Prognostic Value of Nocturnal Blood Pressure Reduction in Resistant Hypertension

Elizabeth Silaid Muxfeldt, PhD; Claudia Regina Lopes Cardoso, PhD; Gil Fernando Salles, PhD

Background: The prognostic value of nocturnal blood pressure (BP) reduction in resistant hypertension (RH) is unknown. The objective of this prospective study was to evaluate its importance as a predictor of cardiovascular morbidity and mortality.

Methods: At baseline, 556 patients with RH underwent clinical and laboratory examinations and 24-hour ambulatory BP monitoring. The primary end points were a composite of fatal or nonfatal cardiovascular events, all-cause mortality, and cardiovascular mortality. Multiple Cox regression was used to assess associations between the nocturnal BP reduction and the subsequent end points.

Results: After a mean follow-up of 4.8 years (range, 1-103 months), 109 patients (19.6%) reached the composite end point, with 70 all-cause and 46 cardiovascular deaths. A nondipping pattern was present in 360 patients (65.0%). After adjustment for age, sex, body mass index, diabetes, smoking status, physical inactivity, dyslipidemia, previous cardiovascular disease, number of antihypertensive drugs in use, and office and 24-hour ambulatory BP readings, the nondipping pattern was an independent predictor of the composite end point (hazard ratio [HR], 1.74; 95% confidence interval [CI], 1.12-2.71) and of cardiovascular mortality (HR, 2.31; 95% CI, 1.09-4.92). In subgroup analysis, the reduced (HR, 1.71; 95% CI, 1.03-2.83) and reverted (HR, 1.89; 95% CI, 1.04-3.43) dipping patterns were predictive of total cardiovascular events. The effect of the nondipping pattern on cardiovascular prognosis was stronger in younger patients and in those with true RH.

Conclusions: The nocturnal BP variability patterns provide valuable prognostic information for stratification of cardiovascular morbidity and mortality risk in patients with RH, above and beyond other traditional cardiovascular risk factors and mean ambulatory BP levels.

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The prognostic value of ambulatory blood pressure (BP) monitoring (ABPM) has been extensively studied,1,2 and the nocturnal BP reduction has been frequently considered an important prognostic marker.3-5 ABPM is particularly useful to refine cardiovascular risk stratification in patients with hypertension, including those with resistant hypertension (RH).1,6

Resistant hypertension is defined as uncontrolled office BP, despite the use of an optimal regimen with at least 3 antihypertensive drugs, always including a diuretic.7,8 Even with a reported prevalence as high as 30% of general hypertensives,7,9 RH is still an understudied clinical condition that has high rates of cardiovascular morbidity and mortality,7,8 and in which the use of ABPM is well established to guide both diagnosis and therapy.7-10 To our knowledge, there are only 3 previous prospective studies that have evaluated the ABPM prognostic value in this high-risk group of patients,6,11,12 and none of them evaluated the importance of the nocturnal BP reduction.

We recently demonstrated that mean ambulatory systolic and diastolic BP levels were important predictors of future cardiovascular morbidity and mortality in patients with RH, whereas office BP readings had no value at all.12 Therefore, the aim of this study was to conduct a detailed analysis, based on our up to 9 years of follow-up data in a large cohort of patients with RH, to verify whether the nocturnal BP reduction and the different dipping patterns would have additive prognostic significance above and beyond other traditional risk factors, including mean ambulatory BP levels, for cardiovascular risk stratification.

