Does Abnormal Circadian Blood Pressure Pattern Really Matter in Patients With Transient Ischemic Attack or Minor Stroke?

WenWen Zhang, PhD; Dominique A. Cadilhac, PhD; Leonid Churilov, PhD; Geoffrey A. Donnan, MD; Christopher O’Callaghan, PhD; Helen M. Dewey, PhD

Background and Purpose—Patients with stroke are more likely to have impaired autonomic nervous function and abnormal circadian blood pressure (BP) patterns. It remains unclear whether circadian BP patterns in patients with transient ischemic attack or minor stroke (National Institutes of Health Stroke Scale ≤3) differ from those in the normal population.

Methods—Participants were assessed using a 24-hour ambulatory BP monitor and a short-term measurement of heart rate variability.

Results—There were 76 patients (mean age, 67.2 years; 57.9% men; and 61.8% transient ischemic attack) and 82 controls (65.6 years; 54.9% men). A history of hypertension was more prevalent in patients (72.4%; controls 48.8%). Circadian BP patterns were distributed similarly among patients and controls, and heart rate variability was also consistent between patients and controls.

Conclusions—In contrast to previous findings among patients with acute stroke, patients with transient ischemic attack or minor stroke had similar BP patterns and autonomic nervous system function, when compared with controls. (Stroke. 2014;45:00-00.)

Key Words: ambulatory blood pressure monitoring ■ autonomic nervous system ■ ischemic attack, transient

Circadian blood pressure (BP) patterns are defined by day and night BP changes measured by 24-hour ambulatory BP monitoring with a dipper pattern considered normal (decline in nocturnal BP ≈10%–20%). Nondipper, reverse dipper, and extreme dipper circadian patterns are considered abnormal because of their association with end organ damage and worse prognosis.1,2 People with hypertension have a greater prevalence of abnormal circadian BP patterns, whereas people with normal circadian BP variation have a high risk of stroke, and abnormal circadian BP patterns are more prevalent in patients with stroke (70%–90% versus <50% in nonstroke populations).3,4 The mechanisms of altered circadian BP patterns are unclear and considered multi-factorial, with the autonomic nervous system likely playing an important part, especially among patients with hypertension.7 Acute stroke may alter autonomic function8 and thereby affect circadian variation; however, there are limited data about circadian BP patterns and autonomic function among patients with transient ischemic attack (TIA) or minor stroke.

Given the similarities in the pathogenesis of stroke and TIA, we hypothesized that abnormal BP patterns would be more common, and autonomic nervous system function more frequently impaired, in patients with TIA or minor stroke when compared with controls.

Methods

Patients aged ≥18 years with TIA or minor stroke (National Institutes of Health Stroke Scale ≤3) with no prior history of stroke were recruited within 7 days after their initial event (Austin Hospital or the Northern Hospital TIA Clinic, Melbourne, Australia). Controls were age and sex group-matched and recruited among family members or friends of patients; people attending the Austin Health Hypertension clinic; or volunteers via local newspaper advertisements. Definitions of TIA and minor stroke and detailed inclusion/exclusion criteria are presented in Table I in the online-only Data Supplement.

The sample size was estimated to be 80 for both patient and control groups with 0.8 power, 0.05 α (2-sided test) based on differences in proportions of BP patterns among stroke populations because no data from TIA populations were available when this study was designed.23 This study was approved by the Human Research Ethics Committees at Austin Health and the Northern Hospital.
A face-to-face interview, clinic BP measurements, 15-minute ECG-based heart rate variability (HRV) for autonomic nervous system function assessment were conducted for all participants. Patients with atrial fibrillation were excluded from HRV analysis. All patients had brain imaging within 24 hours of presentation to hospital.

Circadian BP pattern classification was based on the percent decline in nighttime BP compared with daytime BP (Table II in the online-only Data Supplement).1

The normal ranges of ambulatory BP were defined as follows: daytime BP <135/85 mm Hg, nighttime BP <120/75 mm Hg, 24-hour BP <130/80 mm Hg.11

Statistical analysis software STATA/IC 10.1 was used. Comparisons of categorical variables were made using χ² test or Fisher exact tests, and Student t test or Wilcoxon–Mann–Whitney rank-sum test for continuous variables. Risk differences were calculated to describe the difference in proportions of abnormal BP patterns between patients and controls.

Results
We screened 309 patients and 124 were invited to participate; 76 provided consent. Eighty-two controls were recruited (46 family members/relatives, 11 from Hypertension Clinic, and 25 volunteers).

Table 1 shows the characteristics of participants. Acute ischemic changes were identified in 12 patients (12/76, 15.8%) using computed tomography and in 27 patients (27/50, 54%) using MRI. The mean 24-hour (patients 127/72 mm Hg; controls 125/70 mm Hg) day and night ambulatory BPs were not significantly different between patients and controls, and all were within the normal range (Table III in the online-only Data Supplement).

