Extent of Cerebral White Matter Lesions Is Related to Changes of Circadian Blood Pressure Rhythmicity

Dirk Sander, MD; Kerstin Winbeck, MD; Jürgen Klingelhoefer, MD; Bastian Conrad, MD

Objective: To evaluate the relationship between circadian blood pressure patterns and the extent of cerebral white matter lesions (WML).

Design: Case-control study.

Participants: A total of 227 healthy subjects older than 55 years were investigated. Extent and occurrence of WML were evaluated using a computer-supported image analysis system. Circadian blood pressure variation was defined as the average percentage change of nighttime blood pressure compared with the daily blood pressure values.

Results: Subjects with WML were significantly older and showed more often a history of hypertension, elevated average systolic daily blood pressure, a reduced systolic circadian blood pressure variation, and an increased incidence of pathological nighttime blood pressure increases. A significant correlation was found between systolic circadian blood pressure variation and the extent of WML. A multiple regression analysis revealed that this parameter was best correlated with the extent of WML.

Conclusion: In addition to the absolute level of blood pressure, systolic circadian blood pressure variation and in particular a systolic nighttime blood pressure increase may play an important role in the pathogenesis of WML.

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WHITE MATTER lesions (WML) are frequently found on magnetic resonance imaging (MRI) scans of elderly patients and are associated with cardiovascular risk factors; impaired cognitive functions, in particular a declined attention and speed of mental processing; and an increased risk for the subsequent development of strokes. The pathogenesis, clinical significance, and morphologic substrate of these changes are incompletely understood. The frequency of WML increases with age, but an increased risk of WML has also been associated with arterial hypertension and heart disease. However, the pathogenic role of elevated blood pressure for the development and extent of WML has not unequivocally clarified so far. Previous investigations found hypertension to be either associated or not associated with WML, depending on whether a univariate or multivariate approach was used. In contrast to these observations, a significant relationship between arterial hypotension and WML has been recently described.

So far, mainly the association between casual blood pressure and WML has been investigated. Interestingly, it has been shown that 24-hour blood pressure readings correlate more closely with target organ damage than casual blood pressure measurements. The absence of a physiological nighttime blood pressure decrease (“non-dippers”) was related to a clearly increased incidence of cerebrovascular disease. Shimada et al observed a relationship between increased ambulatory blood pressure, in particular during night sleep, and the occurrence and extent of WML using an univariate model. In contrast, a recent study found a significant positive univariate correlation between the amplitude of the fall in nighttime blood pressure and the extent of WML in elderly Japanese women but not in men. We investigated the association between circadian blood pressure patterns and extent of WML using a multivariate approach. In addition, a quantitative analysis of WML using MRI morphometry was performed.
SUBJECTS AND METHODS

SUBJECTS

A total of 357 healthy relatives of patients hospitalized in our department older than 55 years were asked to participate. From this series, 227 subjects provided informed consent and were included in the study. The study was approved by the local institutional review board. Information on current health status, medical history, drug use, and evaluation of former cardiovascular risk factors was obtained by a computerized questionnaire. The duration of arterial hypertension was based on the historical information about the date when each subject was first found to have high blood pressure. All subjects underwent MRI, and those with normal MRI findings were used as a control group.

BLOOD PRESSURE MEASUREMENTS

Noninvasive 24-hour blood pressure measurements were performed in all subjects using an automatic portable blood pressure monitor with an oscillometric measurement device (Spacelabs ABD-Monitor 90207; Spacelabs, Redmont, Wash). The noninvasive measurements were obtained with an adult-size cuff (2 sizes available) at a cuff deflation rate of 4 mm Hg/s. Validation studies using this monitor demonstrated no significant differences of average systolic (−2%) and diastolic (+1%) blood pressure values compared with intrarterial measurements.16 We did not perform repeated monitoring regularly, because the reliability and validity of the used blood pressure monitor has been demonstrated in previous studies.16,23 During the measurements, the behavior of the subjects was standardized as much as possible to avoid differences in physical activity or emotional stimulation. The measurements were made at intervals of 15 minutes during the entire 24-hour period. According to the recommendations of population-based studies,24,25 the average daytime values were determined between 6 AM and 10 PM, and the average nighttime values were determined between 10 PM and 6 AM. Circadian blood pressure variation was defined as the average percentage change of nighttime blood pressure compared with the daytime blood pressure values. Daytime blood pressure variability was defined as the within-subject SD of all systolic and diastolic blood pressure readings during the daytime measurement period.26 All measurements marked with an error event code on the monitor due to movement artifacts were manually excluded from the calculations. Based on the results of the 24-hour blood pressure measurements, we defined arterial hypertension (diastolic average daytime blood pressure >85 mm Hg) and isolated systolic hypertension (systolic average daytime blood pressure >135 mm Hg and diastolic average daytime pressure ≤85 mm Hg) according to the recommendations of several population-based studies comparing 24-hour blood pressure measurements with casual blood pressure.23,25 An average daytime systolic value greater than 135 mm Hg in the long-term blood pressure monitoring corresponds to a value of greater than 140 mm Hg in casual measurements.23,25 Onset or changes of antihypertensive medication were not performed during the 24-hour measurement. During the measurement period, none of the subjects used sedatives. The long-term measurement of blood pressure was made on the left side in right-handed subjects and vice versa after relevant differences between the sides had been ruled out by conventional checks of blood pressure. The subjects were instructed to keep their arm as still as possible during the measurement phase. Automatic artifact detection reduced possible measurement mistakes. All subjects kept a record of particular events, specifying the respective time.

