Brain Microbleeds Are Associated With Ambulatory Blood Pressure Levels in a Hypertensive Population

Léon H.G. Henskens, Robert J. van Oostenbrugge, Abraham A. Kroon, Peter W. de Leeuw, Jan Lodder

Abstract—Brain microbleeds, indicative of cerebral small-vessel disease, may occur with increased frequency in patients with hypertension. However, little is known about the relation of these abnormalities with blood pressure levels. We assessed the relation between ambulatory measured blood pressure and the presence of microbleeds in a cohort of hypertensive patients without a history of cerebrovascular disease. A total of 218 participants (110 males, age 52.5 ± 12.6 years) underwent 24-hour ambulatory blood pressure monitoring twice (off-medication) and brain MRI to detect microbleeds and coexisting white matter hyperintensities. We performed logistic regression analyses to relate the following blood pressure components (based on both recordings) to microbleeds: the mean 24-hour, awake, and asleep blood pressures; nocturnal hypertension (asleep pressure ≥ 120/70 mm Hg); nocturnal blood pressure dipping. Models were adjusted for age and sex, and additionally for cardiovascular risk factors and white matter hyperintensities. We detected microbleeds in 35 participants (16.1%; 95% confidence interval, 11.1% to 21.0%). On average, each standard deviation increment in blood pressure, whether 24-hour, awake, or asleep, was significantly and independently associated with a 1.8- to 1.9-fold higher likelihood for microbleeds (all models P < 0.05). Similarly, the adjusted odds ratio for microbleeds was 5- to 6-fold higher in subjects diagnosed with nocturnal hypertension (all models P < 0.05). Microbleeds were not associated with nocturnal dipping. In conclusion, brain microbleeds are frequently found in hypertensive patients without a history of cerebrovascular disease, and are independently associated with higher daytime as well as night-time blood pressure levels. (Hypertension. 2008;51:62–68.)

Key Words: brain microbleeds ■ hypertension ■ blood pressure ■ MRI ■ ambulatory blood pressure monitoring ■ target-organ damage

Brain microbleeds (BMBs) are focal accumulations of hemosiderin-containing macrophages in the perivascular space of small blood vessels in the brain, indicating previous extravasation of blood. These abnormalities, which were described in the mid-1990s for the first time, can be identified as small areas of signal loss on haem-sensitive T2*-weighted gradient echo (GE) MRI and remain detectable for years. In Caucasian populations, the prevalence of BMBs is about 5% in healthy, mostly elderly individuals, increases to around 25% in ischemic stroke patients, and goes even beyond 50% in patients affected by intracerebral hemorrhage; in populations of Asian descent even higher prevalences have been reported. The presence of BMBs has been associated with cognitive impairment, independent of coexisting ischemic brain damage (in particular white matter changes). In addition, prospective data suggest that BMBs predict the recurrence of both ischemic and hemorrhagic stroke, emphasizing their potential clinical relevance.

Although BMBs may occur with increased frequency in patients with hypertension and, accordingly, in conjunction with hypertension-related damage of the heart and the brain, little is known about their relation with blood pressure (BP) levels per se. Some studies have reported higher BP levels in subjects displaying BMBs, but so far no study has primarily focused on the BP-microbleed relationship.

It has been shown that BP obtained by ambulatory BP monitoring (ABPM) correlates closely with hypertension-related organ damage, and that its prognostic value, whether daytime, night-time, or 24-hour, is superior to that of BP measured in the office. Therefore, the objective of the present study was to assess the relation between BMBs and BP measured by ABPM in a cohort of hypertensive patients without a history of cerebrovascular disease.

Methods

Participants

Between July 2004 and September 2006, all consecutive patients referred to our outpatient department for the evaluation of their hypertension have been screened for participation in the present study. From the Department of Internal Medicine (L.H.G.H., A.A.K., P.W.d.L.), Division of General Internal Medicine, Subdivision Vascular Medicine, University Hospital Maastricht and Cardiovascular Research Institute Maastricht (CARIM), and the Department of Neurology (R.J.v.O., J.L.), University Hospital Maastricht and Cardiovascular Research Institute Maastricht (CARIM), Maastricht University, The Netherlands.