The systolic BP patterns were similarly distributed among patients and controls (Figure; risk difference, –0.03; 95% confidence interval, –0.17 to 0.12; P = 0.74). No significant differences were found on HRV parameters when comparing patients with controls (Table 2).

Participants with hypertension were significantly more likely to have abnormal BP patterns (risk difference, –0.17; Table 1. Comparison of Characteristics Between Patients and Controls

<table>
<thead>
<tr>
<th></th>
<th>Patients (n=76)</th>
<th>Controls (n=82)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y, mean (SD)</td>
<td>67.2 (10.6)</td>
<td>65.6 (12.6)</td>
</tr>
<tr>
<td>Men, n (%)</td>
<td>44 (57.9)</td>
<td>45 (54.9)</td>
</tr>
<tr>
<td>Body mass index,* kg/m², mean (SD)</td>
<td>28.7 (4.3)</td>
<td>26.9 (4.2)</td>
</tr>
<tr>
<td>Epworth Sleepiness scale,* mean (SD)</td>
<td>6.7 (4.8)</td>
<td>4.8 (3.8)</td>
</tr>
<tr>
<td>Smoking, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Current smoker</td>
<td>8 (10.5)</td>
<td>6 (7.3)</td>
</tr>
<tr>
<td>Ex-smoker</td>
<td>38 (50.0)</td>
<td>31 (37.8)</td>
</tr>
<tr>
<td>History, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension†</td>
<td>55 (72.4)</td>
<td>40 (48.8)</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>18 (23.7)</td>
<td>15 (18.3)</td>
</tr>
<tr>
<td>Hyperlipidemia</td>
<td>35 (46.1)</td>
<td>39 (47.6)</td>
</tr>
<tr>
<td>Atrial fibrillation†</td>
<td>13 (17.1)</td>
<td>1 (1.2)</td>
</tr>
<tr>
<td>Ischemic heart disease</td>
<td>16 (21.1)</td>
<td>11 (13.4)</td>
</tr>
<tr>
<td>Obstructive sleep apnea</td>
<td>8 (11.3)</td>
<td>2 (2.7)</td>
</tr>
</tbody>
</table>

* t-test: P<0.05.
† Fisher test, P<0.05.

Table 2. Comparison of Heart Rate Variability Between Patients and Controls

<table>
<thead>
<tr>
<th></th>
<th>Patients (n=63)</th>
<th>Controls (n=80)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maximum RR, ms</td>
<td>1007.7 (160.5)</td>
<td>967.3–1048.1</td>
</tr>
<tr>
<td>Minimum RR, ms</td>
<td>731.8 (138.6)</td>
<td>697.0–766.7</td>
</tr>
<tr>
<td>Mean RR, ms</td>
<td>872.0 (149.1)</td>
<td>834.4–909.5</td>
</tr>
<tr>
<td>SDNN, ms</td>
<td>43.1 (24.3)</td>
<td>37.0–49.2</td>
</tr>
<tr>
<td>SD of ∆RR, ms</td>
<td>24.3 (13.8)</td>
<td>20.8–27.8</td>
</tr>
<tr>
<td>RMSSD, ms</td>
<td>24.3 (13.8)</td>
<td>20.9–27.8</td>
</tr>
<tr>
<td>LF, nu</td>
<td>59.5 (20.1)</td>
<td>54.4–64.6</td>
</tr>
<tr>
<td>HF, nu</td>
<td>34.7 (16.6)</td>
<td>30.6–39.0</td>
</tr>
<tr>
<td>LF, ms²</td>
<td>227.5 (304.9)</td>
<td>144.5–271.2</td>
</tr>
<tr>
<td>HF, ms²</td>
<td>152.9 (259.3)</td>
<td>71.0–166.9</td>
</tr>
<tr>
<td>LF/HF ratio</td>
<td>2.6</td>
<td>2.1–3.1</td>
</tr>
</tbody>
</table>

CI indicates confidence interval; HF, high-frequency band, 0.15-0.4 Hz; LF, low-frequency band, 0.04-0.15 Hz; NN, normal-to-normal QRS interval; nu, normalized units; RMSSD, the square root of the mean squared difference of successive NNs; RR, R-wave-to-R-wave interval on ECG; and SDNN, the SD of the average NN intervals.
95% confidence interval, –0.32 to –0.01; \( P=0.04 \) and suppressed HRV (\( P<0.05 \)) than participants without hypertension.

**Discussion**

This study provides the first evidence that the distribution of circadian BP patterns in patients with TIA or minor stroke is similar to controls, in whom the proportion of abnormal BP patterns was no greater than in other nonstroke populations.\(^3,4\) Similarly, this is the first study to examine autonomic function prospectively using HRV in patients with TIA or minor stroke. Our results in patients with TIA contrast with observations of suppressed HRV values in stroke\(^8,12,13\) or after acute brain injury.\(^14\)

Given that brain injury is considered to be an important mechanism for impaired autonomic nervous function and abnormal circadian BP,\(^12\) the mild nature of the ischemic brain injury in our patient sample might explain why autonomic nervous system function was reasonably intact.