RESULTS

Of the 227 subjects, 82 (36%) showed WML and 145 had no signs of WML. The essential data of the groups are given in Table 1. The mean volume of WML was 9.3 cm³ (95% confidence interval, 5.8-12.8 cm³). The WML group was significantly older and showed more often a history of hypertension, elevated systolic daily blood pressure, and a reduced systolic circadian blood pressure variation (Table 1). A pathological increase of systolic nighttime blood pressure (>0%; non-dipper) was significantly more frequent than in the controls (25.6% vs 10.3%; P<.005). In contrast, no significant differences for diastolic nighttime blood pressure increase (18.3% vs 9.7%; P=.06) and decline of nighttime heart rate (Table 1) were found. Univariate regression analysis revealed a significant correlation between systolic circadian blood pressure variation and the extent of WML assessed morphometrically (r=0.59; P<.001; Figure 1). This association was observed in both normotensive and hypertensive subjects (hypertensive: r=0.45; P<.005; normotensive: r=0.52; P<.005). In contrast, no significant correlation was found between diastolic circadian blood pressure variation and WML (r=0.15; P=.13; Figure 1).

In addition, there was a significant association between age and WML in the univariate analysis (r=0.32; P<.05).

To evaluate the influence of different risk factors (age, pack-years of smoking, cholesterol and triglyceride levels, systolic and diastolic blood pressure, systolic and diastolic circadian blood pressure variation, and systolic and diastolic daytime blood pressure variability) on the extent of WML, a stepwise multiple linear regression analysis was performed in the subjects with WML. The model that resulted from the stepwise procedure included the systolic circadian blood pressure variation and age as the sole independent variables (Table 2). All other risk factors did not significantly increase the predictability of the regression (Table 2). The predicted model accounted jointly for 39% in the variation in WML (Table 2).

The odds ratio of having WML was most increased in subjects with systolic nighttime blood pressure increase and elevated blood pressure levels, even when all other risk factors were held constant (Figure 2). Normotensive subjects with systolic nighttime blood pressure increases showed significantly more often WML compared with normotensive subjects with nighttime blood pressure decrease.
hospitalized and nonhospitalized subjects. The aim of previous studies evaluating the MRI incidence of WML in projects. This frequency of WML was similar to that of previous investigations using multivariate analysis. The main and new finding of our study was that the extent of WML evaluated quantitatively using MRI morphometry was most closely related to the absence of a decrease in nighttime systolic blood pressure. Previous investigations also observed an association between the grade of WML and the average of 24-hour systolic blood pressure readings, particularly during sleep, but not with casual blood pressure. However, these studies only performed univariate regression analysis and semiquantitative assessment of WML. Therefore, we used a stepwise multiple linear regression model to control for a possible interaction between the different risk factors and to include only independent determinants of the extent of WML. The regression model revealed the circadian systolic blood pressure variation as the most important variable for the extent of WML. Based on these findings, we believe that a pathological nighttime blood pressure increase was a risk factor for the occurrence and extent of WML and is more important than the actual level of blood pressure.

Because of the case-control paradigm used in our study, one could argue that our results are a consequence rather the cause of WML. We observed a significant correlation only between systolic circadian blood pressure variation and WML. In our opinion, this selective influence of systolic blood pressure patterns points against a WML-induced alteration of blood pressure patterns, because a similar effect of WML on both blood pressure components could be assumed. A recent prospective study also established a correlation only between daytime and nighttime systolic blood pressures and WML. However, to further clarify a possible causal relationship between nighttime blood pressure increase and WML, a prospective study is required.

