Circadian Variation in Ischemic Stroke Subtypes

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Background and Purpose—While previous studies suggest that the peak time period for the occurrence of ischemic stroke is in the mid- to late-morning hours, detailed information pertaining to circadian variations among the various stroke subtypes has been limited. The purpose of our study was to define the circadian patterns of symptom onset in an acute stroke trial with an established system for stroke subtype classification.

Methods—An analysis was conducted on 1272 patients enrolled in the Trial of Org 10172 in Acute Stroke Treatment (TOAST) study. All patients had a documented time of stroke symptom onset, and all stroke subtype determinations were made by a single rater.

Results—The greatest portion of atherothrombotic strokes (25.7%), cardioembolic strokes (30.5%), and strokes of other/unknown mechanism (27.1%) occurred between 6:01 AM and 12:00 noon. The greatest portion of lacunar strokes (31.6%) were present on awakening. More than one half of the infarcts in this series were either present on awakening or occurred in the mid- to late-morning hours. The correlation between stroke subtype and time of symptom onset did not reach statistical significance (P=0.07, Pearson’s χ² method).

Conclusions—Although there is a trend for clustering of ischemic stroke in the morning hours, there is insufficient specificity to predict with any reasonable likelihood the stroke subtype according to the circadian pattern of symptom onset. (Stroke. 1999;30:1793-1795.)

Key Words: cerebral infarction ■ circadian rhythm ■ stroke, ischemic

Several hospital- or community-based studies have examined the time of onset of ischemic stroke.1-5 Most, but not all, studies have found an excess risk for events in the mid- to late-morning hours. A recent meta-analysis by Elliott6 identified a 55% excess risk for ischemic stroke in the time period between 6:01 AM and 12:00 noon. Information pertaining to ischemic stroke subtypes and circadian variation has been more limited; using stroke mechanism–based criteria, only relatively small, hospital-based series have been reported.7 In addition, circadian variation data from acute stroke clinical trials has not been reported in the past. Acute stroke trials have an advantage for this type of analysis, because precise determination of the time of symptom onset is required in these studies. To examine the time of onset of stroke as influenced by the presumed cause, we looked at the data collected in the Trial of Org 10172 for Acute Stroke Treatment (TOAST).

Subjects and Methods

The design of TOAST and the main results have been reported elsewhere.6-9 In brief, TOAST was a multicenter acute stroke trial that compared the effects of an intravenous heparinoid (danaparoid) against placebo in patients with ischemic stroke of <24 hours’ duration. Patients with all ischemic stroke subtypes were included.

Local investigators were asked to give their impression of the ischemic stroke subtype at baseline, at 7 days, and at 3 months. The results of ancillary diagnostic tests such as CT, MRI, vascular imaging, and echocardiography were considered in the stroke subtype determinations. The criteria for stroke subtype determination used in the TOAST study have been published elsewhere.10 To avoid interobserver disagreements, for the main study results as well as for this analysis all stroke subtype determinations were made by the principal investigator (H.P.A.) with data available at the end of follow-up.

The population for this analysis included all randomized patients. For patients with stroke present on awakening, the exact time of symptom onset could not be determined. For study purposes, the time of symptom onset for these individuals was calculated as the time he or she went to sleep, or if the patient awoke during the night, the last time he or she was symptom free. Because this is not an accurate reflection of the true time of symptom onset, these patients were analyzed in a separate category. For the remainder of the patients, the 24-hour day was divided in quartiles (12:01 AM to 6:00 AM, 6:01 AM to 12:00 noon, 12:01 PM to 6:00 PM, and 6:01 PM to 12:00 midnight). All comparisons were made with the Pearson χ² test.11

Results

A total of 958 patients had strokes that were sudden or gradual in appearance, and 323 patients had strokes present on awakening. Because 9 patients in the former category could not be assessed at the 3-month follow-up, 949 patients with sudden/gradual strokes and 323 with symptoms on awakening were included. Therefore, the total number of patients included was 1272.
The principal results of this analysis are presented in the Table. It can be seen that for the atherothromboembolic (ATH, 25.7%), cardioembolic (CE, 30.5%), and other/unknown strokes (OTH/UNK, 27.1%), the peak time for stroke occurrence was between 6:01 AM and 12:00 noon. The greatest portion of small-vessel/lacunar strokes (LAC, 31.6%) were present on awakening; for LAC with a defined time of onset, the peak period was between 12:01 PM and 6:00 PM (25.1%).