Despite potential limitations related to sample size, study design, and the well-controlled BP in patients, this study provides new evidence that patients with TIA and minor stroke are no more likely to have abnormal circadian BP patterns or suppressed HRV than in nonstroke populations.

**Acknowledgments**

We thank all staff members from the Stroke Unit and the Hypertension clinic at Austin hospital for assisting with recruitments.

**Disclosures**

None.

**References**

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Data Supplement (unedited) at:
http://stroke.ahajournals.org/content/suppl/2014/01/14/STROKEAHA.113.004058.DC1

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Supplementary Table I  Eligibility criteria for participants
Supplementary Table II  The four circadian BP patterns
Supplementary Table III  Comparison of the ambulatory BP between patients and control participants
<table>
<thead>
<tr>
<th>Subjects</th>
<th>Inclusion criteria</th>
<th>Exclusion criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Patients</strong></td>
<td>18 years or older</td>
<td>Co-existing life-threatening condition with life expectancy &lt; six months</td>
</tr>
<tr>
<td></td>
<td>Clinical diagnosis of TIA* or minor stroke†</td>
<td>Severe disabilities likely to interfere with the ability to attend the hospital for BP monitoring and to comply with wearing an ambulatory BP monitor device</td>
</tr>
<tr>
<td></td>
<td>TIA or minor stroke within last seven days</td>
<td></td>
</tr>
<tr>
<td></td>
<td>No history of stroke</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Able to give informed consent</td>
<td>Participation in another clinical study</td>
</tr>
<tr>
<td><strong>Controls</strong></td>
<td>18 years or older</td>
<td>Co-existing life-threatening condition with life expectancy &lt; six months</td>
</tr>
<tr>
<td></td>
<td>No history of stroke or TIA</td>
<td>Severe disabilities likely to interfere with the ability to attend the hospital for BP monitoring and to comply with wearing an ambulatory BP monitor device</td>
</tr>
<tr>
<td></td>
<td>Able to give informed consent</td>
<td></td>
</tr>
</tbody>
</table>

* TIA: Transient Ischemic Attack was defined in the classical way as a sudden neurological deficit of presumed vascular origin lasting less than 24 hours.†Minor stroke: defined as NIHSS (the National Institutes of Health Stroke Scale) $\leq 3$, and symptoms lasting $> 24$ hours.
<table>
<thead>
<tr>
<th>BP patterns</th>
<th>The percent decline in nocturnal BP*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dipping pattern or “dippers”</td>
<td>≥ 10% ~ &lt; 20%</td>
</tr>
<tr>
<td>Non-dipping pattern or “non-dippers”</td>
<td>≥ 0 ~ &lt; 10%</td>
</tr>
<tr>
<td>Extreme dipping pattern or “extreme dippers”</td>
<td>≥ 20%</td>
</tr>
<tr>
<td>Reverse dipping pattern or “reverse dippers” or “risers”</td>
<td>&lt; 0</td>
</tr>
</tbody>
</table>

BP: blood pressure; *The percent decline in nocturnal BP (%) = \((\text{mean daytime BP} - \text{mean nighttime BP}) \times 100/ \text{mean daytime BP}\).³
### Supplementary Table III  
Comparison of the ambulatory BP between patients and control participants

<table>
<thead>
<tr>
<th>BP (mm Hg)</th>
<th>Patients (N = 76)</th>
<th>Controls (N = 82)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean (SD)</td>
<td>95% CI</td>
</tr>
<tr>
<td>Daytime</td>
<td></td>
<td></td>
</tr>
<tr>
<td>SBP</td>
<td>129.52 (12.4)</td>
<td>126.5 - 132.5</td>
</tr>
<tr>
<td>DBP</td>
<td>74.2 (10.0)</td>
<td>71.8 - 76.5</td>
</tr>
<tr>
<td>Nighttime</td>
<td></td>
<td></td>
</tr>
<tr>
<td>SBP</td>
<td>119.3 (10.3)</td>
<td>115.6 - 123.1</td>
</tr>
<tr>
<td>DBP</td>
<td>65.9 (8.4)</td>
<td>63.2 - 68.6</td>
</tr>
<tr>
<td>24-hour overall</td>
<td></td>
<td></td>
</tr>
<tr>
<td>SBP</td>
<td>127.3 (13.5)</td>
<td>124.3 - 130.2</td>
</tr>
<tr>
<td>DBP</td>
<td>72.3 (10.6)</td>
<td>70.0 - 74.7</td>
</tr>
</tbody>
</table>

BP: blood pressure; SBP: systolic blood pressure; DBP: diastolic blood pressure; CI: confidence interval; SD: standard deviation.
References:

