Morning Blood Pressure Surge, Dipping, and Risk of Ischemic Stroke in Elderly Patients Treated for Hypertension

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BACKGROUND
The independent prognostic significance of morning surge (MS) in blood pressure (BP) is not yet clear. We investigated the association between MS in systolic BP (SBP) and risk of ischemic stroke in elderly patients treated for hypertension.

METHODS
Occurrence of ischemic stroke was evaluated in 1,191 elderly patients treated for hypertension (aged 60–90 years). Patients were divided according to tertiles of MS in SBP in the population as a whole, dipping status, and group-specific tertiles of MS in SBP in dippers and nondippers.

RESULTS
During follow-up (9.1 ± 4.9 years, range 0.4–20 years), 139 ischemic strokes occurred. The event rate per 100 patient-years was 1.28. After adjustment for various covariates, Cox regression analysis showed that stroke risk was not significantly associated with tertiles of MS in SBP in the population as a whole. When nondippers and dippers were analyzed separately by group-specific tertiles of MS in SBP, stroke risk was not associated with MS in nondippers. Conversely, in dippers, stroke risk was significantly higher in the third tertile (>23 mm Hg) of MS in SBP (hazard ratio, 2.08; 95% confidence interval, 1.03–4.23; P = 0.04). Additional analysis showed that stroke risk was significantly and similarly higher in dippers with MS >23 mm Hg and in nondippers than in dippers with MS <23 mm Hg.

CONCLUSIONS
In elderly patients treated for hypertension, high MS in SBP predicts stroke in dippers but not in nondippers. Nondippers are at high stroke risk with or without MS >23 mm Hg.

Keywords: ambulatory blood pressure; blood pressure; dippers; hypertension; nondippers; morning surge; stroke.

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There is a diurnal variation in the onset of cardiovascular events, with a peak incidence in the morning.1–4 Ambulatory monitoring has revealed that blood pressure (BP) tends to show a similar diurnal variation, reaching the highest level during the morning. This finding gave rise to the hypothesis that a high morning surge (MS) of BP might predict cardiovascular events. Some investigators examined the association between MS in BP and subsequent cardiovascular complications, both in hypertensive patients5–8 and in general populations,9–12 but the results were contradictory.13

On the other hand, ambulatory BP monitoring has shown that nighttime BP pattern is not homogeneous in hypertensive patients. Indeed, some patients show a decrease of BP >10% during the night (dippers), whereas others do not (nondippers). In this context, some studies showed that patients with higher nighttime BP and blunted BP dip from day to night have increased cardiovascular risk.5,14,15

It is worth noting that nondippers show lower MS in BP, whereas dippers show higher MS in BP. Thus, nondippers are at increased cardiovascular risk compared with dippers but show lower MS in BP, which could be protective; dippers are at lower risk than nondippers but show a higher MS in BP that could be hazardous. In such a context, it is difficult to reconcile the adverse prognostic significance of nondipping with the assumption that a high MS in BP is also a predictor of poor outcome when hypertensive patients are analyzed as a whole. We suggest that dippers and nondippers should be analyzed separately with group-specific cutoff points.

With respect to stroke, few studies have specifically evaluated the influence of MS in BP on this outcome in hypertensive patients6 or general populations,9,11 obtaining conflicting results. Our aim was to investigate the relationship between MS in BP and incidence of stroke in an elderly population treated for hypertension analyzed as a whole and according to dipping status.

METHODS
Patients

Starting in 1992, we have built 2 prospective databases of our initially untreated or initially treated hypertensive
patients, with the aim to evaluate the prognostic role of ambulatory BP parameters and other risk markers. The present was carried out using the database of initially treated patients. We studied 1,191 sequential treated hypertensive patients aged ≥60 years (range 60–90 years) prospectively recruited from December 1992 to December 2012 who were referred to our hospital outpatient clinic for evaluation of hypertension. Sixty-two patients were lost during follow-up. Patients with secondary hypertension were excluded. All patients underwent clinical evaluation, electrocardiogram, routine laboratory tests, echocardiographic examination, and noninvasive ambulatory BP monitoring. The study population came from the same geographical area (Chieti and Pescara, Abruzzo, Italy). The study was performed in accordance with the Second Declaration of Helsinki and was approved by the institutional review committee. Patients gave informed consent.