METHODS

Patients and Baseline Procedures

The current prospective study included 556 patients with RH who were enrolled in the hypertension outpatient clinic of our university...
hospital between January 1999 and December 2004. Study protocols were approved by the local ethics committee, and informed consent was obtained from all participants. The enrollment criteria, baseline protocol, and diagnostic definitions have been detailed previously. In brief, all patients referred to our clinic who fulfilled the criteria for RH (office BP ≥140/90 mm Hg, using ≥3 antihypertensive drugs in full doses, always including a diuretic, and considered at least moderately adherent by a validated questionnaire) were submitted to a standard protocol that included a thorough clinical examination, laboratory evaluation, 12-lead electrocardiogram, 2-dimensional echocardiography, and 24-hour ABPM. Patients with proved renovascular hypertension (n=5) and surgical hyperaldosteronism (n=4) were excluded from the cohort. Sleep apnea syndrome was not investigated, and patients with chronic parenchymal kidney diseases were not excluded (19 patients had an estimated creatinine clearance of ≤30 mL/min). Office BP was measured twice by a trained physician, with patients in the sitting position, using a calibrated mercury sphygmomanometer and suitably sized cuffs. First and fifth Korotkoff sounds were the criteria for systolic BP (SBP) and diastolic BP (DBP), and the BP was considered to be the mean between the 2 readings.

AMBULATORY BLOOD PRESSURE MONITORING

Ambulatory BP monitoring was performed with a commercially available recorder (Mobil O Graph Version 12, I.E.M. Americas, Thornhill, ON, Canada). All patients used their prescribed antihypertensive medications during ABPM. A reading was obtained every 15 minutes throughout the day and every 30 minutes at night. The nighttime period was ascertained for each individual patient from registered diaries as well as by using fixed hours from 0 to 6 AM. The parameters evaluated were mean 24-hour, daytime, and nighttime SBP and DBP levels. The nocturnal BP reduction was analyzed as continuous variables (the night to day SBP and DBP ratios) and dichotomized at well-established values, and patients were classified as having a nondipping pattern (night to day SBP ratio >0.9) or a dipping pattern (night to day SBP ratio ≤0.9). We subclassified the patterns as follows: normal dipping (dippers, night to day SBP ratio ≤0.9 and >0.8), extreme dipping (extreme dippers, night to day SBP ratio >0.8), reduced dipping (non-dippers, night to day SBP ratio >0.9 and ≤1.0), and reverted dipping pattern (risers, night to day SBP ratio >1.0). After ABPM, the patients were also classified either as having true RH (mean daytime SBP ≥135 mm Hg or DBP ≥85 mm Hg) or as having white-coat RH (daytime SBP <135 mm Hg and DBP <85 mm Hg).

FOLLOW-UP AND END POINTS

Patients were regularly followed up until December 2007. The observation period was considered to be the number of months from the first clinical evaluation to the date of the last clinical visit or the first end point. The primary end points were a composite of all fatal or nonfatal cardiovascular events and all-cause and cardiovascular mortalities. Definitions of end points have been detailed elsewhere. In brief, cardiovascular events were as follows: fatal and nonfatal acute myocardial infarction (AMI); percutaneous or surgical myocardial revascularization; sudden cardiac death; new-onset heart failure; death due to progressive heart failure; fatal and nonfatal strokes; any aortic or lower limb revascularization procedure; amputation above the ankle; deaths due to aortic or peripheral arterial disease; the beginning of dialysis; and death due to renal failure. Total coronary heart disease (CHD) events (fatal or nonfatal AMI, sudden deaths, and myocardial revascularizations) and total fatal or nonfatal strokes were secondary end points. End points were ascertained from medical records, death certificates, and interviews with attending physicians and patient families by means of a standard questionnaire that was reviewed by an independent observer.