Key Words: brain microbleeds ■ hypertension ■ blood pressure ■ MRI ■ ambulatory blood pressure monitoring ■ target-organ damage

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study. As part of the routine work-up, patients underwent ABPM over a 24-hour period, standard 12-lead electrocardiography, and routine laboratory investigations. Patients who were using antihypertensive medication were also instructed to discontinue treatment at least 2 weeks before the BP measurements. An experienced internist decided, based on the patients’ clinical information provided by the referring physician and independent of the study, whether it was possible to stop temporarily the antihypertensive medication. Accordingly, patients who continued treatment were excluded from participation.

Those patients who stopped or did not receive prior treatment had—to be eligible for inclusion in the present study—to consent to an MRI of the brain and a repeat ABPM, preferably within 1 week after the first one, and also off-medication. In addition, participants had to fulfil the following criteria: (1) men or women aged 18 to 90 years; (2) no indication from history-taking, physical examination, or routine laboratory tests of secondary hypertension; (3) no evidence of atrial fibrillation; (6) no history of transient ischemic attacks and ischemic or hemorrhagic stroke; (7) no diagnosis of obstructive sleep apnea syndrome. All participants gave written informed consent and the Medical Ethics Committee of the University Hospital Maastricht/Maastricht University approved the study. In this way, a total of 218 patients were included into the study. The flow diagram in Figure 1 displays the number of patients screened, those eligible for inclusion into the study, and those who eventually consented to participate.

Evaluation of Blood Pressure

Conventional office BP was measured at the hospital by sphygmomanometry (Korotkoff phases I and V).\(^1^9\) After at least 5 minutes of rest, 3 consecutive measurements were taken at the nondominant arm, with the participant seated, and always by the same trained investigator (L.H.). Hypertension was defined as an untreated conventional office BP \(\geq 140\) mm Hg systolic or \(\geq 90\) mm Hg diastolic, or both.\(^2^0\)

Ambulatory BP was monitored noninvasively on 2 occasions over a 24-hour period using an oscillometric SpaceLabs 90207 or 90217 device (Spacelabs Medical Inc). Both monitors meet the accuracy criteria of the Association for the Advancement of Medical Instrumentation and the British Hypertension Society (http://www.dableducational.com). The devices were programmed to obtain BP recordings every 15 minutes from 0700 to 2300 hours and every 30 minutes thereafter, and set to reject automatically readings with a systolic BP (SBP) \(>240\) or \(<70\) mm Hg, a diastolic BP (DBP) \(>150\) or \(<40\) mm Hg, a mean arterial pressure (MAP) \(>200\) or \(<40\) mm Hg, or a heart rate \(>200\) or \(<20\) beats per minute. We performed duplicate recordings because the assessment of the 24-hour BP profile on the basis of a single ABPM has been shown to be less reliable.\(^2^1\)

Blood pressure was recorded at the nondominant arm using an appropriately sized cuff. Monitoring sessions started at the hospital, always on a weekday, and preferably in the morning. We encouraged participants to adhere to their usual daily activities and regular sleeping hours, but instructed them to keep their arm and fingers motionless during a recording. Furthermore, they completed a diary card documenting their actual awake and asleep times. SpaceLabs data files were transferred to a Windows-based PC system and analyzed using the Pressure Import and Export software version 1.4.0. (Instrument Development Engineering and Evaluation [IDEE], Maastricht University, 2005; http://www-id.unimaas.nl). Data files were not edited manually.

Participant’s awake (daytime) and asleep (night-time) periods were determined by excluding a 2-hour transition period around the reported rising and retiring times. On the basis of this narrow diary time approach we assessed the mean 24-hour, awake, and asleep SBP, DBP, and MAP. Furthermore, we investigated the asleep (nocturnal) BP in terms of: (1) nocturnal hypertension, defined as an average asleep BP \(\geq 120/70\) mm Hg; \(^1^9\) (2) the nocturnal BP dip, quantified as the relative decline in MAP from the awake to asleep periods using the following equation: ((mean awake MAP—mean asleep MAP)/mean awake MAP)\(\times 100\%\); (3) nocturnal nondipping, defined as a nocturnal MAP dip \(<10\%\).\(^1^6\)

Evaluation of Microbleeds and White Matter Hyperintensities

Brain MRI was performed on a 1.5-T clinical MR-system (Intera, Philips Medical Systems) using a standard quadrature head coil. The
standardized imaging protocol consisted of T2-weighted fast spin echo (repetition time [TR] 4820 ms; echo time [TE] 100 ms; flip angle 90°; field of view [FOV] 230 mm; acquisition matrix 512×512), fluid-attenuated inversion recovery (FLAIR) (TR 8000 ms; TE 120 ms; inversion time 2000 ms; FOV 230 mm; acquisition matrix 256×256 [reconstructed to 512X512]) and T2*-weighted GE (TR 736 ms; TE 23 ms; flip angle 15°; FOV 230 mm; acquisition matrix 256×256; in-plane spatial resolution 0.9×0.9 mm/pixel [resolution may be actually higher because of the T2*-effect!) sequences in the axial plane, producing 24 slices with a thickness of 5 mm and a 0.5-mm interslice gap.

We defined BMBs as punctate (diameter <5 mm), homogeneous foci of low signal intensity on T2*-weighted GE images. The presence of BMBs was assessed throughout the brain, e.g., brain stem, cerebellum, basal ganglia, corona radiata, and cortico-subcortical gray and white matter. Symmetric hypointensities in the globi pallidi, likely to represent calcification or iron deposition, and sulcal flow voids from cortical vessels were disregarded.

White matter hyperintensities (WMH) were identified on T2-weighted and FLAIR images and classified according to Fazekas et al into hyperintensities of the deep and subcortical white matter (DWMH) and periventricular hyperintensities (PVH). We considered WMH to be advanced in case of DWMH grades 2 or 3 (ie, beginning confluence of foci or large confluent areas) or PVH grade 3 (ie, irregular hyperintensities extending into the deep white matter). Histopathologic and clinical data indicate that these advanced lesions reflect ischemic brain damage related to a cerebral small-vessel disease.

Figure 2 illustrates, as an example, BMBs and advanced WMH in one of the participants.

Two independent raters (R.v.O. and J.L.), blinded to the participants’ age, sex, and clinical status (including BP data), rated all scans. The inter-rater reliability, expressed as Cohen’s kappa, was 0.68 for the presence of BMBs and 0.76 for advanced WMH. According to Landis and Koch, kappa values between 0.60 to 0.79 indicate substantial agreement. In case of disagreement, lesions were ascertained by consensus.

Evaluation of Risk Factors
Information on lifestyle habits, past and current morbidity (including current treatment), and hypertension history (including the self-reported age of diagnosis and previous use of antihypertensive medication), were obtained by interview and verified by inspection of recently started medical records. The duration of hypertension was estimated as the time (in months) passed since the self-reported age of diagnosis until inclusion into the study. Smoking was classified as never, past, or current. Height and weight were measured to determine the body mass index (BMI, kg/m²). Venous blood samples, routinely drawn after an overnight fast, were analyzed for serum total and high-density lipoprotein (HDL) cholesterol and serum creatinine using standard laboratory procedures. Hypercholesterolemia was considered to be present in subjects who either used lipid-lowering drugs or had untreated total cholesterol levels >6.5 mmol/L.

Statistical Analysis
Before analyzing the relation between ambulatory BP and BMBs we tested the reproducibility of the duplicate ambulatory BP recordings. A detailed description is given in the online supplement to this paper (please see the expanded Methods section at http://hyper.ahajournals.org).

To detect group differences between unpaired data we applied the independent samples t test for normally distributed variables, the Mann–Whitney U test for variables with skewed distributions, and the Pearson χ² statistic or Fisher’s exact test for categorical variables.

We performed logistic regression analyses to evaluate the relation between the aforementioned ambulatory BP components and the presence of BMBs. Models were adjusted for age and sex (model 1), and additionally (ie, exploratory analyses) for cardiovascular risk factors, ie, the duration of hypertension, previous antihypertensive treatment, smoking status, and the ratio of total/HDL cholesterol.

(model 2). Finally, we also adjusted for the presence of advanced WMH (model 3). All covariates were forced into the model simultaneously (enter procedure).