For all stroke subtypes, the least number of strokes occurred in the time period between 12:01 AM and 6:00 AM. Only 9.6% of ATH, 6.8% of CE, 3.9% of LAC, and 7.5% of OTH/UNK strokes occurred during this time period.

As mentioned above, strokes present on awakening were analyzed in a separate category. This was a sizable group of patients, and overall, OTH/UNK (35.0%) and LAC (30.0%) were the most frequent subtypes in this group. More than one half of all strokes in the study were either present on awakening or occurred between 6:01 AM and 12:00 noon (42% excess risk, 95% CI 23% to 63%). The Table also illustrates that for each time period, strokes of OTH/UNK mechanism were the most common. The majority of these events were UNK, because very few strokes in the TOAST study fell in the OTH category. The overall analysis did not reach statistical significance ($P = 0.07$).

An additional analysis was done in which strokes present on awakening were evenly distributed in the 8-hour period of 10:00 PM to 6:00 AM. However, this was far from being statistically significant ($P = 0.55$). A final analysis in which strokes of OTH/UNK cause were excluded also was not statistically significant ($P = 0.35$).

**Discussion**

Several groups of investigators have studied the circadian variation in stroke onset for ischemic stroke.1–5,12–16 Most studies have been in accordance with the findings in this study: the greatest time period for stroke onset is between 6:01 AM and 12:00 noon.

The methodology of previous studies has not been uniform. Some investigators chose to divide the clock in quartiles, as we did. Other researchers narrowed the time epochs further into 2-hour subunits. Using this method, Marler et al12 analyzed 1167 patients from the Stroke Data Bank and identified 10:00 AM to 12:00 noon as the period of greatest ischemic stroke risk. Haapaniemi et al13 evaluated 609 patients from the Helsinki University Hospital and found that during the weekdays 6 to 8 AM was the period of greatest stroke frequency, and the timing was shifted to 8 to 10 AM on weekends.

In terms of stroke subtypes, available information is limited. Marsh et al2 used a modification of the Harvard Cooperative Stroke Registry criteria in a relatively small, hospital-based series. In 151 patients, all stroke subtypes in their schema were most common in the 6:01 AM to 12:00 noon period. These investigators classified strokes as either large artery “atherothrombotic,” large artery “atheroembolic,” small artery, cardioembolic, or other/unknown. Ricci and colleagues14 used the Oxfordshire stroke classification system in their community-based stroke registry. This classification system is a clinical syndrome–based rather than a mechanism-based system, although it does include a category for lacunar strokes. In their analysis of 281 cerebral infarctions, they noted a preponderance of ischemic strokes between 6:01 AM and 12:00 noon, although the percentage of strokes occurring during sleep was significantly higher for lacunar strokes (33%).

Our study does not support the traditional teaching that thrombotic stroke is more likely to occur at night and that embolic stroke occurs during activity. According to this theory, large-artery thrombotic events are present on awakening in the majority of cases, presumably due to physiological, nocturnal dips in blood pressure and subsequent hemodynamic ischemia due to failure of cerebral autoregulation. To partially address this issue, 1 hospital-based series15 of 66 patients included a discrete category for watershed infarcts, but all 3 watershed strokes occurred during the daytime. This finding provides no support for the concept of hemodynamic cerebral ischemia during sleep.

Several explanations can be offered for the circadian patterns seen in our study. Blood pressure follows a circadian pattern, with highest levels achieved in the mid- to late-morning hours.17 Increased blood pressure may lead to higher rates of intraplaque hemorrhage and thereby increase the degree of stenosis in atherosclerotic vessels. Platelet studies have also shown higher rates of aggregation during the morning hours.18 In addition, blood viscosity has been noted to peak in the morning hours.19 Finally, other coagulation components, such as endogenous fibrinolysis, may be relevant. Endogenous tissue plasminogen activator (TPA) activity has been shown to be lowest in the morning, and this altered balance between thrombosis and fibrinolysis may be clinically germane.20

As mentioned above, acute stroke clinical trials rely on precise determination of the time of symptom onset as one of the primary inclusion criteria. Therefore, a clinical trial such as TOAST may be well-suited for studies such as this. On the other hand, deriving such data from a clinical trial analysis of only randomized patients imposes certain limitations as well. For example, patients who were screened but not enrolled because of exclusion criteria would not be included in this report. Similarly, it is possible that some patients may not have been entered in TOAST if they presented to the emergency room at a time when the investigator was “unavailable.” We cannot exclude the possibility that patients presenting in the late evening or early morning hours were underrepresented in TOAST for this reason. However, we do not believe this is a major confounding variable, because most centers in TOAST were experienced in providing “around-the-clock” treatment as part of acute stroke protocols.