STATISTICAL ANALYSES

Statistics were performed with an SPSS version 13.0 software package (SPSS Inc, Chicago, Illinois). Data were expressed as means and standard deviations (SDs), except for serum creatinine levels and a number of antihypertensive drugs, which were expressed as medians and interquartile ranges or proportions. Survival analyses were performed by Kaplan-Meier estimation of event-free survival curves and compared by log-rank tests (with patients grouped according to different dipping patterns) and multivariate Cox proportional hazards regression. For patients with multiple events, analysis was restricted to the first event under study. Results were presented as hazards ratios (HRs) with 95% confidence intervals (CIs). For continuous night to day BP ratios, HRs were standardized by calculating them in 1-SD increments. First, each nocturnal BP reduction parameter was adjusted for age and sex and then fully adjusted for all potential risk factors: age, sex, body mass index, diabetes, current smoking status, physical inactivity, dyslipidemia, previous cardiovascular diseases, serum creatinine levels, number of antihypertensive drugs in use, and office and 24-hour ambulatory BP levels. As expected, the nocturnal BP reduction was strongly correlated with nocturnal BP levels (Pearson correlation, 0.63 for SBP), which prevented us from adjusting for mean nocturnal BP levels owing to collinearity problems. Otherwise, the correlation between the nocturnal BP reduction and the mean 24-hour BP reading was much smaller (Pearson coefficient, 0.18). The serum creatinine levels were log_{10} transformed before they were entered into the analysis owing to their positive skewed distribution. The proportional hazards assumption was tested by inspection of log-minus-log curves, and no violation was observed. Interaction terms were tested between the nocturnal BP reduction variables (night to day BP ratios and dipping/nondipping status) and other covariates. Finally, we compared the prognostic values of each abnormal dipping pattern (extreme dippers, nondippers, and risers) with the normal dipping pattern into the same fully adjusted Cox models. A 2-tailed P value of less than .05 was considered significant.

BASELINE CHARACTERISTICS AND INCIDENCE OF END POINTS DURING FOLLOW-UP

The main baseline characteristics of the 556 patients (29% men; mean [SD] age, 65.8 [11.2] years), who were classified according to different dipping patterns, are shown in Table 1. The distribution of dipping patterns according to individually registered hours of sleeping and being awake was as follows: dippers, 27%; extreme dippers, 8%; nondippers, 46%; and risers, 19%. Older age, diabetes, physical inactivity, and previous cardiovascular diseases were more frequent in nondippers and risers. Patients used a median of 4 antihypertensive drugs at baseline (range, 3 to 6 drugs; 100% of the patients were taking diuretics) and a median of 2 drugs at bedtime (all patients took at least 1 antihypertensive drug at bedtime).
There was no difference in baseline antihypertensive treatment between patients with and without cardiovascular events during follow-up nor between different dipping patterns.

The median duration of follow-up was 4.8 years (range, 1-103 months), corresponding to 2678 patient-years. Thirty-seven patients (6.7%) were unavailable for follow-up and were considered censored observations at the date of their last hospital visit. There were no differences in nocturnal BP reduction variables between the patients who were unavailable for follow-up and those who completed follow-up. Fatal cardiovascular events occurred in 46 patients (8.3%; incidence rate, 1.72 per 100 patient-years of follow-up) among a total of 70 all-cause deaths (12.6%; incidence rate, 2.61 per 100 patient-years). Cardiovascular deaths were due to AMI (n=14), stroke (n=13), sudden cardiac death (n=7), progressive heart failure (n=5), renal failure (n=4), and aortic or peripheral arterial events (n=3). A total of 109 patients (19.6%; incidence rate, 4.32 per 100 patient-years of follow-up) reached the primary composite end point: there were 44 strokes, 21 AMIs, 15 myocardial revascularizations, 34 peripheral arterial events, and 15 aortic events.

### Table 1. Baseline Characteristics and Crude Incidence Rates of End Points During Follow-up in Patients Grouped According to Different Patterns of Nocturnal Systolic Blood Pressure (BP) Reduction

