Blood Pressure Variability and Silent Cerebral Damage in Essential Hypertension

Elisenda Gómez-Angelats, Alejandro de La Sierra, Cristina Sierra, Gianfranco Parati, Giuseppe Mancia, and Antonio Coca

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**Methods:** We studied 43 middle-aged untreated hypertensive patients. Blood pressure variabilities (short-term and long-term) were evaluated by using both non-invasive, beat-to-beat, continuous finger 24-hour monitoring (Portapres) and oscillometric automated discontinuous ambulatory blood pressure monitoring. All patients underwent cerebral magnetic resonance imaging to detect the presence or not of white matter lesions.

**Results:** Hypertensive patients with cerebral white matter lesions exhibited significantly higher values of long-term systolic blood pressure variability (standard deviation of 24-hour blood pressure) measured both by continuous beat-to-beat monitoring ($16.2 \pm 3.7 \text{ vs } 13.7 \pm 3.6 \text{ mmHg; } P = 0.047$) and by ambulatory blood pressure monitoring ($15.2 \pm 3.8 \text{ vs } 12.8 \pm 2.7 \text{ mmHg; } P = 0.022$). However, these differences were not independent on blood pressure elevation and did not maintain their significance after adjusting for 24-hour systolic blood pressure. Neither short-term systolic blood pressure variability, nor short-term or long-term diastolic blood pressure variabilities showed differences between patients with and without white matter lesions.

**Conclusion:** The present study indicates that long-term systolic blood pressure variability is significantly related to the presence of silent cerebral white matter lesions in essential hypertensive patients, although this relationship is partially dependent on absolute blood pressure elevation. Am J Hypertens 2004;17:696–700 © 2004 American Journal of Hypertension, Ltd.

**Key Words:** Blood pressure variability, white matter lesions, hypertension.

**Introduction**

Epidemiological studies have shown that high blood pressure (BP) is the most important risk factor for cerebrovascular diseases in all age groups. This very close correlation between BP and the incidence of both fatal and nonfatal cerebrovascular events has been demonstrated for clinic BP measurements. However, other reports support the view that daytime, nighttime or 24-h average BP values obtained by either non-invasive or invasive 24-h BP monitoring have a better correlation with both target organ damage (TOD) and cardiovascular complications than office BP. In addition to the magnitude of BP elevation, it is increasingly recognized that the degree of BP variability offers additional prognostic significance in terms of the development of TOD, cardiovascular morbidity and mortality. Blood pressure variability can be measured by continuous BP recordings over a long period of time, usually 24 hours (“long-term variability”), or over shorter periods, usually of 30 minutes (“short-term variability”). Long-term variability can be measured by intermittent 24-h ambulatory BP monitoring (ABPM) but rigorous assessment requires the use of intra-arterial continuous beat-to-beat 24-h BP monitoring, or the more-recently developed, non-invasive continuous finger 24-h beat-to-beat BP monitoring. It is not possible to measure short-term variability with intermittent 24-h ABPM and only continuous beat-to-beat monitoring (using intra-arterial or non-invasive devices) is generally accepted as reliable.

He final clinical consequences of high BP on the cerebral arteries (fatal or non-fatal stroke, vascular dementia)

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He final clinical consequences of high BP on the cerebral arteries (fatal or non-fatal stroke, vascular dementia)
are commonly preceded by silent manifestations of target organ damage such as cerebral white matter lesions (WML) or lacunar, although it is well known that other cardiovascular risk factors are associated with WML. Whereas a close relationship between BP variability and LVH as a surrogate end-point of clinical cardiac damage has been reported, the relationship between WML as a surrogate end-point of cerebrovascular damage and BP variability has not been conclusively established.

The aim of the present study was to analyze the relationship between BP variability and the presence of silent cerebral WML as an early marker of cerebral damage in essential hypertension.