Interestingly, there was a direct and linear relationship between the extent of WML assessed morphometri-
cally using MRI and the systolic circadian blood pressure variation not only in hypertensive but also in normotensive subjects. This finding, and the clearly increased odds ratio of having WML in normotensive subjects with nighttime blood pressure increase, further underscores the important role of nighttime blood pressure for the development of WML independent of the level of daytime blood pressure.

There are controversial opinions regarding the clinical relevance and etiopathogenesis of WML in healthy elderly persons. It was demonstrated that WML are associated with impaired cognitive functions, in particular a declined attention and speed of mental processing. Moreover, a vascular cause of death was clearly associated with WML and with the severity of WML, and WML correlate with an increased risk for the subsequent development of strokes. Recently, Longstreth et al stated that WML may not be considered benign, because cognitive function and multiple neurological deficits, such as gait disorders, tendency to fall, pseudobulbar state, and incontinence were correlated with the extent of WML. If WML are markers for these problems, as suggested by their findings, the search for causal risk factors is important because modification of them might reduce the risk of these dysfunctions in the elderly. In a prospective study by van Zagten et al, progression of WML was significantly associated with age but not with hypertension. In addition, the progression of WML over time was not influenced by the usual stroke therapy, including the lowering of elevated blood pressure levels. The authors argued that probably other, as yet unknown, factors influence the pathogenesis of cerebral arteriolosclerosis. Based on our findings, we suppose that

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>WML (n = 82)</th>
<th>No WML (n = 145)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>69 (68 to 70)</td>
<td>63 (62 to 65)</td>
<td>.008</td>
</tr>
<tr>
<td>Sex, M/F</td>
<td>42/40</td>
<td>73/72</td>
<td>.38</td>
</tr>
<tr>
<td>Cholesterol, mmol/L [mg/dL]</td>
<td>6.05 (5.79 to 6.31) [234 (224 to 244)]</td>
<td>5.90 (5.71 to 6.08) [228 (221 to 235)]</td>
<td>.29</td>
</tr>
<tr>
<td>Triglycerides, mmol/L [mg/dL]</td>
<td>1.85 (1.65 to 2.04) [164 (147 to 181)]</td>
<td>1.87 (1.75 to 2.00) [166 (155 to 177)]</td>
<td>.45</td>
</tr>
<tr>
<td>Diabetes mellitus, No. (%)</td>
<td>10 (12)</td>
<td>18 (12)</td>
<td>.88</td>
</tr>
<tr>
<td>Pack-years of smoking</td>
<td>25 (22 to 28)</td>
<td>24 (22 to 26)</td>
<td>.77</td>
</tr>
<tr>
<td>History of hypertension, No. (%)</td>
<td>48 (58)</td>
<td>52 (56)</td>
<td>.93</td>
</tr>
<tr>
<td>Blood pressure, mm Hg†</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systolic</td>
<td>143 (140 to 146)</td>
<td>135 (133 to 138)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Diastolic</td>
<td>87 (85 to 89)</td>
<td>84 (82 to 86)</td>
<td>.19</td>
</tr>
<tr>
<td>Arterial hypertension, No. (%)‡</td>
<td>27 (33)</td>
<td>38 (28)</td>
<td>.18</td>
</tr>
<tr>
<td>Isolated systolic hypertension, No. (%)§</td>
<td>30 (37)</td>
<td>26 (18)</td>
<td>.002</td>
</tr>
<tr>
<td>Blood pressure variation</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systolic</td>
<td>−5.6 (−7.3 to −3.9)</td>
<td>−9.5 (−10.5 to −8.5)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Diastolic</td>
<td>−9.4 (−11.5 to −7.3)</td>
<td>−12.4 (−13.5 to −11.3)</td>
<td>.09</td>
</tr>
<tr>
<td>Heart rate variation, %</td>
<td>−13.2 (−15.1 to −11.4)</td>
<td>−12.5 (−13.8 to −11.2)</td>
<td>.14</td>
</tr>
<tr>
<td>Blood pressure variability, mm Hg¶</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systolic</td>
<td>15.7 (14.7 to 16.7)</td>
<td>14.4 (13.4 to 15.1)</td>
<td>.10</td>
</tr>
<tr>
<td>Diastolic</td>
<td>12.3 (11.5 to 13.1)</td>
<td>11.9 (11.5 to 12.3)</td>
<td>.18</td>
</tr>
</tbody>
</table>

*Values are given as mean (95% confidence interval) unless otherwise specified.
†Average daytime blood pressure values in the 24-hour blood pressure measurement.
‡Diastolic daytime blood pressure > 85 mm Hg.
§Systolic daytime average blood pressure > 135 mm Hg and diastolic daytime average blood pressure ≤85 mm Hg.
¶Average percentage change of nighttime blood pressure compared with the daytime values.
||Within-subject SD of all blood pressure readings during the daytime measurement period.