<table>
<thead>
<tr>
<th>Variable</th>
<th>Dippers (n = 150)</th>
<th>Extreme Dippers (n = 45)</th>
<th>Nondippers (n = 255)</th>
<th>Risers (n = 106)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex, % male</td>
<td>23.5</td>
<td>22.2</td>
<td>32.7</td>
<td>30.2</td>
</tr>
<tr>
<td>Age, mean (SD), y</td>
<td>64.8 (10.8)</td>
<td>61.1 (11.7)</td>
<td>66.9 (11.3)</td>
<td>66.8 (10.8)</td>
</tr>
<tr>
<td>BMI, mean (SD)</td>
<td>30.1 (5.2)</td>
<td>31.9 (5.5)</td>
<td>29.7 (5.9)</td>
<td>29.9 (5.8)</td>
</tr>
<tr>
<td>Diabetes, %</td>
<td>36.9</td>
<td>40.0</td>
<td>32.3</td>
<td>44.3</td>
</tr>
<tr>
<td>Current smoking, %</td>
<td>11.4</td>
<td>13.3</td>
<td>9.8</td>
<td>6.6</td>
</tr>
<tr>
<td>Physical inactivity, %</td>
<td>73.8</td>
<td>64.4</td>
<td>74.8</td>
<td>78.3</td>
</tr>
<tr>
<td>Dyslipidemia, %</td>
<td>89.3</td>
<td>80.0</td>
<td>88.6</td>
<td>90.6</td>
</tr>
<tr>
<td>Renal failure, %a</td>
<td>2.6</td>
<td>2.2</td>
<td>3.8</td>
<td>3.7</td>
</tr>
<tr>
<td>Previous cardiovascular diseases, %</td>
<td>45.6</td>
<td>35.6</td>
<td>47.2</td>
<td>48.1</td>
</tr>
<tr>
<td>Coronary heart disease</td>
<td>26.8</td>
<td>22.2</td>
<td>26.9</td>
<td>28.3</td>
</tr>
<tr>
<td>Cerebrovascular disease</td>
<td>17.4</td>
<td>13.3</td>
<td>18.5</td>
<td>17.9</td>
</tr>
<tr>
<td>Peripheral arterial disease</td>
<td>6.7</td>
<td>4.4</td>
<td>11.4</td>
<td>14.2</td>
</tr>
<tr>
<td>Heart failure</td>
<td>4.0</td>
<td>2.2</td>
<td>6.7</td>
<td>6.6</td>
</tr>
</tbody>
</table>

