Circadian Rhythmicity of Stroke Onset
Intracerebral and Subarachnoid Hemorrhage

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Background and Purpose: Our purpose was to describe and further understand the determinants of the time of onset of parenchymatous intracerebral hemorrhage and subarachnoid hemorrhage in patients enrolled in the Stroke Data Bank.

Methods: We analyzed the observed times of onset of intracerebral hemorrhage (n=237 patients) and subarachnoid hemorrhage (n=243 patients) compared with expected times of onset if the probability of onset was constant across all time intervals. We also analyzed the role of clinical features (if any) in explaining the findings.

Results: For intracerebral hemorrhage, 52.5% of patients reported onset times between 0600 hours and 1400 hours, with peak onset between 1000 and 1200 hours ($\chi^2=62.94$, df=11, $p<0.001$). Patients with subarachnoid hemorrhage were more likely to lack a history of hypertension compared with patients who had intracerebral hemorrhage ($\chi^2=23.3$, df=1, $p<0.001$). Patients with subarachnoid hemorrhage were more likely to have more uniform onset time throughout the day ($\chi^2=12.92$, df=7, $p=0.074$). However, subarachnoid hemorrhage patients with a history of hypertension were more likely to have peak onset times in mid-to-late morning compared with patients without such a history ($\chi^2=35.25$, df=10, $p<0.001$). The nonuniformity of onset times for intracerebral hemorrhage persisted even if patients with unknown onset times were treated as though their onset times were randomly distributed between 0000 and 0800 hours. Seasonal periodicity and the relation between initial systolic or diastolic blood pressure and time of onset for either type of hemorrhage were not observed.

Conclusions: Our data suggest that the time of onset for both intracerebral hemorrhage and subarachnoid hemorrhage patients with a history of hypertension is similar to the diurnal variation in blood pressure. (Stroke 1992;23:1420-1426)

KEY WORDS • circadian rhythm • hypertension • stroke onset

Circadian periodicity characterizes many normal physiological processes (including blood pressure regulation\textsuperscript{1-2} as well as several cardiovascular disorders, such as myocardial infarction.\textsuperscript{3} sudden cardiac death,\textsuperscript{3-4} and stroke.\textsuperscript{5-10} Factors known to be associated with the time of onset of strokes may provide important clues to stroke pathogenesis, treatment, and prevention. For example, occurrence of ischemic stroke tends to cluster during morning hours, particularly mid-to-late morning.\textsuperscript{5,7-10} This periodicity coincides with the peaks for plasma viscosity, hematocrit, protein concentration, and blood pressure.\textsuperscript{1-2,11-13}

Because patients with spontaneous intracranial hemorrhage frequently have higher recorded blood pressures than patients with ischemic infarction, one might expect a correlation between peak blood pressures and time of occurrence of the hemorrhage. Although two studies suggest such a relation,\textsuperscript{6,9} the importance of chronic arterial hypertension as the preeminent cause of intracerebral hemorrhage has recently been questioned.\textsuperscript{14-18} In this article, we extend the analysis of circadian rhythmicity of stroke onset\textsuperscript{10} to the occurrence of intracerebral hemorrhage (ICH) and subarachnoid hemorrhage (SAH) in an attempt to further define their pathogenesis.

Subjects and Methods

The design, methods of data collection, diagnostic categories, and participating institutions in the Stroke Data Bank have been described previously.\textsuperscript{19} Between
June 30, 1983 and June 30, 1986, 480 of 1,805 patients enrolled in the Stroke Data Bank had ICH (parenchymatous) or SAH. Time of onset was determined by the neurologist/investigator questioning either the patient or another person who observed the onset. All times of onset were recorded on a military time clock (0000-2359 hours). Double-entry validation of individual times of onset (and other data items) was not done. However, the entire Stroke Data Bank data set was rigorously recertified with valid value checks and consistency checks. Regardless of whether the time of onset could reliably be ascertained, “upon awakening” was recorded as either “yes,” “no,” or “unknown.” The systolic and diastolic blood pressures at the time of initial patient evaluation were noted.

As previously reported, we assumed that if the onset of the hemorrhage had no relation to the time of day, there would be an even distribution of cases throughout the day. The frequency of observed cases, in 12 2-hour intervals, was compared with the frequency expected as though onset times were uniformly distributed throughout the day. A $\chi^2$ goodness-of-fit test was performed to determine whether there was agreement between the observed distribution of the time of onset and the expected distribution if the time of onset was uniform throughout the day. For analyses in which the null hypothesis of uniformity was rejected, an $F$ test was used to test for a linear trend over time. Hypothesizing the presence of a linear trend is but one of a variety of alternatives. It is recognized that this method depends on the time of day that one begins to analyze the data. The data were first analyzed separately by diagnosis with omission of cases with unknown onset times as randomly distributed throughout the day. For these analyses, we assumed that all strokes with unknown onset times or on awakening occurred during this time period. A $\chi^2$ test of association was used to analyze the relation between a history of hypertension and hemorrhage type.

