Parallel Morning and Evening Surge in Stroke Onset, Blood Pressure, and Physical Activity

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Background and Purpose—A circadian variation with a morning peak on waking and arising is known to occur in both blood pressure (BP) and cardiovascular event onset. A second peak in BP has been described to occur after an afternoon sleep (siesta). This study was designed to investigate the hypothesis that the 2-peak diurnal variation of BP is dependent on physical activity and occurs in parallel with the diurnal variation of stroke onset.

Methods—The diurnal variation of stroke onset was compared with the diurnal variation of BP, pulse rate (PR), and physical activity in 3 independent groups of Greek hypertensives 51 to 80 years of age (633 stroke patients, 379 subjects with 24-hour ambulatory BP monitoring, and 50 subjects with 24-hour physical activity monitoring through wrist devices).

Results—The diurnal variation of stroke onset, BP, and PR all showed 1 morning and 1 evening peak with a decline in the afternoon and at night that occurred in parallel with the diurnal variation in physical activity (P<0.001 for differences among morning, afternoon, evening, and nighttime intervals in BP, PR, activity, and stroke). The afternoon decline in BP, PR, and activity was significant only in subjects with a siesta.

Conclusions—The 2-peak diurnal variation in stroke onset occurred in parallel with the variation in BP, PR, and physical activity. These data support the hypothesis that an abrupt change in physical activity is not only a major determinant of the 2-peak diurnal variation of BP but also an important triggering factor for a cerebrovascular event. (Stroke. 2002; 33:1480-1486.)

Key Words: blood pressure ▪ circadian rhythm ▪ monitoring, ambulatory ▪ stroke ▪ stroke onset

A circadian variation in the onset of cardiovascular events has been observed in several studies, with the highest incidence occurring during morning hours.1–5 Speculations about underlying physiological factors include relationship to diurnal variations observed in the production of hormones such as cortisol, insulin, and catecholamines, as well as sympathetic tone affecting heart rate and blood pressure (BP), platelet aggregability, blood viscosity, and fibrinolytic activity.6–10 The abrupt change in physical activity on awaking and arising is believed to be the major determinant of the diurnal variation of most of the above factors.6–8

Noninvasive ambulatory BP (ABP) monitoring allows BP to be measured repeatedly throughout the full 24-hour period while patients carry out their usual daily activities at work and at home and even during sleep. In a previous study that examined the 24-hour ABP profiles of 203 Greek hypertensives, we found 2 peaks in BP and pulse rate (PR), 1 in the morning and 1 in the evening.11 Assessment of individual patient’s sleeping times showed that 75% of participants had an afternoon nap (siesta) while undergoing 24-hour ABP monitoring. This period was associated with a significant drop in systolic and diastolic BPs close to the levels of the nighttime period.11,12 Thus, both the morning and evening peaks of BP and PR seemed to be activity dependent because all occurred on awaking and arising.

We hypothesized that the activity-dependent 2-peak pattern of BP diurnal variation might be related to the circadian variation of stroke onset. To investigate this hypothesis, we compared the circadian variation of stroke onset with 24-hour ABP and PR profiles and 24-hour physical activity profiles in 3 independent groups of Greek hypertensives.

Patients and Methods

Three independent groups of hypertensive subjects 51 to 80 years of age with data on stroke onset, ABP, PR, and physical activity were included in the study. Data on stroke onset, ABP, and PR were obtained from a stroke database and an ABP monitoring database; physical activity data were obtained prospectively. A group of normotensive stroke patients was also studied.

Stroke Database

Stroke data were provided by a prospective observational study in patients admitted to the Acute Stroke Unit or the wards of the...
University Department of Clinical Therapeutics (Alexandra Hospital, Athens) from 1992 to 2000. All patients had brain CT scan on admission, and 70% had a repeated CT scan after 4 to 10 days. Eligibility criteria were as follows: age >18 years, first-ever stroke, atherothrombotic stroke or intracerebral hemorrhage, and time between onset and hospitalization <7 days. Patients with transient ischemic attack, subarachnoid hemorrhage, or recurrent stroke were excluded. Time of stroke onset was obtained from relatives or patients themselves when possible. Patients with unknown onset or onset during sleep (symptoms on awakening) were excluded. Patients with treated or untreated hypertension (history of hypertension before admission for stroke) who were 51 to 80 years of age were included in this analysis. Normotensive patients (no history of hypertension) who fulfilled the same inclusion criteria were also studied as a different group. Single supine BP measurements were taken by physicians on admission using standard mercury sphygmomanometers (Korotkoff phase V for diastolic BP).