The findings of our study also have practical implications for current and future treatment of stroke patients. First, hospitals that propose to treat stroke patients with acute interventions such as intravenous or intra-arterial thrombolysis will require heightened levels of awareness during the mid- to late-morning hours. It is obvious, however, that 24-hour-a-day availability will be required for acute stroke teams.
Another important implication of our study is that to extend the benefits of acute stroke treatment, an agent with a longer time window is desperately needed. At present, intravenous TPA has been found to be useful for patients who can be treated within 3 hours of symptom onset.21 Because the pivotal TPA study relied on the time at which the patient was last seen in a normal state, most patients with strokes present on awakening (25.4% of the patients in our study) are excluded from TPA consideration. A pharmacological agent with 12- or 24-hour benefits would allow some of these patients to be treated.

In conclusion, our study has found that most ischemic stroke events occur either on awakening or in the mid- to late-morning hours. Further studies are warranted to see whether the biological causes of the early-morning increase in thrombotic risk can be modified.

## Appendix

The following clinical centers (hospital and local principal investigator are named) participated in the TOAST study: University of Iowa Hospitals and Clinics, B.H. Bendixen; Albuquerque VA Medical Center, A. Bruno; Long Island Jewish Medical Center, R.B. Libman; University of California San Diego Medical Center, C.M. Jackson; J.F. Rothrock; Marshfield Clinic, P.N. Karanjia; St Louis University, C.M. Burch, C.R. Gomez; University of Southern California, M.J. Fisher; University of Illinois Medical Center, Chicago, C.M. Helgason; Indiana University, J. Biller; University of Mississippi Medical Center, D.L. Gordon; Rush–Presbyterian–St Luke’s Medical Center, P.B. Gorelick; Montefiore Medical Center, D.M. Rosenbaum; SUNY Health Sciences Center, Syracuse, A. Culebras; Mt Sinai Medical Center, J.M. Weinberger; Rhode Island Hospital, E. Feldmann; Columbia–Presbyterian Medical Center, J.P. Mohr; Northwestern University, J. Biller; University of South Carolina, T.L. Hwang; University of Missouri, J.A. Byer, H.H. White; University of South Alabama, J.F. Rothrock, R.M. Zweifler; Rochester General Hospital, J. Hollander; Oregon Health Sciences University, B.M. Coull; Hennepin County Medical Center, D.C. Anderson; Kern Medical Center, C.J. Wrobel; Iowa Methodist Medical Center, B.B. Love; Medical University of South Carolina, E.L. Hogan; Washington University, C.Y. Hsu; Yale University, P.B. Fayad, L.M. Brass; University of California at Los Angeles, J.L. Saver; Wayne State University, S. Chaturvedi; Beth Israel Hospital, Boston, S.J. Warach, C.I. Mayman; Wichita Institute for Clinical Research, M.A. Mandelbaum; Maimonides Medical Center, A.E. Miller; Medical College of Ohio, N.N. Futrell; St Paul–Ramsey Medical Center, M. Ramirez-Lassepas; Boston University, C.S. Kase; and Evanston Hospital, D. Homer.

## Acknowledgments

The TOAST study was funded by the US Public Health Service, the National Institutes of Health, and the National Institute of Neurological Disorders and Stroke grants R0-1-NS-27863 and R01-NS-27960. The authors acknowledge the assistance of Michael Hansen in statistical analysis. Additional support, including a supply of the study drug, was given by Organon, Inc, West Orange, NJ.

## References

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Stroke. 1999;30:1792-1795
doi: 10.1161/01.STR.30.9.1792
Stroke is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0039-2499. Online ISSN: 1524-4628

The online version of this article, along with updated information and services, is located on the
World Wide Web at:
http://stroke.ahajournals.org/content/30/9/1792