An attempt was made to associate the time of onset with history of hypertension (“no,” “yes—untreated,” “yes—treated”), initial systolic blood pressure (“low—119,” “120–149,” “150–179,” “180-high”), initial diastolic blood pressure (“low—79,” “80–94,” “95–109,” “110–high”), day of the week, month of the year, and alcohol intake (“never,” “1 drink/day,” “2–5 drinks/day,” “>5 drinks/day,” “unknown”). For parenchymatous ICH, an attempt was made to associate the time of onset with size of intracerebral hematoma (“absent,” “<1 cm,” “<½ lobe,” “<1 lobe,” “>1 lobe”) and site of hematoma (“deep” [sum of “putamen,” “thalamus,” “basal ganglia not further specified,” “internal capsule,” “pons,” “cerebellum,” and “brain stem not further specified”], “lobar” [sum of “subcortical” and “named lobar locations”]). In each instance, a $\chi^2$ goodness-of-fit test was used to determine whether any of the above variables were related to the time of onset. For some analyses, the frequency of observed cases was also compared by six 4-hour intervals to the frequency expected as though onset times were uniformly distributed throughout the day. Because of the expected small numbers of patients within each level of blood pressure and alcohol intake for several of these analyses, we used 4-hour intervals as the basis for analysis.

**Results**

The median age of the patients with parenchymatous ICH ($n=237$) was 61 years (range, 20–95 years). The male:female ratio was 134:103, or 1.3:1. The white:nonwhite ratio was 154:83, or 1.86:1. The median age of the patients with SAH ($n=243$) was 52 years (range, 17–88 years). The male:female ratio was 76:167, or 1:2.2. The white:nonwhite ratio was 117:126, or 1:1.08. For 105 of the 480 patients (ICH, $n=58$; SAH, $n=47$), the precise time of onset was unknown, since symptoms were noted on awakening.

For both ICH and SAH, statistical analyses were performed for the relation between time of onset and sex, race, day of the week, month of the year, history of hypertension, initial systolic blood pressure, initial diastolic blood pressure, and alcohol consumption during the previous 24 hours. There were no differences in onset times across sex and race groups. Collection of data pertaining to alcohol ingestion was incomplete in 46.4% and 43.2% of the patients with ICH and SAH, respectively. For the other analyses, the small numbers of observations in each cell (data not shown) did not permit statistically valid conclusions.

**Intracerebral Hemorrhage**

Figure 1 shows the frequency distribution, in 12 2-hour intervals, of the known time of onset of 179 patients with parenchymatous ICH. The majority of these patients (52.5%) reported onset times between 0600 and 1400 hours, with a peak between 1000 and 1200 hours. There was a smaller peak between 1800 and 2000 hours. The null hypothesis of uniformity of time of onset is rejected ($\chi^2=62.94$, df=11, $p<0.001$). In addition, the more sensitive $F$ test for linear trend was significant ($F_{(6,10)}=13.7$, $p=0.010$). Even if the entire cohort of 237 patients is analyzed by treating the cases with unknown onset times as randomly distributed between 0000 and 0800 hours, the null hypothesis of uniformity is still rejected ($\chi^2=21.78$, df=11, $p=0.0261$; Figure 2). There was no relation between time of onset and the site (deep versus lobar, $p=0.76$) or size ($p=0.61$) of the ICH. The pattern of mid-to-late morning preponderance of cases was consistent throughout the week.

**Subarachnoid Hemorrhage**

Figure 3 shows the frequency distribution, in 12 2-hour intervals, of the known time of onset of 196 patients with SAH. The majority of patients (50.5%) reported onset times between 0800 and 1600 hours, with peak occurrence between 1000 and 1200 hours. There was a smaller peak between 1400 and 1600 hours. The null hypothesis of uniformity of time of onset is rejected ($\chi^2=41.1$, df=11, $p<0.001$). When the sample is restricted to the 162 patients with onset times between 0800 hours and midnight, the null hypothesis of uniformity is not rejected ($\chi^2=12.92$, df=7, $p=0.074$). In addition, the more sensitive $F$ test for linear trend was
significant ($F_{(1,11)} = 11.8, p = 0.014$). When the entire cohort of 243 patients is analyzed by treating the cases with unknown onset times as randomly distributed between 0000 and 0800 hours, the null hypothesis of uniformity is not rejected ($\chi^2 = 15.62, df = 11, p = 0.1558$; Figure 4). Patients with SAH were more likely to lack a
FIGURE 3. Bar graph showing frequency distribution of subarachnoid hemorrhages with known times of onset. Null hypothesis of uniformity is rejected ($\chi^2=41.1$, df=11, $p<0.001$).