Office BP measurements

Clinic systolic BP (SBP) and diastolic BP (DBP) recordings were taken by a physician using a mercury sphygmomanometer and appropriate-sized cuffs. Phase V was used to determine DBP. Measurements were performed in triplicate, 2 minutes apart, and the mean value was used as the BP for the visit.

Ambulatory BP monitoring

Ambulatory BP monitoring was performed with a portable noninvasive recorder (SpaceLabs 90207, Redmond, WA) on a day of typical activity, within 1 week after clinic BP measurement. Each time a reading was taken, patients were instructed to remain motionless and to record their activity on a diary sheet. Technical aspects have been previously reported.16 Ambulatory BP readings were obtained at 15-minute intervals from 6 a.m. to midnight and at 30-minute intervals from midnight to 6 a.m. The following ambulatory BP parameters were evaluated: daytime (awake period), nighttime (asleep period) and 24-hour SBP and DBP, the extent of BP reduction from day to night (those with BP reduction <10% were defined as nondippers and those with MS in SBP of the population as a whole and of dippers analyzed separately, or specific subgroups).

Then, we analyzed nondippers according to group-specific tertiles of MS in SBP (<2.5 mm Hg; >2.5 and ≤11.5 mm Hg; >11.5 mm Hg) and dippers according to group-specific tertiles of MS in SBP (<14.5 mm Hg; >14.5 and ≤23 mm Hg; >23 mm Hg) separately.

Echocardiography

End-systolic and end-diastolic measurements of interventricular septal thickness, left ventricular (LV) internal diameter, and posterior wall thickness were taken according to the American Society of Echocardiography recommendations17 within 1 month after the clinic visit. LV mass was calculated using the formula introduced by Devereux et al.18 Individual values for LV mass were indexed by height2.7 and LV hypertrophy was defined as LV mass/height2.7 >50 g/m2.7 in men and >47 g/m2.7 in women.19

Follow-up

Patients were followed up in our hospital outpatient clinic or by their family physician. The occurrence of cardiovascular events was recorded during follow-up visits or by telephone interview of the patient followed by a clinical visit. The authors of this study collected the data. Those reviewing the endpoints were blinded to MS in SBP data. In the present study, we focused on fatal and nonfatal stroke (rapid onset of localizing neurological deficit lasting ≥24 hours with computer tomography evidence).

Statistical analysis

Standard descriptive statistics were used. Groups were compared using one-way analysis of variance and unpaired t test where appropriate. Bivariate correlation was used when needed. Event rates are expressed as the number of events per 100 patient-years based on the ratio of the observed number of events to the total number of patient-years of exposure up to the terminating event or censor. Survival curves were estimated using the Kaplan–Meier product-limit method and compared using the Mantel (log-rank) test.20 Cox regression analysis was used to evaluate univariate and multivariate association of factors with outcome.20 First, univariate association between various variables and stroke was evaluated. Then, multiple regression analysis was performed, reporting in the final model variables that were significantly associated (P <0.05) with outcome in univariate analysis and tertiles of MS in SBP of the population as a whole and of dippers and nondippers analyzed separately, or specific subgroups. The forced entry model was used. Statistical significance was defined as P <0.05. Analyses were made with the SPSS 12 software (SPSS Inc., Chicago, IL).

RESULTS

Characteristics and BP values of the study population as a whole by tertiles of MS in SBP of all the patients and by dipping status are summarized in Table 1. Low-density lipoprotein cholesterol, antihypertensive drug distribution, clinic and
ambulatory BP, preawakening and postawakening BP, and MS in SBP (by definition) were significantly different across tertiles of MS in SBP. Age, antihypertensive drug distribution, clinic and ambulatory BP, preawakening BP, and MS in SBP were significantly different between dippers and nondippers. Values of DBP are reported in Supplementary Table S1.

Characteristics of nondippers and dippers according to group-specific tertiles of MS in SBP are reported in Table 2. Gender distribution, clinic and nighttime BP, preawakening and postawakening BP, and MS in SBP (by definition) were different across tertiles in nondippers. Clinic and ambulatory BP, postawakening BP, and MS in SBP were significantly different across tertiles in dippers. Values of DBP are reported in Supplementary Table S2.

At baseline, 274 (23%) patients received antiplatelet drugs and 138 (12%) received statin therapy. For both drugs, there was no difference across tertiles of MS in SBP of the study group as a whole, between dippers and nondippers, and across group-specific tertiles of MS in SBP in dippers and nondippers. The reduction of SBP from day to night was significantly correlated with MS in SBP (r = 0.64; P < 0.01).