Normally distributed variables are presented as mean±SD, variables with skewed distributions as median with interquartile ranges (IQR), and categorical variables as frequencies. Odds ratios are presented with corresponding 95% confidence intervals. A 2-tailed probability value <0.05 was considered statistically significant. Analyses were performed using the statistical software package SPSS (version 11.0.4 for Macintosh, SPSS Inc).

Results
Of the 389 patients eligible for inclusion into the study, 218 consented to participate (Figure 1). The remainder (n=171) did not differ significantly from the participants in terms of age (50.4±14.4 versus 52.5±12.6 years, P=0.283) and sex.
Advanced WMH were present in 46 of 218 participants (21.1%; 95% CI, 15.6% to 26.6%), being more prevalent in subjects with BMBs than in those without (48.6% versus 15.8%, respectively; \( P < 0.001 \)).

### Reproducibility of Ambulatory Blood Pressure

Of the 218 participants who underwent ABPM, duplicate recordings were available in 213 (97.7%). Monitoring sessions were repeated with a median interval of 7 (IQR 5, 9) days. Detailed reproducibility data are given in the online supplement to this paper (please see expanded results section, Table S1 and Figure S1A and S1B). Briefly, the reproducibility of the mean 24-hour, awake, and asleep BP was acceptable (concordance ranging between 22.4 and 27.7% of nearly maximal variation)\(^{20}\) and higher than that of the relative nocturnal BP dip (40.8%). The nocturnal BP status as well as the dipping pattern were moderately reproducible (Cohen’s kappa 0.48 and 0.43, respectively).\(^{26}\) Therefore, and because an increasing number of BP readings improves the reliability of ambulatory BP components,\(^{20}\) all further analyses have been performed on the basis of both ABPMs (\( n = 213 \)). That is, we calculated the mean for continuous BP data and classified participants as nocturnal hypertensive or non-dipper when they confirmed their initial status on the second ABPM, otherwise subjects were labeled as normotensive or dipper, respectively (please see Table S1).

### Ambulatory Blood Pressure and Brain Microbleeds

Brain MRI was performed with a median interval of 10 (IQR, 7, 16) days after the first ABPM. Odds ratios quantifying the relation between the different ambulatory BP components and BMBs are summarized in Table 2. Higher 24-hour, awake, and asleep BP levels, and nocturnal hypertension were significantly associated with the presence of BMBs, independent of age and sex (Table 2, model 1; all \( P < 0.01 \)). For every SD increase in SBP, MAP, or DBP, the odds ratios ranged between 1.84 and 2.01 for the 24-hour period, between 1.75 and 1.87 for the awake period, and between 1.80 and 1.90 for the asleep period; a diagnosis of nocturnal hypertension was associated with a 5.45-fold higher likelihood for BMBs (Table 2, model 1). Additional adjustments (exploratory analyses) for cardiovascular risk factors, ie, the duration of hypertension, previous antihypertensive treatment, smoking, and the ratio of total/HDL cholesterol, did not affect the associations substantially (Table 2, model 2). Final adjustments for coexisting advanced WMH modified the results of model 2 only slightly (Table 2, model 3).

### Discussion

The present study demonstrated that, in this hypertensive population without a history of cerebrovascular disease, the prevalence of microbleeds in the brain was 16.1% (95% CI, 11.1% to 21.0%), and that the daytime, nighttime, and 24-hour BP levels and a diagnosis of nocturnal hypertension were associated with the presence of BMBs, independent of age and sex, other cardiovascular risk factors, and coexisting ischemic brain damage.
The prevalence of BMBs in our hypertensive cohort is approximately 3 times higher than that reported in the general population. Importantly, in our study the microbleed-count could not have been influenced by a history of symptomatic nighttime BP. The finding that the likelihood for BMBs remained significantly related to the presence of BMBs, in addition to the awake pressure, suggests that hypertension is a substantial and independent risk factor for the development of BMBs.

The associations between the various ambulatory BP components and the presence of BMBs were robust and independent of age and sex, other cardiovascular risk factors, and advanced WMH. On average, every SD increment in BP, whether 24-hour, daytime, or night-time, was associated with a 1.8- to 1.9-fold higher likelihood for BMBs. In the adjusted models the asleep BP, in addition to the awake pressure, remained significantly related to the presence of BMBs. Moreover, the associations were even stronger, confirming earlier observations supporting the importance of a high nighttime BP. The finding that the likelihood for BMBs was 5- to 6-fold higher in subjects who were diagnosed with nocturnal hypertension further supports this.