Figure 1. Relationship between systolic circadian blood pressure variation (top) and diastolic circadian blood pressure variation (bottom) and extent of white matter lesions (WML).
one of these factors may be an elevated nighttime blood pressure. In our study, the extent of WML was strongly associated with differences in systolic circadian blood pressure. Contrary to earlier beliefs that the diastolic component of blood pressure is the major determinant of cardiovascular risk, there is a growing body of evidence that systolic hypertension may be a more important contributor to risk than its diastolic counterpart. Borderline isolated systolic hypertension was found to be the most common type of untreated hypertension among adults older than 60 years in the Framingham Heart Study, and was associated with an increased risk of progression to definite hypertension and the development of cardiovascular disease. Recently, Hachinski pointed out that vascular dementia is currently the only preventable major cause of dementia. Prevention should be best tried in persons at the “brain-at-risk” stage. Thus, from a clinical point of view, demonstration of cardiovascular disease should lead to a careful evaluation of nighttime blood pressure even in the absence of daytime arterial hypertension. If a pathological nighttime blood pressure increase was present, antihypertensive treatment in the evening or use of a long-acting agent may be useful to normalize nighttime blood pressure and thus may decrease the risk of further cerebrovascular complications.

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Table 2. Results of the Stepwise Multiple Linear Regression Analysis*

<table>
<thead>
<tr>
<th>Variable</th>
<th>Coefficient (95% Confidence Interval)</th>
<th>Standardized Partial Regression Coefficient</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Systolic circadian blood pressure variation†</td>
<td>1.93 (0.73 to 3.13)</td>
<td>0.905</td>
<td>.001</td>
</tr>
<tr>
<td>Age</td>
<td>0.96 (0.02 to 2.06)</td>
<td>0.397</td>
<td>.02</td>
</tr>
<tr>
<td>Diastolic circadian blood pressure variation†</td>
<td>0.840 (−0.31 to 1.99)</td>
<td>0.211</td>
<td>.07</td>
</tr>
<tr>
<td>Triglyceride level</td>
<td>0.033 (−0.044 to 0.11)</td>
<td>0.146</td>
<td>.11</td>
</tr>
<tr>
<td>Cholesterol level</td>
<td>−0.049 (−0.168 to 0.07)</td>
<td>−0.142</td>
<td>.10</td>
</tr>
<tr>
<td>Systolic blood pressure‡</td>
<td>0.093 (0.415 to 0.801)</td>
<td>0.078</td>
<td>.18</td>
</tr>
<tr>
<td>Diastolic blood pressure‡</td>
<td>0.466 (−0.343 to 1.28)</td>
<td>0.240</td>
<td>.07</td>
</tr>
<tr>
<td>Blood pressure variability§</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systolic</td>
<td>0.764 (−0.767 to 2.29)</td>
<td>0.207</td>
<td>.09</td>
</tr>
<tr>
<td>Diastolic</td>
<td>0.713 (−1.22 to 2.65)</td>
<td>0.164</td>
<td>.10</td>
</tr>
</tbody>
</table>

* The coefficient gives estimates for how much the dependent variable (white matter lesions) will change if the respective variable is increased by 1 and the other variables are held constant. The standardized partial regression coefficient gives the coefficients that would be obtained if all variables were standardized. If there was just one predictor, then this parameter would be its correlation with the dependent variable. Multiple R² = 0.39, P = .005.
† Average percentage change of nighttime blood pressure compared with the daytime values.
‡ Average daytime blood pressure values in the 24-hour blood pressure measurement.
§ Within-subject SD of all blood pressure readings during the daytime measurement period.

Figure 2. Odds ratio (mean and 95% confidence interval) of having white matter lesions (WML) according to circadian blood pressure variation and blood pressure levels. Normotensive subjects with systolic nighttime blood pressure decrease were used as controls (odds ratio = 1). Decrease indicates decrease of systolic nighttime blood pressure compared with daytime values; increase, increase of systolic nighttime blood pressure compared with daytime values.

REFERENCES


40. Hachinski V. Preventable senility: a call for action against the vascular demen-