Methods

Patient Selection

We studied 43 never treated essential hypertensive patients (WHO/ISH Grades I to II) aged 50–60 years. All patients had a complete clinical work-up to rule out secondary hypertension. No patient had diabetes mellitus, clinically relevant renal insufficiency (serum creatinine >1.5 mg/dl), cardiac failure, or history of myocardial ischemia or infarction, stroke, or peripheral vascular disease. Patients with severe concomitant pathological conditions or a daily alcohol intake >80 g for men and >60 g for women were also excluded. All subjects gave their written consent to participate in the study after being informed of its nature and purpose. The study was approved by the Hospital Ethics Committee.

Office BP Measurements

Office BP was measured three times with a mercury sphygmomanometer after 5 minutes of rest with the patient in the sitting position. Office BP was considered as the average of the last two readings, and hypertension was defined as systolic BP ≥140 mm Hg and/or diastolic BP ≥90 mm Hg in at least three different sets of measurements taken at 1-week intervals.

Intermittent 24-Hour Ambulatory BP Monitoring

Twenty-four hour ABPM was carried out with an automatic oscillometric device (Spacelabs 90207; Spacelabs Inc, Redmond, WA). Patients engaged in their normal daily activities and BP was measured automatically at 15-minute intervals during the whole 24-hour period. The following parameters were measured: average 24-hour systolic, diastolic, mean and pulse (difference between systolic and diastolic) pressures, as well as their standard deviations, taken as indexes of BP variability. The difference between daytime and nighttime BP was also computed by defining daytime and nighttime periods as those included between 8 and 23 hours and between 23 and 8 hours, respectively. Patients were classified as extreme-dippers (nocturnal systolic BP fall ≥20%), dippers (nocturnal systolic BP fall between 10% and 19%) or non-dippers (nocturnal systolic BP fall <10%).

Non-Invasive Continuous (Beat-To-Beat) BP Monitoring

Twenty-four hour beat-to-beat non-invasive finger BP was monitored using the validated Portapres model-II, a portable version of the Finapres device (TNO, BioMedical Instrumentation, The Netherlands) while the patient was hospitalized. A high level of correspondence between Portapres and intra-arterial measurements has been documented in different populations, in particular when tracking BP changes over time. The finger arterial pressure signal was recorded continuously through small cuffs placed on the third and the fourth fingers, shifting from one finger to the other every 30 minutes. During the recording period, subjects were free to move within the hospital area and to engage in the usual activities of inpatients not confined to bed. The Portapres device has a height-correcting system which measures the position of the finger relative to heart level and automatically corrects finger BP values for the finger-heart hydrostatic height difference with a time constant of 2 seconds. Short-term BP variability was obtained by calculating the standard deviations of mean systolic and diastolic BP values for each 48 half-hour period, and then computing the average of these 48 standard deviations (“within half-hour standard deviation”). Long-term variability was calculated by obtaining the average of the 48 half-hour systolic and diastolic mean values and then calculating the standard deviation of this average (“among half-hour standard deviation”). Long-term and short-term variabilities exhibited significant correlation between them $r = 0.397; P = 0.011$ for systolic and $r = 0.716; P < 0.001$ for diastolic variabilities.

Magnetic Resonance Imaging

MRI was carried out in all patients. Recordings were independently analyzed by two investigators who agreed on a final diagnosis. The severity of WML was graded as: absence (scans showing no or fewer than 5 focal and non-confluent periventricular hyperintensities) and presence: (scans showing five or more focal periventricular hyperintensities, or confluent lesions). The presence of lacunar infarcts or brain atrophy was marginal in the present sample and was not included.

Statistical Analysis

Values are expressed as mean ± standard deviation (SD). Comparisons between patients with and without cerebral white matter lesions were made by the unpaired Student t test. For blood pressure variability, these analyses were complemented by a covariance analysis adjusted for the corresponding absolute blood pressure value. A value of $P < 0.05$ (two-sided) was considered statistically significant.
Our study included 43 essential hypertensive patients (23 men and 20 women) with a mean age of 53.9 ± 3.4 years. Baseline office blood pressure values were 164 ± 18/97 ± 9 mm Hg. Mean body mass index was 27.8 ± 3.7 Kg/m², and mean urinary albumin excretion was 22.2 g/min [range 1.4 to 112].

Magnetic resonance imaging revealed the presence of cerebral white matter lesions in 16/43 patients (37.2%), compared with 7.7% in a control group of 26 normotensive healthy subjects matched for age and gender (office BP 124 ± 11/74 ± 8 mm Hg).

Compared to patients with normal MRI scans, essential hypertensives with cerebral WML exhibited significantly higher values of 24-h systolic BP, measured by both ABPM and continuous finger monitoring (Table 1). Differences in diastolic BP were only significant when measured by ABPM.

In addition to these absolute BP differences, patients with cerebral WML showed a significant increase in long-term systolic BP variability (Table 2). In fact, both the standard deviation of 24-h systolic BP obtained by either ABPM (15.2 ± 3.8 v 12.8 ± 2.7 mm Hg; \( P = 0.022 \)) and the among half-hour standard deviation obtained by con-

### Table 1. Comparison of blood pressure (BP) values obtained at the office, by ambulatory BP monitoring (ABPM) or by beat-to-beat continuous monitoring in patients with or without the presence of cerebral silent white matter lesions (WML)

<table>
<thead>
<tr>
<th>BP (mm Hg)</th>
<th>With WML (( n = 16 ))</th>
<th>Without WML (( n = 27 ))</th>
<th>( P )</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Office BP</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systolic BP</td>
<td>169.1 ± 19.2</td>
<td>160.5 ± 17.6</td>
<td>.151</td>
</tr>
<tr>
<td>Diastolic BP</td>
<td>98.8 ± 10.5</td>
<td>95.6 ± 7.7</td>
<td>.269</td>
</tr>
<tr>
<td>Mean BP</td>
<td>122.2 ± 13.0</td>
<td>117.2 ± 10.1</td>
<td>.175</td>
</tr>
<tr>
<td>Pulse BP</td>
<td>70.3 ± 11.4</td>
<td>64.9 ± 13.6</td>
<td>.200</td>
</tr>
<tr>
<td><strong>ABPM</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>24-h systolic BP</td>
<td>150.3 ± 17.1</td>
<td>137.6 ± 14.6</td>
<td>.013</td>
</tr>
<tr>
<td>24-h diastolic BP</td>
<td>95.1 ± 12.6</td>
<td>87.7 ± 8.9</td>
<td>.029</td>
</tr>
<tr>
<td>24-h mean BP</td>
<td>115.0 ± 14.0</td>
<td>105.4 ± 9.9</td>
<td>.012</td>
</tr>
<tr>
<td>24-h pulse BP</td>
<td>55.2 ± 10.7</td>
<td>49.9 ± 10.9</td>
<td>.128</td>
</tr>
<tr>
<td><strong>Continuous beat-to-beat monitoring</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>24-h systolic BP</td>
<td>149.6 ± 25.4</td>
<td>132.8 ± 15.6</td>
<td>.013</td>
</tr>
<tr>
<td>24-h diastolic BP</td>
<td>80.4 ± 8.9</td>
<td>74.9 ± 10.7</td>
<td>.105</td>
</tr>
<tr>
<td>24-h mean BP</td>
<td>102.5 ± 11.3</td>
<td>94.5 ± 11.1</td>
<td>.035</td>
</tr>
<tr>
<td>24-h pulse BP</td>
<td>67.4 ± 22.9</td>
<td>54.3 ± 11.4</td>
<td>.021</td>
</tr>
</tbody>
</table>

### Table 2. Comparison of the different components of blood pressure (BP) variability obtained by ambulatory BP monitoring (ABPM) and by beat-to-beat continuous monitoring in patients with or without white matter lesions (WML)