history of hypertension in comparison to patients with parenchymatous ICH; this difference was highly significant statistically ($\chi^2=23.3$, df=1, $p<0.001$). In addition, there was a robust tendency for patients with a history of hypertension to have onset times in the mid-to-late morning compared with patients without a history of hypertension ($\chi^2=35.25$, df=10, $p<0.001$; Table 1).

FIGURE 4. Bar graph showing frequency distribution of subarachnoid hemorrhages with known times of onset and with unknown times of onset randomly distributed between 0000 and 0800 hours. Null hypothesis of uniformity is not rejected ($\chi^2=15.62$, df=11, $p=0.1558$).
TABLE 1. Relation Between History of Hypertension and Time of Onset of Subarachnoid Hemorrhage

<table>
<thead>
<tr>
<th>Hypertension status</th>
<th>Time of onset of subarachnoid hemorrhage (hours)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0000-0359</td>
</tr>
<tr>
<td>None</td>
<td>5</td>
</tr>
<tr>
<td>Treated</td>
<td>3</td>
</tr>
<tr>
<td>Untreated</td>
<td>2</td>
</tr>
<tr>
<td>Total</td>
<td>10</td>
</tr>
</tbody>
</table>

Distribution of known onset times is shown with numbers of cases occurring in each 4-hour time period. For patients with a history of hypertension, relative proportion of cases occurring between 0800 and 1159 hours compared with other 4-hour intervals is significantly different ($\chi^2=35.251$, df=10, $p<0.001$) from proportion of cases in patients without a history of hypertension. Data for this analysis were missing from seven patients with subarachnoid hemorrhage.

Discussion

It has been well established that a diurnal variation in measured blood pressure occurs, with the peak reached in the period from midmorning to early afternoon. This pattern exists for normotensive and hypertensive individuals,1 as well as patients with stroke.1,2 This periodicity may be a consequence of circadian variations in the levels of plasma cortisol (which peaks at 0700 hours) and catecholamines (epinephrine peaks at 1100 hours, norepinephrine at 1100–1300 hours).2 Since patients with intracranial hemorrhage tend to have higher blood pressure levels than patients with ischemic infarction, diurnal and seasonal variation in the occurrence of hemorrhagic stroke would be expected.

Previous studies have suggested a diurnal variation in the occurrence of intracranial hemorrhage.5,9 Tsementzis et al5,9 who found no such relation in a study of 194 patients with SAH and 118 patients with ICH. Both types of hemorrhage showed a bimodal distribution, with a prominent initial peak between 1000 and 1200 hours. A less prominent peak was observed between 1800 and 2000 hours for SAH and between 1600 and 1800 hours for ICH. Intracerebral hemorrhage was found to be significantly less likely to occur between 0400 and 0600 hours than SAH or cerebral infarction. Intracerebral hemorrhage was more likely to occur during driving or alcohol consumption, while SAH was more likely to occur during use of the bathroom, sports, or sexual activity. Marshall6 reported 153 patients with intracranial hemorrhage and found that this diurnal effect was prominent in women, but that men had the highest incidence between 1800 and 2400 hours. In that study, however, the type of hemorrhage and associated variables (e.g., physical activity, alcohol intake) were not reported, and it is likely that some patients with hemorrhage were excluded from this analysis, since it was done before the use of computed tomographic scans.

Several investigations suggest the existence of seasonal rhythmicity in the incidence of intracranial hemorrhage.22–28 In some studies, increased incidence of24,27,28 and mortality from25,25 intracerebral hemorrhage in the winter months (December to March) have been documented. On the basis of physiological observations,2 exposure to severe cold, with resultant augmentation of catecholamine output, might contribute to the pathogenesis of ICH in certain cases.26 In one Japanese study, there was a highly significant ($p<0.001$) negative correlation between atmospheric temperature and blood pressure.29 We did not find a seasonal periodicity in the occurrence of ICH or SAH. The study of patients in climates less severe than Minnesota24 or Iowa28 may have minimized seasonal effects on the incidence of intracranial hemorrhage.