**ABP Database**

ABP data were taken from the Hypertension Center ABP database (Third University Department of Medicine, Sotiria Hospital, Athens) collected from 1993 to 2001. ABP was measured with SpaceLabs 90207, a noninvasive portable oscillometric device (SpaceLabs Inc), using the same standardized protocol in all subjects as follows. The recorders were programmed to measure BP at 20-minute intervals for 24 hours and were always applied on a routine workday. Before each ABP monitoring, the accuracy of the devices was tested against a mercury column (Y connector) by manual activation. Three succeeding readings were taken to ensure that BP values did not differ by >5 mm Hg from measurements made with a mercury sphygomanometer. Patients were instructed to follow their usual daily activities but to stay still with the forearm extended during each ABP reading. They were asked to keep a brief diary specifying the time when they went to bed and were out of bed during sleep times.

Subjects 51 to 80 years of age who were untreated with elevated clinic BP (≥140/90 mm Hg on at least 2 visits) or treated regardless of BP levels were included. Each patient was represented by 1 ABP monitoring record in this study. In patients with repeated ABP records, the last one was selected. ABP recordings were excluded if there were missing data on patient’s age, sex, antihypertensive treatment status, or sleeping times during ABP monitoring. Recordings with <30 successful daytime and/or <12 nighttime measurements of BP were excluded. BP measurements flagged by the monitor’s software as technically erroneous were also excluded, as were measurements with systolic BP <70 or >260 mm Hg or diastolic BP <40 or >150 mm Hg. Early readings taken <20 minutes after the monitor was attached to patient were also excluded because they were taken in the clinic.

**Physical Activity Database**

A sample of treated or untreated hypertensives 51 to 80 years of age was studied prospectively. Activity level and pattern were assessed during the entire 24-hour period on a usual workday with Advanced Mini Logger Actigraph devices (Ambulatory Monitoring, Inc). These devices are worn on the wrist of the nondominant arm and sense motion in 3 planes of acceleration above the threshold of normal motion in humans (zero crossing mode units). Patients were instructed to undertake their usual daily activities and to activate the event marker buttons of the device to indicate the times of going to bed for nighttime or daytime sleep (siesta) and arising from bed on awakening. The number of accelerated movements per time was plotted for the purpose of this study. These devices have been validated to distinguish sleep from wakefulness with >90% accuracy.

**Statistical Analysis**

One-way analysis of variance and Student’s t tests were used to compare multiple or 2 mean values, respectively. Stroke onset rate per hour was calculated for each period of the day (morning, afternoon, evening, and nighttime) by dividing the number of strokes observed by the number of hours in this time interval. Expected rate of strokes per hour is the total number of observed strokes divided by 24 (hours), and expected percent rate per hour is 100:24. Stroke percent per hour is the proportion of strokes observed during each time interval divided by the number of hours in this period. Figure 1 is based on percent rates of stroke onset per 2-hour interval. The chi-square test was used to compare the number of observed versus expected strokes in the morning, siesta, evening, and nighttime periods. Bonferroni’s correction for multiple comparisons was applied when appropriate. Results are expressed as mean±SD. A value of P<0.05 was considered statistically significant.

**Results**

**Stroke Data Set**

The stroke database included 1418 patients (mean age, 70±12 years; 60% men). According to study criteria, 183 patients were excluded because of unknown stroke onset and 131 because of stroke onset during nighttime sleep. Of the remaining 1104 subjects, 64 and 229 were also excluded because they were <51 and >80 years of age, respectively. A total of 811 stroke patients were included in the analysis (Table 1), of whom 633 had a history of hypertension (mean age, 69±7.6 years; 62% men; 73% treated) and 178 were normotensives (no history of hypertension; mean age, 68±8 years; 65% men). Eight-one percent of hypertensive subjects had thromboembolic stroke; 19% had intracerebral hemorrhage (89% and 11%, respectively, in normotensive subjects). The diurnal variation of stroke onset in the 633 hypertensive patients is shown in Figure 1a. Stroke onset rate was higher in the morning and evening hours and lower in the afternoon and at night (Table 2). Thus, 1 morning and 1 evening peak in stroke onset were observed. Normotensive subjects also had a 2-peak circadian variation with low stroke onset rate in the afternoon and at night (Figure 2, Table 2).

On admission, the average BP of hypertensive stroke patients was 161±33/90±15 mm Hg (systolic/diastolic). Untreated hypertensives had 10/4 mm Hg higher BPs compared with treated patients (P<0.0001). Patients with intracerebral hemorrhage had higher BPs (185±33/100±16 mm Hg) than those with thromboembolic stroke (P<0.0001). Normotensive subjects had lower BPs than both untreated and treated hypertensives (143±20/83±9.2 mm Hg, P<0.001).

**ABP Data Set**

A total of 1386 ABP records were drawn out of the computer, and 1268 (93%) could be evaluated (adequate ABP data with available information on patient’s age, sex, and treatment). These data were obtained from 735 subjects (many had ≥2 recordings) in the context of clinical trials or for diagnostic purposes (mean age, 52.0±12 years; 55% men). Forty-five subjects (6%) in whom sleeping times during ABP monitoring were not available were excluded, as were 318 subjects (43.3%) <50 and 9 (1.2%) >80 years of age. A total of 379 hypertensives (50% treated) fulfilled all the study selection criteria and were included in the analysis (Table 1). Patients’ characteristics are shown in Table 1. Afternoon sleep (siesta) during ABP monitoring was reported by 75% (n=285) of the subjects included in the study (90% of those ≥70 years of age).
The 24-hour profiles for systolic and diastolic BPs and PR are presented in Figure 1b through 1d. One morning and 1 evening peak in BP and PR were observed. The lower levels of BP were observed in the afternoon and at night and corresponded to the average patient-reported sleeping periods for both daytime and nighttime sleep. There was a large decline in PR during the night compared with the morning levels ($P<0.0001$) and a small decline in the afternoon ($P<0.05$) (Table 3). The afternoon declines in BP and PR were prominent in subjects who reported a siesta during ABP monitoring ($P<0.001$, Figure 3). On the other hand, in patients without a siesta, the BP decline was attenuated, and there was no change in PR (Figure 3). Because individuals wake up and rise at different times, to show the actual effect of rising on BP and PR, we took as time zero the reported rising time of all subjects (from diaries) and then plotted the changes in BP and PR at fixed 20-minute intervals for 3 hours before and after time zero. In Figure 4, the morning surge in BP and PR is presented by the use of reported waking times of individual subjects or the time of the day.

Physical Activity Data Set (Actigraphy)
A total of 52 hypertensive subjects (50% treated) were studied prospectively, and 2 were excluded because of inadequate actigraphy data (Table 1). The 24-hour profile of physical activity is presented in Figure 1e. The curve of the diurnal pattern of activity paralleled those of BP, PR, and stroke onset, with clear dissociation between high-activity morning and evening periods and low-activity afternoon and nighttime sleep (Figure 1e and Table 3). The low-activity periods corresponded to the average patient-reported sleeping periods for both daytime and nighttime sleep. As expected, an afternoon decline in activity was observed in only 41 subjects who had a siesta (data not shown). Twenty-four-hour curves for BP, PR, and physical activity in a subgroup of 23 subjects who had simultaneous ABP and actigraphy recordings are presented in Figure 5.

Discussion
This study provides information on the circadian variation of stroke onset compared with the diurnal profiles of BP, PR, and physical activity in 3 independent groups of Greek hypertensives of similar age. The major findings are that there were 2 peaks in stroke incidence and that these peaks occurred in parallel with peaks in BP, PR, and physical activity.

Acceleration of physical activity is regarded as the major determinant of the morning surge in BP.16–18 This was clearly shown in a study by Khoury et al,16 who found little change in BP and PR before and after awakening in subjects who remained supine and a sharp rise immediately on arising from bed 1 hour after awakening. In fact, the actual morning rise in BP is steeper than that shown in Figure 1b and 1c, which are
The causal factors of the evening peak in cardiovascular event onset are poorly understood and rarely discussed. It has been suggested that a secondary evening peak in myocardial infarction onset may be related to the ingestion of the evening meal or other trigger factors concentrated in those hours.19 However, in this study, the evening peak in BP and PR occurred in parallel with the evening peak in stroke onset, together with an acceleration of activity on arising from the afternoon sleep (Figures 1 and 3). Although there is no information in this study on whether stroke patients had a siesta on the day of the event or on their previous sleeping habits, these patients were similar to those in the ABP group (the same age and studied in the same city in the same period), 75% of whom had a siesta during ABP monitoring.

Therefore, it can be speculated that >50% of stroke patients in this study used to have a siesta and that many of the

TABLE 2. Stroke Onset Rate in Different Periods of the Day in Hypertensive and Normotensive Subjects

<table>
<thead>
<tr>
<th>Period</th>
<th>Time Interval</th>
<th>Strokes per Hour, n</th>
<th>Stroke Percent per Hour</th>
<th>Strokes per Hour, n</th>
<th>Stroke Percent per Hour</th>
</tr>
</thead>
<tbody>
<tr>
<td>Morning</td>
<td>6 to noon</td>
<td>39.2</td>
<td>6.2</td>
<td>12.7</td>
<td>7.1</td>
</tr>
<tr>
<td>Afternoon</td>
<td>Noon to 4</td>
<td>23.3</td>
<td>3.7</td>
<td>6.5</td>
<td>3.7</td>
</tr>
<tr>
<td>Evening</td>
<td>4 to 8</td>
<td>36.8</td>
<td>5.8</td>
<td>8.0</td>
<td>4.5</td>
</tr>
<tr>
<td>Night</td>
<td>8 to 6</td>
<td>15.8</td>
<td>2.5</td>
<td>4.4</td>
<td>2.5</td>
</tr>
<tr>
<td>Expected rate</td>
<td></td>
<td>26.4</td>
<td>4.2</td>
<td>7.4</td>
<td>4.2</td>
</tr>
</tbody>
</table>

P for χ² = <0.001

Figure 2. Diurnal variation of stroke onset in 178 normotensive patients (stroke database).
participants of previous studies showing a secondary evening peak in cardiovascular event onset had a period of afternoon inactivity (rest or nap), followed by an acceleration of activity. The finding that in this study the evening peak was more marked compared with that reported by previous studies may be attributed to the high proportion of participants with a siesta. Probably as a result of climatic, social, and cultural factors, the practice of siesta is common in Greece. Furthermore, in this study, siesta was found to be more common with increasing age (90% in participants >70 years of age). Although siesta is simply a cultural characteristic of Greece and other Mediterranean countries, this finding can be used to show that a change in the awake-asleep diurnal pattern may be associated with a parallel change in the diurnal pattern of BP, PR, and stroke onset, thereby supporting the hypothesis that activity-dependent phenomena may trigger a cerebrovascular event.

Limitations of the present study include bias as a result of subject selection and limits in generalizing the findings to other populations. Most important, because this study provided descriptive data for 3 separate patient populations, the findings cannot simply be combined for conclusions about causal relationships of stroke onset. Inaccuracies in data on stroke onset time are expected to have little impact on the study findings because patients with unknown time of onset or with symptoms on awakening were excluded. Although the physical activity data set included data from only 50 subjects, the probability value for the differences in activity among time intervals was lower than for the corresponding differences in BP or PR, which are based on data from a much larger sample (Table 3). Indeed, wrist actigraphy proved to be a more powerful tool for the discrimination between awake and asleep periods than ABP monitoring (eg, 75% nocturnal drop in activity compared with 10% to 15% for ABP or PR; Table 3); therefore, fewer subjects with actigraphy were required.

Altogether, these data support the view that endogenous factors play a major role in the pattern of the diurnal variation of cerebrovascular event onset because an alteration in the diurnal pattern of physical activity (because of the practice of siesta) appeared to result in an alteration in the diurnal pattern of hemodynamic factors and thus in the pattern of the stroke onset in a parallel manner. To define the precise role of the diurnal variation of several variables in the pathogenesis of cerebrovascular events, prospective outcome studies that take into account factors such as activity at onset, timing of last

<table>
<thead>
<tr>
<th>Period</th>
<th>Time Interval</th>
<th>Systolic BP, mm Hg</th>
<th>Diastolic BP, mm Hg</th>
<th>Pulse Rate, bpm</th>
<th>Physical Activity (n=50), zero crossing mode units</th>
</tr>
</thead>
<tbody>
<tr>
<td>Morning</td>
<td>7 to 3</td>
<td>136.7±14.5</td>
<td>85.3±10.7</td>
<td>76.3±11.1</td>
<td>204.5±33.3</td>
</tr>
<tr>
<td>Afternoon</td>
<td>3 to 6</td>
<td>128.9±15.7</td>
<td>78.0±12.0</td>
<td>74.2±11.8</td>
<td>149.9±50.8</td>
</tr>
<tr>
<td>Evening</td>
<td>6 to 11</td>
<td>135.3±15.6</td>
<td>83.3±11.3</td>
<td>73.2±10.8</td>
<td>173.7±45.4</td>
</tr>
<tr>
<td>Night</td>
<td>11 to 7</td>
<td>123.7±14.4</td>
<td>72.1±10.0</td>
<td>64.5±8.7</td>
<td>54.9±24.9</td>
</tr>
</tbody>
</table>

P for ANOVA <0.001 <0.001 <0.001 <0.0001

bpm indicates beats per minute.

Figure 3. Twenty-four–hour profiles of systolic and diastolic BP and PR in hypertensive subjects with (a) or without (b) a siesta during ABP monitoring.

Figure 4. Morning surge in BP and PR plotted according to reported time of waking (left) or clock time (right) (379 hypertensive subjects from the ABP monitoring database).
meal, and medication use are needed. Whether modifications of the diurnal BP and PR patterns (eg, with β-blockers administered in high-risk patients on awakening and waiting 1 hour before arising compared with standard dosing after arising) may affect cerebrovascular event incidence and onset timing also requires investigation in future trials.

Several other factors known to interfere with vasoconstriction and thrombus formation have been shown to exhibit activity-dependent diurnal variation. Platelet aggregability, which is an established prothrombotic factor, exhibits a sharp morning rise that is decidedly dependent on activity acceleration because it does not occur in subjects who remain supine and inactive. Morning elevations in catecholamines on assuming an upright posture have been described and are in accord with the observed morning rise in PR (Figure 1), which is regarded as a gross index of sympathetic nervous system activity. Finally, fibrinolytic activity exhibits major circadian fluctuations, which have been linked with the time of onset of myocardial infarction and stroke. It can be speculated that platelet aggregation, catecholamine release, fibrinolysis, and other activity-determined factors also exhibited parallel 2-peak diurnal variation in the patients of this study, thus contributing to the 2-peak diurnal variation of stroke onset.

There were some differences among the 3 data sets in the time and duration of the peak and trough periods in the 24-hour profiles (Figure 1). Therefore, the morning, afternoon, evening, and night intervals were arbitrarily chosen for each data set (Tables 2 and 3). In the ABP and actigraphy data sets in which individual patient’s sleeping times were available, the trough “in bed” periods in the 24-hour curves were precisely predicted (Figure 1b through 1e). Differences in the time intervals are probably due in part to the fact that the data sets were obtained from independent groups of subjects with different profiles of activity. Indeed, BP, PR, and activity curves obtained simultaneously from the same subjects in a subgroup of 23 participants in this study showed all these curves to have a strictly parallel pattern (Figure 4). On the other hand, hemodynamic factors may be associated more closely with physical activity than with cerebrovascular event onset.

What is noteworthy from these data are (1) the striking parallelism in the surge in stroke onset, BP, PR, and physical activity in the morning and evening (Figure 1) and (2) the similarity in the diurnal pattern of the stroke onset curve between hypertensives and normotensives (Figures 1a and 2). Considered together, these data support the hypothesis that the acceleration of physical activity on waking and arising results in abrupt changes in several activity-dependent factors, thereby creating thrombogenic and vasoconstricting conditions that in the presence of a vulnerable (prone to rupture) atherosclerotic plaque, might trigger a cerebrovascular event.3,4

References


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