### Antihypertensive treatment

<table>
<thead>
<tr>
<th>Variable</th>
<th>No. of drugs, median (IQR)</th>
<th>No. of drugs at bedtime, median (IQR)</th>
<th>ACE inhibitors/AR blockers, %</th>
<th>β-Blockers, %</th>
<th>Calcium channel blockers, %</th>
<th>Direct vasodilators, %</th>
<th>Central α-agonists, %</th>
<th>Total cholesterol, mean (SD), mg/dL</th>
<th>HDL cholesterol, mean (SD), mg/dL</th>
<th>Serum creatinine (RR), mg/dL</th>
<th>Echocardiographic LVH, %</th>
<th>Echocardiographic LVMI, g/m²</th>
<th>Echocardiographic LVEF, %</th>
<th>Systolic BP, mean (SD), mm Hg</th>
<th>Diastolic BP, mean (SD), mm Hg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Office</td>
<td>175 (27)</td>
<td>172 (25)</td>
<td>178 (27)</td>
<td>184 (29)</td>
<td>134 (19)</td>
<td>133 (15)</td>
<td>139 (20)</td>
<td>142 (21)</td>
<td>138 (19)</td>
<td>140 (16)</td>
<td>141 (20)</td>
<td>140 (21)</td>
<td>119 (17)</td>
<td>106 (12)</td>
<td></td>
</tr>
<tr>
<td>24-Hour</td>
<td>134 (19)</td>
<td>133 (15)</td>
<td>139 (20)</td>
<td>142 (21)</td>
<td>138 (19)</td>
<td>140 (16)</td>
<td>141 (20)</td>
<td>140 (21)</td>
<td>138 (19)</td>
<td>140 (16)</td>
<td>141 (20)</td>
<td>140 (21)</td>
<td>119 (17)</td>
<td>106 (12)</td>
<td></td>
</tr>
<tr>
<td>Daytime</td>
<td>76 (11)</td>
<td>61 (9)</td>
<td>75 (14)</td>
<td>81 (14)</td>
<td>81 (12)</td>
<td>84 (13)</td>
<td>82 (14)</td>
<td>80 (13)</td>
<td>78 (12)</td>
<td>80 (11)</td>
<td>80 (13)</td>
<td>80 (14)</td>
<td>67 (11)</td>
<td>61 (9)</td>
<td></td>
</tr>
<tr>
<td>Nighttime</td>
<td>59.1</td>
<td>62.2</td>
<td>62.2</td>
<td>59.4</td>
<td>98 (18)</td>
<td>98 (13)</td>
<td>98 (18)</td>
<td>101 (20)</td>
<td>98 (18)</td>
<td>98 (13)</td>
<td>98 (18)</td>
<td>101 (20)</td>
<td>2.02 (15)</td>
<td>0.80 (2)</td>
<td></td>
</tr>
<tr>
<td>Incidence rate of all-cause deaths per 100 patient-years of follow-up (No. of patients)</td>
<td>0.94 (7)</td>
<td>0.80 (2)</td>
<td>2.29 (28)</td>
<td>1.98 (9)</td>
<td>0.7 (1)</td>
<td>0.5 (0.1)</td>
<td>2.3 (0.1)</td>
<td>2.9 (0.4)</td>
<td>0.5 (0.1)</td>
<td>2.3 (0.1)</td>
<td>2.9 (0.4)</td>
<td>0.5 (0.1)</td>
<td>2.3 (0.1)</td>
<td>2.9 (0.4)</td>
<td>0.5 (0.1)</td>
</tr>
<tr>
<td>Incidence rate of total cardiovascular events per 100 patient-years of follow-up (No. of patients)</td>
<td>2.96 (21)</td>
<td>2.52 (6)</td>
<td>5.09 (58)</td>
<td>5.63 (24)</td>
<td>2.96 (21)</td>
<td>2.52 (6)</td>
<td>5.09 (58)</td>
<td>5.63 (24)</td>
<td>2.96 (21)</td>
<td>2.52 (6)</td>
<td>5.09 (58)</td>
<td>5.63 (24)</td>
<td>2.96 (21)</td>
<td>2.52 (6)</td>
<td>5.09 (58)</td>
</tr>
</tbody>
</table>

Abbreviations: ACE, angiotensin-converting enzyme; AR, angiotensin II receptor; BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); BP, blood pressure; HDL, high-density lipoprotein; IQR, interquartile range; LVEF, left ventricular ejection fraction; LVH, left ventricular hypertrophy; LVMI, left ventricular mass index; RH, resistant hypertension; RR, reference range.

SI conversion factors: To convert cholesterol values to millimoles per liter, multiply by 0.0259, and to convert creatinine values to micromoles per liter, multiply by 88.4.

a Estimated creatinine clearance (Cockcroft-Gault formula) less than or equal to 30 mL/min.

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Systolic hypertension, 10 cases of new-onset heart failure, 5 sudden deaths, 3 lower limb amputations, and 2 deaths due to aortic or peripheral arterial disease; 7 patients underwent dialysis and 2 died of renal failure. Nondippers and risers had a higher incidence of all-cause and cardiovascular deaths and of total cardiovascular events.

**SURVIVAL ANALYSIS**

**Table 2** shows the results of Cox proportional hazards regression of the nocturnal BP reduction variables (night to day SBP and DBP ratios, dipping/nondipping status, and the 4 subgroups of dipping patterns) for the 3 primary end points after adjustment for age and sex and after full adjustment for all traditional cardiovascular risk factors, including mean 24-hour ambulatory BP levels. The nondipping pattern was the best independent predictor of cardiovascular morbidity and mortality. It was associated with a 74% higher risk of having a fatal or nonfatal cardiovascular event and with a 2.3-fold increased risk of cardiovascular death. When the 4 different dipping patterns were analyzed, both the nondippers and the risers were associated with future increased rates of cardiovascular morbidity and mortality, whereas the extreme dippers did not have a worse prognosis. The nocturnal BP reduction variable was not an independent predictor of all-cause mortality.

