Circadian Variation in the Frequency of Ischemic Stroke

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The frequency of myocardial infarction and sudden death is increased between 6 AM and noon.

To determine whether the same is true for the onset of ischemic stroke, we studied 426 consecutive patients within 12 hours after the onset of their first hemispheric stroke. The frequency of onset of hemispheric stroke was significantly \( p=0.0001 \) higher from 6:01 AM to noon (56.1%) than from 12:01 PM to 6 PM (20.2%), from 6:01 PM to midnight (8.2%), and from 12:01 AM to 6 AM (15.5%). The identification of periods of high risk for vascular events may have important therapeutic implications, such as matching drug effects with vulnerability.

Ischemic events have been reported recently to follow a circadian rhythm.\(^1\)\(^2\) Myocardial infarction was shown to occur predominantly between 6 AM and noon\(^1\); similar circadian variation was seen in the occurrence of ST depression in patients with stabilized coronary artery disease.\(^2\) A circadian variation of cerebral ischemia was also reported, but with contradictory findings.\(^3\)\(^–\)\(^9\)

To investigate further the variability of the onset of cerebral ischemia, we studied 426 consecutive patients with hemispheric ischemic stroke in whom the time of onset of symptoms was prospectively determined at admission.

Subjects and Methods

Between January 1981 and December 1986, we screened all patients admitted to the University Hospital of Rome Policlinico Umberto I° because of a focal neurologic deficit. Those patients with clinical signs or symptoms of cerebral hemispheric ischemia were hospitalized in the Stroke Unit of the Department of Neurology. All patients had cerebral computed tomography within 48 hours to exclude other etiologies mimicking an ischemic stroke.

At admission, the time of onset of their symptoms was obtained from the patients whenever possible and otherwise was elicited from relatives. We included patients in our study only if it was possible to determine within approximately 30 minutes the time of onset of their stroke.

For patients who had their stroke while asleep, we considered the time of onset to be the hour in which the patient or a relative first became aware of the event. Assuming that the stroke could have occurred at any time during sleep, we also distributed the times of onset between the apparent onset and the hour 11 PM–midnight, when approximately all the patients went to sleep.

Frequency of onset was analyzed for the 24 hours and for the four 6-hour intervals in a day. The \( \chi^2 \) test for goodness of fit was applied to the number of observed versus expected strokes during each 6-hour interval. The interval with the highest incidence of events was quantified by calculating the ratio between the frequency of onset during it and the average frequency during the remaining three 6-hour intervals.

Results

During the 5 years of our study, 426 patients (183 women and 243 men, mean±SEM age 66±10 years) with a first ischemic hemispheric stroke were referred to our Stroke Unit; 335 patients were awake when their stroke occurred (onset between 6:01 AM and 11 PM), and the remaining 91 awoke with stroke symptoms (onset between 11:01 PM and 8 AM).

Frequency of onset of hemispheric stroke was 56.1% \((n=239)\) during the interval from 6:01 AM to noon (with an hourly peak between 7:01 and 8 AM).
FIGURE 1. Top: Graph of circadian variation of observed ischemic stroke onset. Between 11:01 PM and 8 AM, 91 patients had onset of stroke while asleep (individuals with onset while asleep not indicated). Bottom: Graph of circadian variation of ischemic stroke onset after redistribution of patients with onset while asleep between time of apparent onset and 11 PM. [n=70] (Figure 1), 20.2% (n=86) during the interval from 12:01 to 6 PM, 8.2% (n=35) from 6:01 PM to midnight, and 15.5% (n=66) from 12:01 to 6 AM. Thus, the incidence of stroke onset during the first interval was 3.8 times the average incidence during the remaining three intervals. The $\chi^2$ test quantified the significance of the difference ($p=0.0001$). Redistribution of the 91 patients who had their strokes while asleep shifts the percentages only to 51.6% for those with onset from 6:01 AM to noon and 12.6% for those with onset from 6:01 PM to midnight. The statistical evaluation is not significantly modified by these moderate shifts.

Cerebral computed tomography revealed no areas of low attenuation in 7% and lacunar lesions in 3% of the patients; the remaining 90% had lesions localized in the territory of the great vessels, primarily the internal carotid and middle cerebral arteries. No pattern of time of onset was defined for these different lesions with respect to the total population.

To evaluate the effect of risk factors for stroke on circadian rhythm, we analyzed subgroups of patients who smoked (n=130), were hypertensive (n=217), or had diabetes mellitus (n=65). For these subgroups (Figure 2), the circadian variation of stroke is similar to that for the entire population. A similar pattern was also detected for the subgroup of patients with atrial fibrillation (n=54) (Figure 3).

**Discussion**

Our data show that stroke onset is not random during 24 hours but that it has a characteristic...
distribution. Previous reports\textsuperscript{3–9} have identified a circadian rhythm of the onset of ischemic stroke. One such study by Marshall\textsuperscript{9} excluded embolic strokes, resulting in a selection bias. In that series, cerebral ischemic events showed a higher incidence of onset between midnight and 6 AM. Hemodynamic mechanisms, such as profound nocturnal fall in blood pressure due to impairment of vasomotor reflexes in older individuals, could have decreased cerebral blood flow to below critical values, thus determining the observed pattern. Hossman\textsuperscript{4} assumed that in the presence of stenosis of the extracranial and intracranial vessels, similar hemodynamic mechanisms were the likely cause of the event in the majority (30\%) of his patients who had their strokes between 1 and 5 AM. In contrast, other authors\textsuperscript{5–9} have shown a circadian variation very similar to that of our patients.

In our series, subgroups of patients identified by their risk factors for stroke showed similar circadian variations of the onset of symptoms. Such risk factors probably represent only a background against which pathogenetic mechanisms having rhythmic variations act. Thrombotic strokes could result from an increase in platelet aggregation and a reduction in fibrinolytic activity, which both occur during the morning.\textsuperscript{10,11} In fact, changes in platelet aggregation correlate with changes in plasma catecholamine levels, which actually increase between 6 and 9 AM.\textsuperscript{10} On the other hand, the fibrinolytic system represents reciprocal changes in the concentrations of tissue plasminogen activator (tPA) and its fact-acting inhibitor (PAI) during the morning; Kluft et al\textsuperscript{12} found high PAI activity in contrast to low tPA activity during the early morning, while this pattern was completely reversed at noon, when an increase in tPA activity and a decrease in PAI activity were observed.

Blood pressure demonstrates a circadian rhythm that overlaps that of stroke onset.\textsuperscript{13} The rupture and fragmentation of a carotid plaque provoked by an increase in arterial blood pressure, such as is already postulated for myocardial infarction,\textsuperscript{1} could lead to an embolic stroke as a result of the fragments lodging in the distal intracranial arterial tree.

Dewar and Weightman\textsuperscript{14} demonstrated an increased frequency of embolism in patients with valvular heart disease and atrial fibrillation between 8 AM and 4 PM. This agrees with the higher incidence of ischemic stroke onset during the early morning among our patients with atrial fibrillation and strongly suggests that the occurrence of cardiogenic embolic accidents, including stroke, follows a circadian rhythm.

The onset of myocardial infarction also demonstrates a circadian pattern, with most events occurring between 6 AM and noon, except in patients receiving \(\beta\)-adrenergic blocking agents during the 24 hours preceding the onset of infarction.\textsuperscript{1} In our series of patients, too few subjects took these drugs to allow statistical analysis. However, the pattern of incidence of myocardial infarction in individuals not treated with \(\beta\)-blockers closely overlaps that of our stroke patients, suggesting that both the cerebral and the cardiac circulations are affected by similar pathophysiologic mechanisms leading to ischemia.

In conclusion, our study contributes further evidence for a susceptibility to ischemic events between 6 AM and noon and gives further insights into the possible mechanisms leading to cerebrovascular ischemia. These observations may also be applicable to implementation of pharmacologic agents directed toward the prevention of strokes during these most vulnerable periods.

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References


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