Relationship Between Circadian Blood Pressure Patterns and Progression of Early Carotid Atherosclerosis
A 3-Year Follow-Up Study

Dirk Sander, MD; Christian Kukla, MD; Jürgen Klingelhofer, MD; Kerstin Winbeck, MD; Bastian Conrad, MD

Background—Arterial hypertension is a major risk factor for cardiovascular damage. The results of several studies suggest that target organ damage is greater in hypertensive persons with high blood pressure variability.

Methods and Results—During 3.3 years of follow-up, we studied the relationship between circadian blood pressure changes and the progression of early carotid atherosclerosis in 286 patients aged >55 years. Blood pressure patterns were evaluated with a long-term blood pressure monitor, and the extent of atherosclerosis was measured as the intima-media wall thickness (IMT) of the common carotid artery. Patients were subdivided according to blood pressure variability. The progression of IMT was significantly greater in the patients with increased systolic blood pressure variability (0.11 mm/y [95% CI 0.09 to 0.14] versus 0.05 mm/y [0.03 to 0.08]; \( P < 0.005 \)) even after adjustment for other risk factors. Multivariate regression analysis revealed the daytime systolic blood pressure variability to be the best predictor for the progression of IMT. Raised daytime systolic blood pressure variability (>15 mm Hg) is associated with an increased relative risk of the development of early atherosclerosis (3.9 [1.4 to 11.1]; \( P < 0.01 \)) and of cardiovascular events (1.87 [1.08 to 3.20]; \( P < 0.01 \)).

Conclusions—The daytime systolic blood pressure variability is a strong predictor of early carotid atherosclerosis progression and is useful to define the risk-benefit ratio of therapeutic approaches. (Circulation. 2000;102:1536-1541.)

Key Words: blood pressure ■ intima-media thickness ■ carotid arteries ■ ultrasonics ■ cardiovascular diseases

Arterial hypertension is a major risk factor for cerebrovascular diseases. One causal link for this association was the development of atherosclerosis. The use of B-mode ultrasound offers the opportunity to assess the intima-media wall thickness (IMT) of the common carotid artery (CCA) as a reliable marker for the extent of atherosclerosis. Previous investigations found hypertension to be either associated or not associated with carotid atherosclerosis. Interestingly, it has been shown that 24-hour blood pressure recordings correlate more closely with target organ damage than do casual blood pressure readings.

Intra-arterial beat-to-beat blood pressure monitoring has clearly shown that blood pressure is highly variable. Despite the difficulties in the assessment of blood pressure variability, particularly with noninvasive techniques, evidence from cross-sectional studies suggests that target organ damage is greater in hypertensive persons with high blood pressure variability. In a longitudinal study, blood pressure variability assessed intra-arterially before treatment predicted the severity of target organ damage after several years of follow-up. In a retrospective study, we demonstrated the major impact of circadian blood pressure patterns on the development of early carotid atherosclerosis and found that systolic daytime blood pressure variability was most closely related to the extent of IMT. The objective of our study was to prospectively analyze the relationship between changes in circadian blood pressure patterns and the progression of early carotid atherosclerosis.

Methods

Subjects
From a series of 424 initial evaluated inpatients >55 years old (mean age 68 years [95% CI 66 to 70 years], 200 women and 224 men) who were hospitalized to rule out a neurological disorder and were without previous cerebral infarction on brain CT/MRI or a known history of cerebrovascular disease or myocardial infarction, 286 patients were included in this follow-up study. To minimize a possible referral bias caused by the hospital-based study population, hypertensive patients for whom a secondary cause of arterial hypertension was revealed were excluded in the initial series. Follow-up was not possible in 138 patients because these patients decided not to participate further in the study (n=59) or because no further follow-up information could be obtained (n=79). We found no significant differences for age, sex, and several risk factors (pack-years of smoking, cholesterol, triglycerides, ischemic...
heart disease (IHD), systolic and diastolic blood pressure values, circadian blood pressure variation, daytime systolic and diastolic blood pressure variability, heart rate, heart rate variability, IMT) between the follow-up group and the excluded 138 patients. Follow-up was possible for at least 3 years in 272 patients, whereas 14 patients died during the 3-year follow-up period. The study was approved by the local institutional review board. All patients provided informed consent before they were entered into the study. Based on the results of the initial 24-hour blood pressure measurement (average of 2 measurements with an time interval of 3.9 days [3.2 to 4.6 days]), the patients were subdivided into 2 groups (Table 1): 68 patients showed an increased systolic blood pressure variability (>15 mm Hg), and 204 patients showed a normal systolic blood pressure variability (≤15 mm Hg).