Kaplan-Meier analysis of survival curves showed that the nondipping pattern was associated with a significantly worse prognosis regarding total cardiovascular event-free and total and cardiovascular survival rates (Figure 1). When analyzed as the 4 different dipping patterns, it confirmed that the nondippers and the risers had a significantly worse cardiovascular event-free survival rate (Figure 2).

Among the various interactions tested, there were borderline significant interactions between the night to day SBP ratio and age (P = .08) and between dipping/nondipping status and the ABPM diagnosis of true/white-coat RH (P = .10) in fully adjusted analysis. The predictive performance of the nondipping pattern for the composite end point was stronger in younger patients (<65 years) (HR, 2.05; 95% CI, 1.04-4.05; P = .04) than in older patients (HR, 1.64; 95% CI, 0.90-2.98; P = .11). It was also stronger in patients with true RH (HR, 2.07; 95% CI, 1.22-3.50; P = .007) than in patients with white-coat RH (HR, 1.06; 95% CI, 0.43-2.61; P = .90).

**Table 3** presents the Cox analysis for the secondary end points. The nondipping pattern was a predictor of total CHD events, but not of stroke, after full statistical adjustment. Changing the definition of the nighttime period to fixed hours (0 to 6 AM) did not qualitatively alter the results of the survival analysis for any of the end points evaluated (data not shown).

**COMMENT**

This prospective study of a large group of patients with RH who were followed up for up to 9 years showed that the nondipping pattern is an important cardiovascular prognostic marker, above and beyond office BP, mean ambulatory BP, and other traditional risk factors. Moreover, the effect of the nondipping pattern on cardiovascular outcome is observed both in the nondippers and the risers, whereas extreme dipping does not affect prognosis. This effect is stronger in younger patients and in patients with true RH, and it is more important for CHD events than for stroke. To our knowledge, there are only 3 previous prospective RH studies that have analyzed the prognostic importance of ABPM parameters.6,11,12 But this study is the first to specifically evaluate the nocturnal BP reduction in patients with RH. Many studies demonstrated that ambulatory BP was a better predictor of cardiovascular risk than office BP,2,3,15,16 and the majority of them suggested that a blunted or absent nocturnal BP re-

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**Table 2. Results of Cox Survival Analyses for Associations Between Nocturnal Blood Pressure (BP) Reduction Measurements and Follow-up End Points**

<table>
<thead>
<tr>
<th>Nocturnal BP Reduction Parameter</th>
<th>Composite End Point (n=109)</th>
<th>Age and Sex Adjusted</th>
<th>Multivariate Adjustedb</th>
<th>Cardiovascular Mortality (n=46)</th>
<th>Age and Sex Adjusted</th>
<th>Multivariate Adjustedb</th>
</tr>
</thead>
<tbody>
<tr>
<td>Night-to-day systolic BP ratio</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>(1 SD=0.09)</td>
<td>1.26 (1.03-1.53)c</td>
<td>1.22 (1.00-1.49)</td>
<td>1.18 (0.92-1.51)</td>
<td>1.13 (0.88-1.45)</td>
<td>1.16 (0.85-1.57)</td>
<td>1.13 (0.82-1.55)</td>
</tr>
<tr>
<td>Night-to-day diastolic BP ratio</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(1 SD=0.10)</td>
<td>1.15 (0.96-1.38)</td>
<td>1.13 (0.94-1.37)</td>
<td>1.03 (0.81-1.29)</td>
<td>0.98 (0.77-1.25)</td>
<td>1.06 (0.80-1.41)</td>
<td>1.02 (0.76-1.38)</td>
</tr>
<tr>
<td>Nondipping vs dipping</td>
<td></td>
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<tr>
<td>Categories of dipping</td>
<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Extreme dippers</td>
<td>0.91 (0.37-2.26)</td>
<td>1.05 (0.42-2.61)</td>
<td>0.44 (0.10-1.94)</td>
<td>0.50 (0.11-2.19)</td>
<td>0.94 (0.20-4.54)</td>
<td>1.16 (0.24-5.71)</td>
</tr>
<tr>
<td>Nondippers</td>
<td>1.67 (1.01-2.76)c</td>
<td>1.71 (1.03-2.83)c</td>
<td>1.46 (0.81-2.66)</td>
<td>1.51 (0.82-2.79)</td>
<td>2.31 (1.01-5.29)c</td>
<td>2.41 (1.03-5.67)c</td>
</tr>
<tr>
<td>Risers</td>
<td>1.87 (1.04-3.73)c</td>
<td>1.89 (1.04-3.43)c</td>
<td>1.38 (0.67-2.88)</td>
<td>1.45 (0.67-3.05)</td>
<td>1.94 (0.72-5.22)</td>
<td>2.31 (0.82-6.51)</td>
</tr>
</tbody>
</table>

