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Larger ischemic cores and poor collaterals among large vessel occlusions presenting in the late evening

Anirudh Sreekrishnan, MD, MHS¹, Steffen Tiedt, PhD², Pierre Seners, MD, PhD^{1,3,4}, Nicole Yuen, MSc¹, Jean-Marc Olivot, MD⁵, Michael Mlynash, MD, MS¹, Maarten G Lansberg, MD, PhD¹, Jeremy J Heit, MD, PhD⁶, Sarah Lee, MD¹, Patrik Michel, MD⁷, Davide Strambo, MD⁷, Alexander Salerno, MD, PhD⁷, José Bernardo Escribano Paredes, MD⁸, Emmanuel Carrera, MD⁸, Gregory W Albers, MD¹

¹Department of Neurology, Stanford Hospital, Palo Alto, CA

²Institute for Stroke and Dementia Research, University Hospital, LMU Munich, Munich, Germany

³Neurology Department, Hôpital Fondation A. de Rothschild, Paris, France

⁴Institut de Psychiatrie et Neurosciences de Paris (IPNP), UMR_S1266, INSERM, Paris

⁵Department of Neurology and UMR Clinical investigating Center 1436 Centre Hospitalier, Hospitalier Universitaire de Toulouse, Toulouse, France

⁶Department of Neurosurgery, Stanford Hospital, Palo Alto, CA

⁷Department of Neurology, Lausanne University Hospital, Lausanne, Switzerland

⁸Department of Neurology, Geneva University Hospital, Geneva, Switzerland

Abstract

Correspondence to Anirudh Sreekrishnan, MD, MHS, Division of Stroke, Department of Neurology, Stanford Health Care, 213 Quarry Rd, Palo Alto, CA 94304. asreekri@stanford.edu.

Guarantors

A. Sreekrishnan serves as guarantor and accepts full responsibility for the design and analysis of the study as well as allocation of the study data.

Contributorship

Study conception and design: Anirudh Sreekrishnan, Steffen Tiedt

Data collection: Anirudh Sreekrishnan, Pierre Seners, Nicole Yuen, Jean-Marc Olivot, Maarten G Lansberg, Patrik Michel, Davide Strambo, Alexander Salerno, José Bernardo Escribano Paredes, Emmanuel Carrera

Analysis and interpretation of results: Anirudh Sreekrishnan, Steffen Tiedt, Pierre Seners, Michael Mlynash, Maarten G Lansberg, Jeremy J Heit, Gregory W Albers

Draft manuscript preparation: Anirudh Sreekrishnan, Steffen Tiedt

All authors reviewed the results and approved the final version of the manuscript.

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Conflicts of Interest and Funding

All other authors have nothing to declare.

Ethics Approval and Informed Consent

The individual registry data was approved by the local ethics committee at each center. Data acquired from Switzerland, ethical commission approval and patient consent were not required according to current local and national legislation as all data were anonymized before analysis and as patient's refusal of scientific use of their data was duly honored. Study design and analysis of this cohort was approved by the Stanford institutional review board (IRB), assurance # FWA00000935 (SU), on 9/15/2022.

Background: Components critical to cerebral perfusion have been noted to oscillate over a 24-hour cycle. We previously reported that ischemic core volume has a diurnal relationship with stroke onset time when examined as dichotomized epochs (i.e. Day, Evening, Night) in a cohort of over 1,500 large vessel occlusion (LVO) patients. In this follow-up analysis, our goal was to explore if there is a sinusoidal relationship between ischemic core, collateral status (as measured by HIR), and stroke onset time.

Methods: We retrospectively examined collection of LVO patients with baseline perfusion imaging performed within 24 hours of stroke onset from four international comprehensive stroke centers. Both ischemic core volume and HIR, were utilized as the primary radiographic parameters. To evaluate for differences in these parameters over a continuous 24-hour cycle, we conducted a sinusoidal regression analysis after linearly regressing out the confounders age and time to imaging.

Results: A total of 1506 LVO cases were included, with a median ischemic core volume of 13.0 cc (IQR: 0.0–42.0) and median HIR of 0.4 (IQR: 0.2–0.6). Ischemic core volume varied by stroke onset time in the unadjusted ($p = 0.001$) and adjusted ($p = 0.003$) sinusoidal regression analysis with a peak in core volume around 7:45PM. HIR similarly varied by stroke onset time in the unadjusted ($p = 0.004$) and adjusted ($p = 0.002$) models with a peak in HIR values at around 8:18PM.

Conclusion: The results suggest that critical factors to the development of the ischemic core vary by stroke onset time and peak around 8PM. When placed in the context of prior studies, strongly suggest a diurnal component to the development of the ischemic core.