**Blood Pressure Measurements**

Long-term blood pressure measurements (ABD-Monitor 90207; Spacelabs) were made with an oscillometric device. Validation studies with this monitor demonstrated no significant differences...
compared with intra-arterial measurements. The measurements were made at 15-minute intervals. The daytime values were determined between 6 AM and 10 PM, and the nighttime values were determined between 10 PM and 6 AM. Blood pressure measurements and duplex ultrasonography were repeated once a year during follow-up. Circadian blood pressure variation was defined as the average percentage change in mean blood pressure values at night compared with the daytime values. Heart rate variability was defined as the within-subject SD of mean heart rate during the daytime measurement period. Blood pressure variability was defined as the within-subject SD of all systolic and diastolic readings during the daytime measurement period. A daytime systolic blood pressure variability of >15 mm Hg was defined as pathologically increased. This cutoff point was chosen because this value was exceeds the upper 95% CI (14.9 mm Hg) of the average daytime systolic blood pressure variability of all 286 patients. Thus, patients with a blood pressure variability below or above this value were classified as having normal or increased blood pressure variability, respectively. A comparable cutoff value was used in other studies. During follow-up, blood pressure variability changed in 12 patients from ≤15% to >15% variability and in 10 patients from >15% to ≤15% variability. However, for statistical analysis, the average value of the initial measurements was used. Based on the results of the initial 24-hour blood pressure measurement, 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 blood pressure <85 mm Hg). If hypertension was diagnosed, blood pressure was optimized according to the guidelines of the International Society of Hypertension with lifestyle changes and antihypertensive drugs (ACE inhibitors, diuretics, β-blockers) to attain normotensive blood pressure values. The long-term measurement of blood pressure was made on the left side in right-handed patients and vice versa after relevant differences between the sides had been ruled out through conventional checks of blood pressure. The 24-hour blood pressure measurements, no patient received additional medication that might have affected the circadian blood pressure rhythmicity. All patients maintained a number-coded diary in which activities and particular events were recorded. The analysis of this diary revealed no significant differences for several activities between both subgroups.

**Carotid Artery Measurements**

All Duplex ultrasonography investigations were performed by the same investigator with a 7.5-MHz linear-array transducer. Both internal carotid arteries were categorized as normal, plaque (1% to 29% reduction), moderate stenosis (30% to 70% reduction), or severe stenosis (>70% reduction) according to the European Carotid Surgery Trial (ECST) criteria. The measurements of CCA IMT were made according to the Atherosclerosis Risk in Communities (ARIC) study protocol. When an optimal longitudinal image was obtained, it was stored on a videotape. This procedure was repeated 3 times for each side. The longitudinal B-scan frames were digitized and analyzed with a computerized image analysis system by an investigator blinded to the blood pressure measurements. IMT measurements were performed 8 to 18 mm proximal to the tip of the flow divider. In this 1-cm segment, 11 measurements of the IMT of the far wall were automatically attempted at 1-mm increments with the image analysis system, and the IMT of the segment was estimated as the mean of these 11 measurements. To enhance the reproducibility of carotid measures, standardized interrogation angles were used according to the recommendations described previously. From the average of 3 images per artery, a mean lumen diameter and a mean IMT (1/2[left plus right]) were determined as measures of current lumen diameter and wall thickness of the CCA, respectively. In every patient, the follow-up measurements were performed at the same location as in the initial measurement. The Spearman correlation between all the IMT measurements at baseline and all the measurements performed 3 years later was 0.86 (variability between 15 mm Hg and 0.82 variability >15 mm Hg), indicating a good reproducibility of the IMT measurements during follow-up. The intraobserver reproducibility between the 3 baseline IMT measurements was high (r=0.96). Early atherosclerosis was defined as an age-adjusted IMT of >1.5 mm. The progression of early carotid atherosclerosis was defined as the difference between the last and the first IMT measurement and was normalized as the change of IMT per year.