<table>
<thead>
<tr>
<th>BP Variability (mm Hg)</th>
<th>With WML (( n = 16 ))</th>
<th>Without WML (( n = 27 ))</th>
<th>( P )</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ABPM</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SD of 24-h systolic BP</td>
<td>15.2 ± 3.8</td>
<td>12.8 ± 2.7</td>
<td>.022</td>
</tr>
<tr>
<td>SD of 24-h diastolic BP</td>
<td>11.5 ± 3.4</td>
<td>10.5 ± 2.3</td>
<td>.262</td>
</tr>
<tr>
<td>SD of daytime systolic BP</td>
<td>13.4 ± 3.1</td>
<td>12.2 ± 3.6</td>
<td>.266</td>
</tr>
<tr>
<td>SD of daytime diastolic BP</td>
<td>9.7 ± 2.7</td>
<td>9.4 ± 2.5</td>
<td>.790</td>
</tr>
<tr>
<td>SD of nighttime systolic BP</td>
<td>11.4 ± 2.3</td>
<td>11.3 ± 2.5</td>
<td>.937</td>
</tr>
<tr>
<td>SD of nighttime diastolic BP</td>
<td>9.2 ± 2.9</td>
<td>9.2 ± 2.8</td>
<td>.979</td>
</tr>
<tr>
<td>Nocturnal systolic fall</td>
<td>12.8 ± 11.9</td>
<td>10.7 ± 9.1</td>
<td>.522</td>
</tr>
<tr>
<td>Nocturnal diastolic fall</td>
<td>10.4 ± 9.5</td>
<td>9.9 ± 6.2</td>
<td>.840</td>
</tr>
<tr>
<td>Nondippers (%)</td>
<td>31.3</td>
<td>48.1</td>
<td>.348</td>
</tr>
<tr>
<td>Dippers (%)</td>
<td>31.3</td>
<td>33.3</td>
<td></td>
</tr>
<tr>
<td>Extreme dippers (%)</td>
<td>37.5</td>
<td>18.5</td>
<td></td>
</tr>
<tr>
<td><strong>Continuous beat-to-beat monitoring</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Long-term systolic BP variability</td>
<td>16.2 ± 3.7</td>
<td>13.7 ± 3.6</td>
<td>.047</td>
</tr>
<tr>
<td>Long-term diastolic BP variability</td>
<td>8.6 ± 1.8</td>
<td>8.9 ± 3.0</td>
<td>.740</td>
</tr>
<tr>
<td>Short-term systolic BP variability</td>
<td>15.3 ± 3.1</td>
<td>14.4 ± 2.6</td>
<td>.345</td>
</tr>
<tr>
<td>Short-term diastolic BP variability</td>
<td>8.0 ± 1.1</td>
<td>8.0 ± 2.0</td>
<td>.999</td>
</tr>
</tbody>
</table>
Discontinuous finger monitoring (16.2 ± 3.7 v 13.7 ± 3.6 mm Hg; P = 0.047) were significantly increased in patients with WML. No differences were observed concerning 24-h diastolic BP variability. Furthermore, short-term systolic and diastolic BP variabilities (“within half-hour standard deviation” of BP) were not significantly different between patients with or without WML.

No differences were observed in the absolute nocturnal fall of BP between patients with and without WML. Moreover, the proportion of non-dippers (31.3% v 48.1%), dippers (31.3% v 33.3%) or extreme dippers (37.5% v 18.5%) did not differ (P = 0.348) between patients with or without WML (Table 2). Finally, the SD computed separately for the awake and night periods were also similar between groups.

These differences in long-term systolic BP variability were not independent on absolute BP elevation. In fact, after adjusting for 24-hour systolic BP values, differences in systolic BP variability lost their statistical significance (P = 0.188 for SD obtained by ABPM and P = 0.244 for the among half-hour standard deviation obtained by continuous finger monitoring).