Key Terms:

Ischemic stroke; Large Vessel Occlusions; Perfusion Imaging; Circadian Rhythm

Introduction

Components critical to cerebral perfusion, including blood pressure¹ and cerebral blood flow,^{2,3} have been noted to oscillate over a 24-hour cycle in both clinical and pre-clinical studies. These discrepancies are thought to be primary drivers of the differences in stroke incidence^{4,5} and perfusion parameters^{5,6} over a 24-hour period. We have previously reported⁵ that ischemic core volume has a diurnal relationship with stroke onset time. In a cohort of over 1,500 large vessel occlusion (LVO) patients, we observed the highest core volumes in the evening. We also found a similar relationship with the Hypoperfusion Intensity Ratio (HIR), a known marker of collateral status.^{7,8} Our primary conclusions were that factors critical to the establishment to the ischemic core seem to fail most often in the late evening, explaining the large cores observed in this timeframe. However, this analysis evaluated stroke onset time in epochs (i.e. Day, Evening, Night) with an inability to examine the relationship at a more granular level (i.e. over a 24-hour continuous cycle).

A previous study⁶ has suggested that ischemic core volumes may follow a sinusoidal relationship with stroke onset time, peaking around 11:00PM. The goal of this follow-up analysis was to re-examine the relationship between perfusion parameters critical for the establishment of an ischemic core against a 24-hour continuous cycle. Our primary aim was

to evaluate if these radiographic markers follow a sinusoidal curve and secondarily establish a peak in these parameters as a direct comparison to prior work.⁶ These results would better hone our understanding of when factors critical to perfusion, like collateral status, fail and could guide clinical management, from the development of neuroprotection trials to the patient selection for thrombectomy.

Methods

Full details of the original analysis have been previously reviewed in detail.⁵ Briefly, this cohort is a retrospective collection of LVO cases (ICA, M1 or M2) with baseline perfusion imaging performed within 24 hours of stroke onset from four comprehensive stroke centers in United States, France, and Switzerland. All sites included both thrombectomy-treated and untreated patients and had approval from local ethics committees in-line with individual guidelines. Stroke onset time was systematically defined⁵ as the midpoint between last seen well (LSW) and symptom discovery, in line with prior work for unwitnessed strokes.⁹ Both core (defined as an apparent diffusion coefficient $<620 \times 10^{-6} \text{ mm}^2/\text{s}$ on diffusion-weighted imaging or relative cerebral blood flow $<30\%$ on CT-perfusion) and HIR (defined as the volume of $T_{\text{max}} > 6\text{s}$ divided by $T_{\text{max}} > 10\text{s}$) were utilized as the primary radiographic parameters. To evaluate for differences in these parameters over a continuous 24-hour cycle, we conducted a sinusoidal regression analysis using the 'R' package 'DiscoRhythm' after linearly regressing out the confounders age and time to imaging similar to previous work.⁶ All statistics were performed using 'R', V.4.2.2.

Results

A total of 1506 LVO cases were included in this subsequent sinusoidal analysis, for which the demographics have been previously described in detail⁵ and briefly reviewed in Table 1. In our cohort, the median ischemic core volume was 13.0 cc (IQR: 0.0–42.0) and varied by stroke onset time ($p = 0.001$) with a peak in ischemic core at approximately 8:30PM (Figure 1.A). When adjusted for age and time to image, the relationship remained significant ($p = 0.003$) with the peak shifted to approximately 7:45PM. Among only the witnessed strokes ($n = 1091$), a significant sinusoidal relationship ($p = 0.002$) remained, however the peak was notably later at 10:09PM (Supplementary Figure 1.A). Regarding occlusion site sub-types, there was a significant relationship for the M1 cases ($n = 716$, $p = 0.026$) with a peak around 8:45PM (Supplementary Figure 2.C), and a trend for the ICA cases ($n = 290$, $p = 0.061$). However, there was no significant relationship when examining exclusively the M2 cases ($n = 500$, $p > 0.05$).

In regard to collateral status, the median HIR was 0.4 (IQR: 0.2–0.6) in this cohort. The relationship between HIR and stroke onset was also significant in sinusoidal regression analysis ($p = 0.004$), with a peak in value at approximately 6:22PM (Figure 1.B). Adjusted for age and time to image ($p = 0.002$), the peak shifted to approximately 8:18PM mirroring the peak for the ischemic core analysis. The peak was similarly around 8:11PM when exclusively examining witnessed strokes ($p = 0.034$; Supplementary Figure 1.B). Regarding occlusion site sub-types, there was a significant relationship for M1 ($p = 0.001$) with a peak around 6:04PM (Supplementary Figure 2.D), but not for ICA or M2 cases (both $p > 0.05$).

Discussion

In this large retrospective analysis, we demonstrate a significant sinusoidal relationship between perfusion imaging parameters and time of stroke onset, with a peak in both ischemic core volume and HIR around 8:00PM. The sinusoidal relationship between ischemic core volume and stroke onset time mirrors a prior study,⁶ however the noted peak in previous work was approximately 11:00PM. The difference between peaks may be attributable to the differences in patient selection, with previous analyses⁶ utilizing a cohort with a slightly older population, higher proportion of ICA occlusions, and larger overall core volumes. We also observed within our sub-group analysis of exclusively witnessed strokes a peak closer to this prior work at 10:00PM, which may suggest that the true peak in ischemic core volume exists at some time in the early nighttime period.