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*For continuous variables calculated for 1-SD increments. Adjusted for sex, age, body mass index, diabetes, current smoking status, physical inactivity, dyslipidemia, previous cardiovascular diseases, serum creatinine level (log10 transformed), number of antihypertensive drugs in use, and office and ambulatory 24-hour BP levels. cP < .05.*
46 strokes, and no prognostic association with nocturnal BP reduction parameters was demonstrated. Otherwise, the nondipping pattern was associated with a 2-fold higher risk of future fatal or nonfatal CHD events.

A recent meta-analysis of 7458 individual ABPM data demonstrated that the night to day BP ratio predicted cardiovascular and noncardiovascular mortality. Patients were also categorized into the 4 dipping patterns: the nondipping patterns predicted total mortality, while the rising patterns predicted all-cause death and cardiovascular mortality and morbidity. In our study, the nondipping and the rising patterns predicted fatal and nonfatal cardiovascular events even after full adjustments. Moreover, similar to our results, extreme dipping did not provide prognostic value. Furthermore, the MONICA study found that a blunted nocturnal BP reduction was a cardiovascular risk predictor only in patients with uncontrolled daytime BP. Our findings support this observation by showing that the main influence of the nondipping pattern on cardiovascular prognosis was in patients with true RH.

Several other studies have evaluated the prognostic value of the nocturnal BP reduction in hypertensive populations, but there are controversial findings in relation to cardiovascular morbidity. Supporting our findings, an evaluation of 1268 Japanese hypertensives with and without type 2 diabetes showed that the rising pattern was associated with an almost 150% increase in risk of cardiovascular diseases in both groups. Otherwise, 2 large studies of hypertension did not find any prognostic value of the night to day BP ratio for cardiovascular outcome. These results are in agreement with ours, although the HR of the night to day SBP ratio for the composite end point was of borderline significance (HR, 1.22; 95% CI, 1.00-1.49; P = 0.06) after full adjustment.

In a previous cross-sectional analysis, which involved 907 patients with RH, we concluded that a widened pulse pressure seemed to be a better cardiovascular risk predictor only in patients with uncontrolled daytime BP.
lar risk marker than the nocturnal BP reduction based on the association between enlarged pulse pressure and all target-organ damage (the nondipping pattern was associated only with hypertensive nephropathy). However, in the present longitudinal study, the nondipping pattern was significantly associated with fatal and nonfatal cardiovascular events after adjustment that included mean 24-hour SBP monitoring, whereas in a previous report we demonstrated that ambulatory SBP and DBP levels were better cardiovascular risk markers than pulse pressure. From a clinical standpoint, our results raise an important question: Which should be the primary therapeutic goal in patients with RH, the control of mean ambulatory BP levels or the reversion of an unfavorable dipping pattern? We demonstrated that the prognostic importance of the nondipping pattern was greater in patients with true RH than in those with white-coat RH. Moreover, in relation to secondary end points (coronary and cerebrovascular diseases), we found a differential prognostic impact, with mean BP being more important for stroke occurrence and the nondipping pattern being more important for CHD events. In patients with true RH, control of 24-hour BP levels is a well-established primary therapeutic goal, but we believe that reversion of the unfavorable circadian BP pattern should also be beneficial for these patients, although future interventional studies are necessary to confirm this point of view.