At follow-up, 405 (34%) patients received antiplatelet or anticoagulant drugs, 294 (25%) received statin therapy, 266 (22.5%) received single antihypertensive therapy, 458 (38.5%) received double therapy, and 467 (39%) received triple therapy. During follow-up (9.1 ± 4.9 years, range 0.4–20 years), 139 strokes occurred. Specifically, there were 47 fatal strokes and 92 nonfatal strokes. The stroke rate of the population as a whole was 1.28/100 patient-years. According to tertiles of MS in SBP of the population as a whole, there were 51, 39, and 49 events, respectively. Stroke-free survival curves according to the aforementioned tertiles are provided in Figure 1. No significant difference was found across the groups.

There were 88 events in nondippers and 51 events in dippers. Stroke-free survival curves according to dipping status are provided in Figure 2. As described, there was a significant difference between the groups. According to group-specific tertiles of MS in SBP of nondippers, there were 33, 30, and 25 events, respectively. Stroke-free survival curves according to the abovementioned tertiles are provided in Figure 3. No significant difference was observed across the groups. In dippers, according to group-specific tertiles of MS in SBP, there were 12, 13, and 26 events, respectively. Stroke-free survival curves according to the aforementioned tertiles are provided in Figure 4. As shown, there was a significant difference across the groups.

Univariate analysis was performed to assess the association between risk of ischemic stroke and age; gender; body mass index; smoking habit; previous events; diabetes; creatinine; low-density lipoprotein cholesterol; LV hypertrophy; single, double, or triple antihypertensive therapy at baseline; antiplatelet therapy; statin therapy; and BP values.
Table 2. Characteristics of nondippers and dippers according to group-specific tertiles of morning surge in systolic blood pressure

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Nondippers</th>
<th>Dippers</th>
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<tbody>
<tr>
<td></td>
<td>1-Tertile (n = 220)</td>
<td>2-Tertile (n = 223)</td>
</tr>
<tr>
<td>Age, years</td>
<td>70 ± 6</td>
<td>29 ± 6</td>
</tr>
<tr>
<td>Men, n (%)</td>
<td>94 (43)</td>
<td>90 (40)</td>
</tr>
<tr>
<td>Body mass index, kg/m²</td>
<td>27 ± 4</td>
<td>28 ± 4</td>
</tr>
<tr>
<td>Smokers, n (%)</td>
<td>20 (9)</td>
<td>27 (12)</td>
</tr>
<tr>
<td>Previous events, n (%)</td>
<td>19 (9)</td>
<td>22 (10)</td>
</tr>
<tr>
<td>Diabetes, n (%)</td>
<td>31 (14)</td>
<td>28 (13)</td>
</tr>
<tr>
<td>Creatinine, mg/dl</td>
<td>1.01 ± 0.23</td>
<td>1.04 ± 0.22</td>
</tr>
<tr>
<td>Low-density lipoprotein cholesterol, mg/dL</td>
<td>126 ± 29</td>
<td>126 ± 31</td>
</tr>
<tr>
<td>Left ventricular hypertrophy, n (%)</td>
<td>76 (34)</td>
<td>68 (30)</td>
</tr>
<tr>
<td>Single therapy, n (%)</td>
<td>42 (19)</td>
<td>57 (25)</td>
</tr>
<tr>
<td>Double therapy, n (%)</td>
<td>103 (47)</td>
<td>95 (43)</td>
</tr>
<tr>
<td>Triple therapy, n (%)</td>
<td>75 (34)</td>
<td>71 (32)</td>
</tr>
<tr>
<td>Clinic SBP, mmHg</td>
<td>147 ± 18</td>
<td>148 ± 16</td>
</tr>
<tr>
<td>Daytime SBP, mmHg</td>
<td>134 ± 14</td>
<td>133 ± 14</td>
</tr>
<tr>
<td>Nighttime SBP, mmHg</td>
<td>133 ± 16</td>
<td>127 ± 14</td>
</tr>
<tr>
<td>24-hour SBP, mmHg</td>
<td>133 ± 14</td>
<td>131 ± 13</td>
</tr>
<tr>
<td>Pre-awakening SBP, mmHg</td>
<td>140 ± 17</td>
<td>130 ± 15</td>
</tr>
<tr>
<td>Post-awakening SBP, mmHg</td>
<td>137 ± 16</td>
<td>137 ± 15</td>
</tr>
<tr>
<td>Morning SBP surge, mmHg</td>
<td>−3 ± 6</td>
<td>7 ± 3</td>
</tr>
</tbody>
</table>

Abbreviation: SBP, systolic blood pressure.