This analysis also examined collateral status by examining HIR, where a larger values have been suggested to reflect poor collaterals in prior work.^{7,8} We observed that HIR values in our cohort peaked in the late evening, mirroring ischemic core volumes. Taken together, results of this cohort suggest that critical factors to the development of the ischemic core vary by stroke onset time and may peak around 8PM. Similar to our prior work,⁵ these findings support that these radiographic parameters peak in the evening. When placed in the context of prior studies,⁶ strongly suggest a diurnal component to the development of the ischemic core.

Limitations of these findings include the retrospective study design and assumptions for stroke onset defined in line with prior studies.⁹ We also chose to combine perfusion imaging techniques, CTP and MR-DWI/PWI, an approach supported by prior work,¹⁰ suggesting high correlation between modalities. Reassuringly in our original analysis,⁵ our core findings were seen in both our witnessed stroke population and among exclusively MRI perfusion scans. Finally, sub-group analyses according to occlusions site were limited by smaller sample size, which may explain the lack of association observed in the ICA and M2 subgroups.

These results continue to expand on our understanding of differences in perfusion imaging of stroke that vary based on onset time. This mirrors work in pre-clinical mouse models suggesting a larger ischemic core during the 'inactive' period of mice.² The underlying physiology has yet to be fully established, but may reflect variations in cerebral blood flow^{2,3} and/or mitochondrial function³ that also exhibit diurnal variations. A working theory of these findings is that mitochondrial activity is reduced during the 'inactive' period (i.e. nighttime for humans), leading to increased susceptibility to neuronal damage which can be exploited during an ischemic stroke further limiting key components of energy generation by the mitochondria. Implications of these findings may have direct results on clinical management of stroke, from understanding the effectiveness of thrombectomy based on time of day,¹¹ to appropriate staffing of stroke units to account for noted diurnal incidence.⁵

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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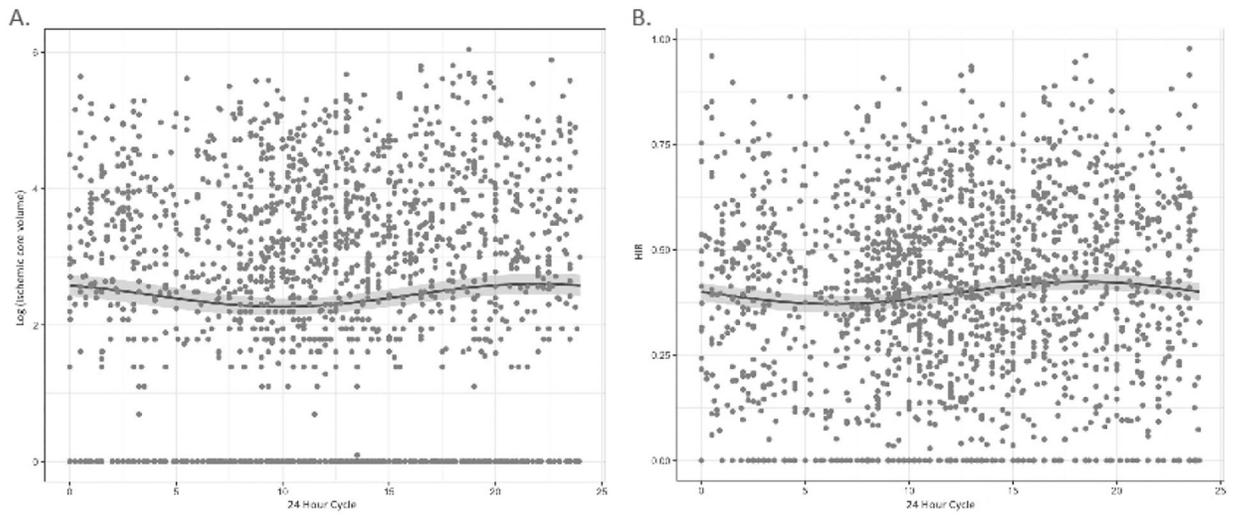


Figure 1.
Sinusoidal regression analysis of LVO cases across a 24 hour cycle for both (A) log of ischemic core volume, and (B) HIR.

Table 1.

Clinical presentation and radiographic features of the total cohort.

	Total Cohort n = 1506
Age, mean years (IQR)	74.9 (63.0–84.0)
NIHSS, median (IQR)	14.0 (8.0–20.0)
Blood Glucose, median mg/dL (IQR)	120.6 (104.4–151.0)
<i>Occlusion Site</i> , n (%)	
ICA	290 (19.3)
M1	716 (47.5)
M2	500 (33.2)
Wake-up Stroke, n (%)	256 (17.0)
<i>Medical History</i> [*] , n (%)	
Hypertension	932 (61.9)
Diabetes	297 (19.7)
Dyslipidemia	700 (46.5)
Witnessed Stroke, n (%)	1091 (72.4)
<i>Type of Acquisition</i> , n (%)	
MRI Perfusion	752 (49.9)
CT Perfusion	754 (50.1)
Time to Imaging, median (IQR)	220.0 (104.4–381.3)
Core, median (IQR)	13.0 (0.0–42.0)
HIR, median (IQR)	0.4 (0.2–0.6)

* Data missing for 21 cases.