Discussion

The most important finding of the present study is that, in asymptomatic never-treated hypertensive patients, long-term SBP variability measured by either ABPM or continuous beat-to-beat monitoring was significantly associated with the presence of silent cerebrovascular lesions (WML) detected by MRI. However, this association was not independent on BP elevation and statistical significance was lost in a covariance analysis after adjusting for absolute BP values. On the other hand, as shown by other studies, found no association between the diastolic component of BP variability and cerebral WML.

Previous studies have suggested a close relationship between the presence of WML and the circadian profile in elderly hypertensive patients. Using a multivariate approach, Sander et al and Shimada et al evaluated the impact of circadian BP on the extent of WML and found that it was related to the absence of nocturnal dipping of systolic BP assessed by 24-h ABPM. Moreover, Kario et al have also observed that, in addition of non-dippers, elderly patients having the most pronounced nocturnal BP decrease (≥20%), those called extreme-dippers, also had increased silent cerebrovascular lesions and a worse prognosis after a stroke, compared with those with a nocturnal BP decrease between 10% and 19% (dippers). Although we found no relationship between silent brain damage and the dipping (extreme or not) or non-dipping profile of blood pressure, the present study included a small sample of middle-aged patients with lower degrees of target organ damage.

The association between WML and long-term BP variability during the entire period of 24 hours suggests that changes of BP in daily life, other than the BP changes between day and night, are more important determinants of cerebral damage in hypertension. This is supported by the fact that no association between either daytime or nighttime BP variabilities and WML was found in this study.

Our results regarding WML and BP variability are in agreement with those of Toghi et al, who reported that patients with Binswanger-type dementia, which is characterized pathologically by diffuse white matter changes and multiple small infarcts in the cerebral white matter, had a significantly greater incidence of hypertension and increased systolic BP variability than other subgroups (controls, patients with lacunar stroke or dementia). However, patients in our study were younger and BP variability was also assessed by non-invasive continuous beat-to-beat monitoring, thus increasing the reliability of the measurement and reducing the confounding factor of age with respect to the presence of WML. Toghi et al suggested that wide oscillations in systolic BP could contribute to the development of ischemic changes in the end-fields of penetrating arteries of the cerebral white matter, which are susceptible to frequent reductions in BP.

Previous studies support the hypothesis that wide oscillations in systolic BP contribute to the genesis of ischemic changes in cerebral white matter. Kukla et al reported that patients older than 55 years (mean age 70 years) with silent lacunae in MRI exhibited an increase in systolic BP circadian variability assessed by 24-h ABPM in comparison with a control group of normal subjects. In the univariate analysis patients with lacunar infarction were significantly older and showed an increased daytime systolic BP variability and a flattened nighttime BP variation. More recently, Kario et al have shown that cerebrovascular disease in elderly hypertensives is also related with orthostatic hypotension and with morning BP surge. Unfortunately, the present study was not designed to look at these specific features.

Finally, as reported by Frattola et al regarding left ventricular hypertrophy, we found no association between short-term BP variability and the presence of WML. It is not clear why organ damage is related to “among half-hour” but not to “within half-hour” blood pressure standard deviation. Mancia et al have suggested that the long-term variability, calculated as the “among half-hour” BP standard deviation, represents a greater component of overall BP variability than the “within-half-hour” BP standard deviation, presumably because fluctuations over a longer period are greater than those in a shorter period. Frattola et al suggested that the most substantial variations are not those taking place within short periods, but those occurring between half-hours (those responsible for the hour-to-hour circadian BP profile), as we observed in hypertensive patients with WML. These findings may also be partly due to the limited reproducibility of short-term BP changes, the between-subject differences in their magnitude being influenced mainly by differences in short
lasting daily activities and emotional influences, the standardization of which during ambulatory BP monitoring is hardly possible.20

In addition, while the prognostic significance of long-term BP variability seems to be supported by our findings, further studies in which behavioral conditions are carefully standardized will be needed to determine the real prognostic value of short-term variability.

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References