masked hypertensives. In the present study, masked hypertensives presented the same circadian pattern as normotensives, white-coat and true hypertensives, characterized by a clear morning surge and a distinct nocturnal fall, as well the same prevalence of non-dipping status. This means that neither a blunted nocturnal fall, nor an excessively high surge in morning blood pressure, could explain the target organ damage and the increased cardiovascular risk in those patients. Konstantopoulou et al⁴¹ suggest that feelings of security and trust in the doctor's office are responsible for the lower clinic BP measurements in masked hypertensives. Grassi et al have shown a marked sympathetic overdrive in masked hypertension, possibly contributing to target organ damage.²⁴ However, Fagard et al¹⁸ observed that heart rate recovery was not different between masked hypertensives and normotensives, but was significantly higher in sustained hypertension, suggesting that the sympathetic nervous system is not involved in this type of hypertension and that lifestyle factors such as smoking and alcohol consumption are

possibly related with the development of masked hypertension.

In this hospital-based cross-sectional study, the main finding was that the circadian profile of BP and HR in white-coat hypertension and masked hypertension presented the same pattern as in normotensive and hypertensive subjects, treated or untreated. This persistence of the same basic circadian pattern could be more evidence of the direct influence of autonomic nervous system activity on the circadian profile of BP and HR, independently of 24-hour BP and HR levels. Based on our findings, we could hypothesize that factors other than disturbances in circadian pattern are likely to be implicated in the pathogenesis of white-coat hypertension and masked hypertension. However, the elucidation of the pathophysiology underlying these two conditions could be a very important step towards their diagnosis and their effective treatment. The cross-sectional nature of this study precludes causal inference, but provides valuable directions for future prospective investigations.

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