**Statistical Analysis**

All values are given as mean and 95% CI. Independent t tests were used to test differences between the groups. Adjustment for multiple comparisons was made with the Bonferroni method. The variation in IMT between subgroups according to age, pack-years of smoking, cholesterol, triglycerides, prevalent IHD, circadian blood pressure variation, daytime systolic and diastolic blood pressure variability, systolic and diastolic blood pressure, heart rate, and heart rate variability was tested by ANCOVA with SYSTAT (SPSS Inc). The covariate adjusted mean values were computed with this software. Multivariate linear regression analysis was performed with forward selection followed by backward elimination of covariates, resulting in an equation in which only covariates that significantly increase the predictability of the dependent variable are included. All covariates included in the final model were tested for interactions with each other. Because the tolerance values for each covariate were >0.5, no correction for collinearity of the data was necessary. Age, pack-years of smoking, cholesterol, triglycerides, prevalent IHD, systolic and diastolic blood pressure values, circadian blood pressure variation, heart rate, heart rate variability, and daytime systolic and diastolic blood pressure variability were selected as independent variables; IMT was the dependent variable. The IMT data were entered as continuous values in the mode. The outcome events studied were fatal plus nonfatal cardiovascular morbidity events. Survival curves in patients with normal and increased blood pressure variability were estimated by the Kaplan-Meier product-limit method and compared by the Mantel (log-rank) test. A calculated difference of P<0.05 was considered to be statistically significant.

**Results**

No significant differences were found between the patient groups regarding several cardiovascular risk factors (Table 1). The development of sustained hypertension was comparable between both groups. In contrast, patients with increased variability showed an increased incidence of isolated systolic hypertension and of IHD (Table 1). These patients also developed a significantly larger progression of IMT (Table 1). This association remains nearly unchanged even after adjustment for the other risk factors with ANCOVA. Accordingly, a significant and linear relationship was found between IMT progression and initial systolic blood pressure variability (r=0.52; P<0.01). However, there were distinct differences in the progression of IMT depending on circadian blood pressure patterns. We observed the most increased age-adjusted IMT progression in patients with increased daytime systolic blood pressure variability (>15%) and additional nighttime blood pressure increases (0.15 mm Hg [0.068 to 0.239 mm Hg]). In contrast, patients with normal variability (≤15 mm Hg) and nighttime blood pressure decrease revealed the lowest IMT progression (0.06 mm Hg [0.047 to 0.073 mm Hg]).

To evaluate the influence of the different risk factors in IMT progression, a stepwise multivariate linear regression analysis was performed. The daytime systolic blood pressure variability was the best predictor of the IMT progression (Table 2). In addition, systolic blood pressure, age, and pack-years of smoking were also significantly correlated with the IMT progression (Table 2). All other tested risk factors
did not significantly increase the predictability of the regression. The predicted model accounted jointly for 36% of the variation in IMT progression.

Early atherosclerosis (age-adjusted IMT > 1.5 mm) was initially observed in 36 of the 272 patients (13.2%) with a follow-up of at least 3 years. During this period, 70 patients (29.7%) of the 236 patients with an initial IMT of ≤1.5 mm developed early atherosclerosis. We observed no significant relationship between baseline IMT and change in blood pressure variability during follow-up ($r = 0.13$; NS). Univariate comparisons of the different baseline risk factors between patients with and without the development of early atherosclerosis during follow-up revealed significant differences for pack-years of smoking, systolic blood pressure, IMT progression, and daytime systolic and diastolic blood pressure variability (Table 3). The effect of antihypertensive treatment was comparable between both groups. The relative risk of the development of early atherosclerosis (age-adjusted IMT > 1.5 mm) increased significantly with raised daytime systolic blood pressure variability (> 15 mm Hg; Table 4), even after adjustment for the other risk factors. During follow-up, 36 patients developed fatal (n = 14) and nonfatal cardiovascular events (transient ischemic attack, myocardial infarction, stroke). Kaplan-Meier survival analysis (Figure 1) revealed a significantly higher rate of cardiovascular morbidity in patients with increased blood pressure variability (log-rank test). Accordingly, the relative risk of cardiovascular events was significantly increased (1.87 [1.08 to 3.20]; $P < 0.01$) in patients with raised blood pressure variability, even if all other risk factors were held constant.

### TABLE 2. Determinants of CCA IMT

<table>
<thead>
<tr>
<th></th>
<th>Coefficient (95% CI)</th>
<th>Standardized Partial Regression Coefficient</th>
<th>$P$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Systolic blood pressure variability</td>
<td>0.008 (0.005–0.012)</td>
<td>0.435</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Systolic blood pressure</td>
<td>0.001 (0.0006–0.002)</td>
<td>0.245</td>
<td>&lt;.01</td>
</tr>
<tr>
<td>Age</td>
<td>0.001 (0.0004–0.003)</td>
<td>0.182</td>
<td>&lt;.04</td>
</tr>
<tr>
<td>Pack-years of smoking</td>
<td>0.002 (0.001–0.004)</td>
<td>0.172</td>
<td>&lt;.05</td>
</tr>
<tr>
<td>Multiple $R^2$</td>
<td>. . .</td>
<td>0.36</td>
<td>&lt;.0001</td>
</tr>
</tbody>
</table>

The coefficient provides estimates for how much the dependent variable (IMT) 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.