Figure 1. Stroke-free survival curves for the population as a whole by tertiles of morning surge in systolic blood pressure.

Figure 2. Stroke-free survival curves for dippers and nondippers.
The analysis showed that age; clinic, 24-hour, daytime, and nighttime SBP; diabetes; and LV hypertrophy were significantly associated with risk of stroke ($P<0.05$; Table 3). Other variables were not significantly associated with risk. When we assessed the impact of antiplatelet/anticoagulant or statin use and number of antihypertensive drugs at follow-up, results were substantially similar. We included age, 24-hour SBP (because of stronger association with risk than clinic BP and because it comprises daytime and nighttime BP), diabetes, and LV hypertrophy in the multivariate model together with tertiles of MS in SBP or specific subgroups.

Results of multivariate analysis by tertiles of MS in SBP in the population as a whole and in nondippers and dippers evaluated separately and by specific subgroups are provided in Table 4. After adjustment for the abovementioned covariates, there was no significant difference across tertiles of MS in SBP in the population as a whole and in nondippers. On the contrary, in dippers, those in the third tertile (MS in SBP >23 mm Hg) had significantly higher risk of stroke than those in the first tertile (hazard ratio [HR], 2.08; 95% confidence interval [CI], 1.03–4.23; $P = 0.04$), whereas there was no difference between those in the second tertile and those in the first tertile. When we analyzed specific subgroups (dippers with MS <23 mm Hg, dippers with MS >23 mm Hg, and nondippers), the risk of stroke was significantly and similarly higher in dippers with MS >23 mm Hg and in nondippers than in dippers with MS <23 mm Hg (Table 4). If 24-hour BP was replaced by daytime or nighttime BP, results remained substantially similar. We also analyzed a model including daytime BP (in place of 24-hour BP) and tertiles of postawakening BP (in place of tertiles of MS). Only in dippers was the risk of stroke significantly higher in the third tertile (>146 mm Hg) of postawakening BP (HR, 2.7; 95% CI, 1.01–7.42; $P = 0.049$).