Contrary, the nondipping status, in general considered to be a strong determinant of hypertension-related organ damage, was not related to the presence of BMBs. Also when we analyzed the day-to-night BP decline as a continuous variable, adjusted associations were not significant. However, the prevalence of nondippers was small (n = 15, 7.0%). This, along with the narrow and nearly significant 95% confidence intervals of the odds ratios for BMBs associated with the relative nocturnal BP dip, reflects the low statistical power of these analyses to detect associations with BP dipping.

The mechanism behind hypertension-related BMBs remains speculative. Histopathologic studies have shown that BMBs consist of macrophages containing hemosiderin—a blood breakdown product—adjacent to small blood vessels affected by moderate to severe fibrohyalinosis or arteriolar sclerosis. Hence, a high BP during the day and additionally at night, ie, a higher cumulative 24-hour BP load, could induce structural changes of the brain microvasculature with subsequent extravasation of blood. A similar concept, ie, blood-brain barrier leakage of plasma components with hypertension as a major risk factor, has been proposed previously as a cause of other types of small-vessel disease in the brain, namely WMH and lacunar stroke. The associations between BMBs and ambulatory BP in our study were not explained by coexisting WMH, suggesting that the occur-
rence and mechanisms of both abnormalities are, at least in part, independent.

The present study has limitations, such as the cross-sectional design and the relatively small number of participants displaying BMBs. Although the group size was sufficient to carry out the logistic regression analyses corrected for age and sex, the additional adjustments (models 2 and 3), having an exploratory nature, need to be interpreted within the context of their statistical limitations. Hence, our findings require confirmation in longitudinal and adequately powered studies. Another limitation is the lack of a local, preferably community-based, control population. Such a control group would have enabled us to assess whether the prevalence of BMBs in our hypertensive cohort was really increased.

Furthermore, it is possible that we failed to include patients with more severe hypertension, because they were not allowed to stop their antihypertensive medication. However, we would expect an even higher prevalence of BMBs and more robust associations with ambulatory BP when participants with more severe hypertension had been included.

On the other hand, we performed our study in a large cohort of well-defined hypertensive patients whose data were collected prospectively. Moreover, demographic and BP data of the participants were similar to those who did not consent to the study. Another strength of the study is that the BP was measured by ABPM and, importantly, on two occasions. Based on the reproducibility analyses we used the data of both recordings. Other investigators previously have shown that this improves the reliability of the calculated BP components.21–30 Finally, the observed associations were not biased by concurrent antihypertensive treatment36 or a history of symptomatic stroke.31,32 The latter implies that the detected BMBs in our participants were all silent.

### Perspectives

Our study showed that BMBs are a frequent finding in hypertensive patients without a history of cerebrovascular disease. Moreover, the data suggest that participants with a high daytime and especially nighttime BP, ie, a high 24-hour BP load, were more likely to display BMBs on MRI. In contrast to the general belief that BMBs are clinically silent, recently reported associations with cognitive impairment7,6 and an increased risk of stroke recurrence8,8.6—processes that may be accelerated in the face of a persistently high BP—illustrate the potential clinical relevance of these small lesions. Considering all this, we postulate that BMBs should be considered as an additional (besides WMH and lacunar infarcts) and independent marker of hypertensive target-organ damage of the brain. Our findings need, however, confirmation in adequately powered and preferably long-term follow-up studies, which also should address the role of BMBs in risk estimation and prevention of both future stroke and impairment of brain function.

### Disclosures

None.