### TABLE 3. Comparison of Patients With and Without the Development of Early Carotid Atherosclerosis (IMT > 1.5 mm) During Follow-Up

<table>
<thead>
<tr>
<th></th>
<th>Early Atherosclerosis</th>
<th>No Early Atherosclerosis</th>
<th>$P$</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of patients</td>
<td>70</td>
<td>166</td>
<td></td>
</tr>
<tr>
<td>Age, y</td>
<td>69 [64–73]</td>
<td>66 [64, 68]</td>
<td>NS</td>
</tr>
<tr>
<td>Sex, M/F</td>
<td>43/27</td>
<td>81/75</td>
<td>NS</td>
</tr>
<tr>
<td>Pack-years of smoking</td>
<td>28 [24–32]</td>
<td>20 [18, 22]</td>
<td>&lt;.01</td>
</tr>
<tr>
<td>Diabetes mellitus, n (%)</td>
<td>15 (21.4)</td>
<td>24 (14.5)</td>
<td>NS</td>
</tr>
<tr>
<td>Blood pressure, mm Hg</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systolic</td>
<td>140 [135–146]</td>
<td>132 [129, 135]</td>
<td>&lt;.05</td>
</tr>
<tr>
<td>Diastolic</td>
<td>84 [80–88]</td>
<td>80 [78, 82]</td>
<td>NS</td>
</tr>
<tr>
<td>Cholesterol, mg/dL</td>
<td>248 [238–258]</td>
<td>225 [209, 241]</td>
<td>NS</td>
</tr>
<tr>
<td>Triglycerides, mg/dL</td>
<td>173 [155–199]</td>
<td>145 [111, 179]</td>
<td>NS</td>
</tr>
<tr>
<td>Blood pressure variation, %§</td>
<td>−9.9 [−13.7 to −6.1]</td>
<td>−8.6 [−10.3 to −6.9]</td>
<td>NS</td>
</tr>
<tr>
<td>Nighttime blood pressure increase, no. of patients, (%)</td>
<td>16 (22.8)</td>
<td>32 (19.2)</td>
<td>NS</td>
</tr>
<tr>
<td>Daytime blood pressure variability, mm Hg</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diastolic</td>
<td>12.9 [11.6–14.1]</td>
<td>10.7 [10.2–11.1]</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Daytime heart rate, bpm</td>
<td>70 [66–74]</td>
<td>71 [67–75]</td>
<td>NS</td>
</tr>
<tr>
<td>Daytime heart rate variability, bpm¶</td>
<td>8.9 [7.7–10.1]</td>
<td>8.3 [7.5–9.1]</td>
<td>NS</td>
</tr>
<tr>
<td>Initial IMT, mm</td>
<td>1.21 [1.10–1.32]</td>
<td>1.15 [1.12–1.20]</td>
<td>NS</td>
</tr>
<tr>
<td>IMT progression, mm/y</td>
<td>0.14 [0.11–0.17]</td>
<td>0.06 [0.05–0.07]</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Adjusted IMT progression, mm/y**</td>
<td>0.12 [0.09–0.15]</td>
<td>0.05 [0.04–0.06]</td>
<td>&lt;.005</td>
</tr>
</tbody>
</table>

Values in brackets indicate 95% CI. See Table 1 for explanation of footnotes.
Discussion

The results of this prospective 3-year follow-up study showed that circadian blood pressure patterns, and particularly the systolic daytime blood pressure variability, are positively associated with the progression of ultrasound measures of carotid artery wall thickness, a marker of atherosclerosis. A multivariate regression analysis revealed that this parameter is the strongest independent predictor of IMT progression. Our data suggest an additional 0.005 to 0.012 mm/y progression of IMT for every mm Hg increase in blood pressure variability and a significantly increased relative risk of the development of early atherosclerosis (age-adjusted IMT >1.5 mm) with raised daytime systolic blood pressure variability (>15 mm Hg). The results cannot be explained in terms of established risk factors for cardiovascular disease, because the association remains nearly unchanged after adjustment for several other indices of disease risk. In addition to blood pressure variability, there was a significant impact of systolic blood pressure on IMT progression in the multivariate model. Our results corroborate previous findings. In some studies, hypertension was found to be associated with carotid atherosclerosis, whereas no correlation was found in other investigations. A recent investigation with casual blood pressure measurements reported both systolic hypertension and pulse pressure to be risk factors for the progression of atherosclerosis.