**DISCUSSION**

This study shows that in elderly patients treated for hypertension, MS in SBP is an independent predictor of stroke in dippers but not in nondippers. However, nondippers remain at high risk of stroke. To the best of our knowledge, only 3 other studies have specifically evaluated the influence of MS in SBP on the incidence of stroke.\(^6\),\(^9\),\(^11\) In these studies, beyond sleep-trough MS in SBP, the prognostic value of preawakening MS in SBP was evaluated, as performed in the present study. Kario et al.\(^6\) studied 519 older hypertensive patients (untreated or in washout) who were followed for an average of 41 months. Mean age was 72 years. During follow-up there were 44 strokes (30 strokes were ischemic). After adjustment for various covariates, without...
taking into account nighttime BP pattern, preawakening MS in SBP was not significantly associated with stroke risk (10 mm Hg increase; RR, 1.14; 95% CI, 0.99–1.31; *P* = 0.07). In another analysis, however, both sleep-trough MS (10 mm Hg increase; RR, 1.25; 95% CI, 1.06–1.48; *P* = 0.008) and risers, a subgroup of nondippers (RR, 2.71; 95% CI, 1.02–7.21; *P* = 0.047) were significantly associated with increased risk of stroke. Metoki *et al.* followed a cohort of 1,430 Japanese patients selected from a general population for an average period of 10.4 years. Mean age was 61 years, and about 30% of patients were taking antihypertensive drugs at baseline. During follow-up there were 128 strokes (86 strokes were ischemic). After adjustment for various covariates, without taking into account nighttime BP pattern, preawakening MS in SBP did not predict the risk of ischemic stroke. Only the risk of hemorrhagic stroke was increased in the fifth quintile (≥25 mm Hg) of the MS in SBP. In another analysis, taking into account only nighttime BP pattern, Metoki *et al.* found that nondippers (including inverted dippers) had a significantly higher risk of ischemic stroke than dippers (including extreme dippers; HR, 1.59; 95% CI, 1.03–2.46; *P* = 0.04). Li *et al.* studied 5,645 patients who were randomly recruited from the general populations of 8 countries. Mean age was 53 years, 20% received antihypertensive therapy at entry, and 40% had hypertension. Patients were followed for a median of 11.4 years. During this period there were 281 strokes (140 strokes were ischemic). After adjustment for various covariates, a preawakening MS in SBP ≥28 mm Hg was not significantly associated with higher risk of ischemic stroke both before (HR, 1.26; 95% CI, 0.82–1.92) and after further adjustment for systolic night:day BP ratio (HR, 1.46; 95% CI, 0.93–2.30). However, additional analyses showed that a preawakening MS in SBP ≥28 mm Hg was associated with all cardiovascular events in patients aged ≥60 years (HR, 1.46; 95% CI, 1.14–1.88; *P* <0.01) and in treated patients (HR, 1.49; 95% CI, 1.07–2.08; *P* <0.05), though specific analysis for stroke in older and treated patients was not performed. In an attempt to define cutoff points for risk stratification, Li *et al.* explored the risk associated with all values of preawakening MS in SBP within the 5th to 95th percentile interval. The overall risk for the global population was used as the reference. For preawakening MS in SBP, the lower boundary of the 95% CI of the risk function crossed unity of the hazard ratio at 21.5 mm Hg increase; RR, 1.25; 95% CI, 1.06–1.48; *P* = 0.008) and in treated patients (HR, 1.49; 95% CI, 1.07–2.08; *P* <0.05), though specific analysis for stroke in older and treated patients was not performed. In an attempt to define cutoff points for risk stratification, Li *et al.* explored the risk associated with all values of preawakening MS in SBP within the 5th to 95th percentile interval. The overall risk for the global population was used as the reference. For preawakening MS in SBP, the lower boundary of the 95% CI of the risk function crossed unity of the hazard ratio at 21.5 mm Hg increase; RR, 1.25; 95% CI, 1.06–1.48; *P* = 0.008) and in treated patients (HR, 1.49; 95% CI, 1.07–2.08; *P* <0.05), though specific analysis for stroke in older and treated patients was not performed. In an attempt to define cutoff points for risk stratification, Li *et al.* explored the risk associated with all values of preawakening MS in SBP within the 5th to 95th percentile interval. The overall risk for the global population was used as the reference. For preawakening MS in SBP, the lower boundary of the 95% CI of the risk function crossed unity of the hazard ratio at 21.5 mm Hg increase; RR, 1.25; 95% CI, 1.06–1.48; *P* = 0.008) and in treated patients (HR, 1.49; 95% CI, 1.07–2.08; *P* <0.05), though specific analysis for stroke in older and treated patients was not performed.
disorganization of the muscular layers of the arterial wall and to plaque rupture. These mechanisms might specifically work in atherosclerotic vessels, in the presence of oxidative stress, and in older patients with impaired baroreflexes.

Our study has some limitations. First, we studied only white patients, thus our results cannot be applied to other ethnic groups. Second, our data were obtained in elderly patients treated for hypertension and cannot be extrapolated to younger and untreated patients. Third, it remains unclear whether higher MS in SBP reflects an intrinsic characteristic of some patients or uncontrolled BP because of treatment features (dosage or timing of drug therapy); however, these aspects do not lessen the impact of our findings. Fourth, the lack of association of stroke risk with treatment strategy does not mean lack of efficacy of therapy because all patients were treated with antihypertensive therapy, most of whom received multiple therapies, and patients were not randomized to antihypertensive or antplatelet or statin therapy. Fifth, we did not specifically design a study to evaluate the risk associated with MS in SBP; this study is part of a prospective assessment of the prognostic value of ambulatory BP parameters and other risk markers in our initially treated hypertensive patients. For patients recruited from 1992 to 2000, MS was calculated by hourly means because single readings were not available, whereas for those recruited after 2000, we used single readings to calculate MS in SBP.

In conclusion, in elderly patients treated for hypertension, high MS in SBP predicts stroke in dippers but not in nondippers. Nondippers are at high risk of stroke with or without MS >23 mm Hg.

SUPPLEMENTARY MATERIALS

Supplementary materials are available at American Journal of Hypertension (http://ajh.oxfordjournals.org).

DISCLOSURE

The authors declared no conflict of interest.

REFERENCES