The present study demonstrates a preponderance of cases of ICH between 0800 and 1400 hours (peak between 1000 and 1200 hours) and cases of SAH between 0800 and 1600 hours (peak between 1000 and 1200 hours). In addition, there were smaller peaks of cases of ICH and SAH occurring at 1800–2000 hours and 1400–1600 hours, respectively. The former finding is similar to the data of Marshall6 but not comparable. The finding of smaller peaks for both ICH and SAH cannot be explained on the basis of available data, and potential mechanisms are purely speculative. Moreover, these smaller peaks represent only a small absolute difference in numbers of patients when compared with neighboring 2-hour time periods and arc thus of doubtful clinical significance. Although these data correlate well with the diurnal variation of blood pressure and confirm the results of previous studies,5,9 we were unable to show a relation between the initial systolic or diastolic blood pressure and the time of day of onset for either type of hemorrhage. One might expect that since most hemorraghes occur in deep structures supplied by vessels susceptible to damage by increased blood pressure, the morning peak in blood pressure would be preferentially associated with parenchymatous ICHs in deep sites and of larger size. On the other hand, some investigators believe that patients without evidence of hypertensive vascular disease (cardiomegaly, left ventricular hypertrophy, or retinopathy) tend to have larger hemorrhages and higher mortality.20 The lack of an observed relation between onset time, systolic and diastolic blood pressure, and the site and size of ICH in this study is somewhat surprising and unexplained.

In cases of SAH, patients were more likely to lack a history of hypertension. In this regard, two observations are of interest. The first is the suggestion of a linear trend in known time of onset of cases of SAH occurring only between 0800 hours and midnight, with a peak in the morning hours and declining frequency throughout the day. Second, for those patients with a history of hypertension, there was a highly significant ($p<0.001$) tendency for cases to cluster in the mid-to-late morning compared with patients without a history of hypertension. These results differ from those of Tsementzis et al, who found no such relation in a study of 194 patients with SAH. Our data suggest that this phenomenon may reflect a greater dependence on circadian variations in blood pressure in this subgroup. However, study of a
A larger group of patients appears necessary to confirm our findings. Practical considerations, as well as limitations inherent in the collection of any large data set, may explain some of the findings in this study. It is usually not possible to know the patient's blood pressure just before the hemorrhage occurs. The occurrence of "spontaneous" ICH in a variety of novel situations, such as cold exposure, drug abuse (cocaine, amphetamines, phencyclidine), dental pain, and after trigeminal manipulation, especially in previously normotensive patients, suggests that a significant acute (and perhaps transient) rise in blood pressure may damage arterioles and thus cause hemorrhage. In some instances patients have high blood pressure on initial evaluation, but others may be normotensive when first seen by medical personnel.

In the Stroke Data Bank, two thirds of the patients were admitted within 24 hours of stroke onset; patients with hemorrhage were admitted somewhat later than those with ischemic infarcts. As in other studies, the recording of certain information for this study, such as alcohol ingestion, was incomplete. Severity of illness, potential importance of longer time intervals between last alcohol use and onset of symptoms, validity of history elicited from patients and other observers, and other factors may have influenced the accuracy of data collection. In addition, patients with ICH were not systematically evaluated for evidence of hypertensive vascular disease. It is also possible that the occurrence of hemorrhage related to unusual causes may have been unsuspected, since the true incidence of intracerebral hemorrhage provoked by them in large populations is frequently unknown. Patient entry into the Stroke Data Bank was not population-based, which suggests potential bias in case enrollment. Some selection bias may be introduced by referral patterns, survival bias by later admission times, exclusion of cases with unknown onset times, or other factors. Although unlikely, it is possible that these factors may be disproportional by time of onset.

This study suggests a similarity between circadian rhythmicity of blood pressure and the time of onset of ICH in general and SAH with known times of onset between 0800 and 2359 hours in particular. However, it is clear that much remains to be learned about the causes of ICH and SAH and their time of occurrence. It is intriguing that there is a similarity in the time of onset for both ischemic and hemorrhagic stroke. Since the pathophysiological process(es) leading to ischemic and hemorrhagic stroke are distinct, it is reasonable to presume that the mechanism(s) of circadian rhythmicity of stroke onset may also differ between these groups of stroke cases, as well as between hemorrhagic stroke subtypes. In future patient encounters and clinical investigations in large populations, we should examine these issues to better understand the pathogenesis of hemorrhagic stroke in individual situations and thus increase the opportunities for prevention and treatment. Rapid evaluation of patients, particularly in the early hours after stroke onset, should facilitate these efforts.

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References


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