The present study has some limitations. First, our study enrolled only patients with RH, which represents a common but generally understudied subgroup of general hypertension. Therefore, our results may not be generalized to other, less severe hypertensive individuals. Second, we used only the baseline ambulatory BP measurements, not considering changes in therapeutic schemes or fluctuations of patient adherence during follow-up, which could influence ambulatory BP levels and variability patterns and hence the final prognosis. Moreover, many of the controversial findings about the prognostic value of the nocturnal BP variability patterns are attributed to methodological problems.

In conclusion, the present prospective study provides evidence that the nondipping pattern represents an important risk marker for future cardiovascular morbidity and mortality, above and beyond other traditional cardiovascular risk factors, in patients with RH, and our findings may contribute to the refinement of cardiovascular risk stratification. Patients with uncontrolled true RH with reduced or reverted dipping patterns should be considered at very high risk for the future occurrence of fatal or nonfatal cardiovascular events and should be treated more aggressively. Future studies are necessary to verify whether achieved BP levels on subsequent ABPM examinations during follow-up are better cardiovascular risk predictors than baseline ambulatory BP levels and dipping patterns. Moreover, interventional prospective studies are needed to answer an important clinical question regarding whether therapeutic interventions directed specifically not only to control nocturnal BP levels but also to change abnormal dipping patterns could actually improve the cardiovascular prognosis of high-risk patients with RH.

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Author Contributions: Dr Muxfeldt had full access to all data in the study and takes responsibility for the integrity of the data and the accuracy of data analysis. Study concept and design: Muxfeldt and Salles. Acquisition of data: Muxfeldt, Cardoso, and Salles. Analysis and interpretative

<table>
<thead>
<tr>
<th>Nocturnal BP Reduction Parameters</th>
<th>Coronary Heart Disease Events</th>
<th>Stroke</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Age and Sex Adjusted Multivariate Adjusted</td>
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</tr>
<tr>
<td></td>
<td>n=44</td>
<td>n=46</td>
</tr>
<tr>
<td>Lights (SD 0.09)</td>
<td>1.27 (0.92-1.71)</td>
<td>1.24 (0.91-1.70)</td>
</tr>
<tr>
<td>Night-to-day diastolic BP ratio (1 SD 0.10)</td>
<td>1.09 (0.62-1.46)</td>
<td>1.11 (0.83-1.48)</td>
</tr>
<tr>
<td>Nondipping pattern (vs dipping)</td>
<td>1.95 (0.96-3.97)</td>
<td>2.05 (1.00-4.20)</td>
</tr>
<tr>
<td>Categories of dipping</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Extreme dippers</td>
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</tr>
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</tr>
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<td>Risers</td>
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</tr>
</tbody>
</table>

For continuous variables calculated for 1-SD increments.

1 Adjusted for sex, age, body mass index, diabetes, current smoking status, physical inactivity, dyslipidemia, previous cardiovascular diseases, serum creatinine level (log10 transformed), number of antihypertensive drugs in use, and office and ambulatory 24-hour BP levels.

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P < .05.
tion of data: Muxfeldt, Cardoso, and Salles. Drafting of the manuscript: Muxfeldt. Critical revision of the manuscript for important intellectual content: Muxfeldt, Cardoso, and Salles. Statistical analysis: Muxfeldt, Cardoso, and Salles. Obtained funding: Muxfeldt and Salles. Administrative, technical, and material support: Muxfeldt, Cardoso, and Salles. Study supervision: Muxfeldt and Salles.

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REFERENCES