One could argue that our results may have been influenced by a selection bias concerning the patient population because blood pressure measurements were performed on an inpatient basis. However, the data for circadian blood pressure variability and blood pressure variability were in general comparable to the findings of an outpatient population. One possible shortcoming of the present study is the high number of patients lost during follow-up. However, we observed no significant differences in the distribution of several risk factors between the follow-up and the nonparticipant group. It seems therefore unlikely that there is an important selection bias concerning our main results.

One major determinant of blood pressure variability is the sensitivity of baroceptor function. Vascular structural changes may reduce baroceptor sensitivity in hypertension; therefore, the question arises of whether the increased blood pressure variability is a cause or simply an index of increased IMT. However, the inverse relationship between blood pressure variability and baroceptor sensitivity was independent of the reduction in baroceptor sensitivity associated with blood pressure and age. We observed no significant relationship between baseline IMT and change in blood pressure variability during follow-up. In addition, we failed to find a significant difference in the extent of initial IMT in patients who developed early atherosclerosis during follow-up compared with those who did not. These observations make it unlikely that a concomitant decrease in baroceptor sensitivity due to vascular structural changes accounts for the significant increased blood pressure variability in this group.

Recently, Karmack et al described an elevated carotid atherosclerosis after exaggerated blood pressure responses during mental stress. They detected a positive and significant association between blood pressure reactivity and average IMT for both systolic and diastolic blood pressures. In contrast to these findings, no clear relationship were obtained between mental stress and heart rate variability changes. Because the arterial wall of large vessels was more susceptible to intermittent stress than to continuous stress, it is conceivable that wide oscillations in blood pressure increase the extent of oscillatory shear stress. Recent studies demonstrated that oscillatory shear stress causes a sustained activation of pro-oxidant processes with increasing NADH oxidase activity and stimulation of adhesion molecule expression, resulting in redox-sensitive gene expression. In contrast, laminar shear stress appears to induce compensatory antioxidant defenses. Furthermore, oscillatory shear stress is associated with an increased macrophage density of atherosclerotic plaques, indicating plaque instability. These results indicate that the alteration of vessel wall tension associated with the increased blood pressure variability may initiate...

![Kaplan-Meier survival analysis for fatal and nonfatal cardiovascular events in patients with increased (>15 mm Hg) and normal (<15 mm Hg) blood pressure variability. Survival analysis adjusted for IHD.](image-url)
early atherosclerosis formation due to unique signals generated by oscillatory shear stress. The increased blood pressure variability observed in patients with increased blood pressure variability is associated with an increased risk of acute myocardial infarction across a 3-year follow-up period. Thus, it is possible that the link between blood pressure variability and cardiovascular risk was the enhanced development and progression of atherosclerotic lesions in the carotid and probably coronary bed. The reactivity hypothesis that exaggerated blood pressure responses exhibit more extensive atherosclerosis implies that stress exposure, as well as stress responsiveness, may contribute to disease risk.

In a prospective study, each incremental 0.1 mm of carotid IMT was associated with an 11% increased risk for acute myocardial infarction across a 3-year follow-up period. Thus, it is possible that the link between blood pressure variability and increased cardiovascular risk was the enhanced development and progression of atherosclerotic lesions in the carotid and probably coronary bed. The reactivity hypothesis that exaggerated blood pressure responses exhibit more extensive atherosclerosis implies that stress exposure, as well as stress responsiveness, may contribute to disease risk.

B-mode ultrasonography provides the opportunity to relate risk factors to atherosclerosis in patients with early lesions. In addition to other well-defined risk factors, we propose to take the daytime systolic blood pressure variability into account in further trials as a strong predictor for the development and progression of early atherosclerosis measured with B-mode ultrasonography. Although it is not known so far whether antihypertensive medication could normalize an increased daytime systolic blood pressure variability, the pronounced contribution of this parameter to the development of early atherosclerosis in hypertensive patients favors early antihypertensive treatment if this constellation is found. In addition, the development of antihypertensive agents with an effect on tonic blood pressure level and blood pressure variability may increase the positive effects of treatment on cardiovascular complications.

References

Relationship Between Circadian Blood Pressure Patterns and Progression of Early Carotid Atherosclerosis: A 3-Year Follow-Up Study
Dirk Sander, Christian Kukla, Jürgen Klingelhöfer, Kerstin Winbeck and Bastian Conrad

Circulation. 2000;102:1536-1541
doi: 10.1161/01.CIR.102.13.1536
Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2000 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circ.ahajournals.org/content/102/13/1536

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Circulation can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Circulation is online at:
http://circ.ahajournals.org//subscriptions/