### References


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Full title: BRAIN MICROBLEEDS ARE ASSOCIATED WITH AMBULATORY BLOOD PRESSURE LEVELS IN A HYPERTENSIVE POPULATION

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ONLINE SUPPLEMENT: REPRODUCIBILITY OF AMBULATORY BLOOD PRESSURE COMPONENTS

Methods

The reproducibility of the 24-hour, awake and asleep BP levels, and the relative nocturnal BP dip, was determined according to Bland and Altman by calculating coefficients of repeatability, defined as twice the standard deviation (SD) of the differences between the duplicate recordings.\(^1\) To enable comparisons between the different BP components, the repeatability coefficients were expressed as a percentage of the nearly maximal variation, calculated as four times the SD of the average of the two recordings.\(^2\) High percentages of nearly maximal variation indicate considerable variation between the repeated recordings, reflecting lower reproducibility. To determine the reproducibility of the nocturnal hypertension status and the non-dipping pattern we investigated the number of participants who confirmed their initial classification on the second ABPM. Kappa statistics were applied to evaluate the consistency of these classifications. According to Landis and Koch, kappa values below 0.40 signified poor, 0.40 to 0.59 moderate, 0.60 to 0.79 substantial, and values above 0.80 outstanding reproducibility.\(^3\) Differences between related BP data were assessed using the paired-samples \(t\)-test or McNemar’s test when appropriate.
Results

Differences in mean 24-hour, awake and asleep BP levels, and the relative nocturnal BP dip between the first and second ABPM were small (all <0.5 mmHg) and not statistically significant (Table S1, \( P > 0.05 \)). The repeatability coefficient (expressed as a percentage of the nearly maximal variation) of the relative nocturnal BP dip was higher, indicating lower reproducibility, than that of the 24-hour, awake as well as asleep BPs (Table S1).

One-hundred-and-fifty-four (72.3%) participants confirmed their initial nocturnal hypertension status on the second ABPM, 24 (11.3%) were normotensive on both sessions and 35 (16.4 %) showed a variable nocturnal normotension/hypertension pattern (Figure S1A). The nocturnal BP status was moderately reproducible (Table S1, Cohen’s kappa 0.48).

Fifteen (7.0%) subjects showed a non-dipping pattern on both sessions, 169 (79.4%) confirmed their initial dipping status and 29 (13.6%) showed a variable dipping/non-dipping pattern (Figure S1B). The dipping status was also moderately reproducible (Table S1, Cohen’s kappa 0.43). Differences in proportions of nocturnal hypertensives as well as non-dippers between the first and second ABPM were non-significant (Table S1, \( P > 0.05 \))
References


**Figure legends**

Figure S1A
Reproducibility of the nocturnal hypertension status. HH indicates hypertensive on both ABPMs (prevalence 72.3%); HN, hypertensive on the first, normotensive on the second ABPM (6.5%); NH, normotensive on the first, hypertensive on the second ABPM (9.9%); NN, normotensive on both ABPMs (11.3%).

Figure S1B
Reproducibility of the dipping pattern. NN indicates non-dipper on both ABPMs (prevalence 7.0%); ND, non-dipper on the first, dipper on the second ABPM (8.9%); DN, dipper on the first, non-dipper on the second ABPM (4.7%); DD, dipper on both ABPMs (79.4%).
Table

Table S1  Reproducibility of ambulatory BP components

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<th>Ambulatory BP†</th>
<th>Reproducibility†</th>
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<td>SBP</td>
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<td>MAP</td>
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<td>DBP</td>
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<td>SBP</td>
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<td>MAP</td>
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<td>DBP</td>
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Table I continued

Asleep BP, mmHg

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<td>SBP</td>
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<td>MAP</td>
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<td>DBP</td>
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Relative nocturnal BP (MAP) dip, %

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<td>17.5 ± 8.0</td>
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Nocturnal hypertension, n (%):

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<td>45 (21.1)</td>
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Nocturnal non-dipping, n (%):

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<td>34 (16.0)</td>
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</tbody>
</table>
* Ambulatory BP levels of the first and second monitoring session, and on the basis of both ABPMs (combined). Differences in continuous as well as categorical ambulatory BP components between the first and second monitoring session were all non-significant ($P>0.05$, paired samples t-test and McNemar's test, respectively).

† Reproducibility of ambulatory BP components expressed as the Bland-Altman coefficient of repeatability (% of nearly maximal variation) for continuous data, and Cohen's kappa for categorical data.

‡ Nocturnal hypertension present on both ABPMs.

§ Non-dipping pattern present on both ABPMs.
Figures

Figure S1A

![Bar chart showing prevalence percentages for HH, HN, and NN categories. The HH category has the highest prevalence, followed by HN and then NN.](image-url)