Circulation Research: The body’s internal clock influences stroke severity and response to treatment

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The study, published in Circulation Research*, reveals that neutrophils—key immune cells—change their behavior in line with circadian rhythms, affecting cerebral perfusion and collateral circulation*

A study led by scientists at the Centro Nacional de Investigaciones Carlos III (CNIC) demonstrates that stroke severity depends on the time of day the event occurs. The research shows that neutrophils—the most abundant immune cells and first responders after stroke—are regulated by the body's internal biological clock. This circadian regulation influences cerebral perfusion, tissue injury, and patient recovery.

Ischemic stroke is a leading cause of death and disability worldwide. Despite advances in acute treatment, patient outcomes vary widely, suggesting the involvement of biological mechanisms that remain poorly understood. This study identifies one such mechanism: the circadian regulation of the immune response.

"These circadian changes directly influence collateral circulation, cerebral perfusion, and the extent of damage after blood flow is interrupted through immunothrombosis-related processes," explains Dra. María Ángeles Moro, principal investigator and head of the Neurovascular Pathophysiology Laboratory at the CNIC.

"Our results show that stroke is not a biologically uniform event," adds Dr. Moro. "The state of the immune system at the moment the stroke occurs can lead to major differences in severity and recovery."

Using mouse models and clinical data from more than 500 patients, the study shows that at specific times of day neutrophils adopt a more pro-inflammatory profile and release higher levels of web-like structures known as neutrophil extracellular traps (NETs). Although NETs play a role in immune defense, excessive NET formation can obstruct the cerebral microcirculation, promote immunothrombosis, and worsen tissue injury.

"When neutrophils release more NETs, blood flow through small vessels is compromised and brain damage is greater," explains Sandra Vázquez Reyes, a CNIC researcher currently at Massachusetts General Hospital / Harvard Medical School.

By contrast, at other phases of the circadian cycle, neutrophils exhibit less damaging behavior, allowing better perfusion and limiting stroke progression. "This helps explain why patients with similar clinical profiles can experience very different outcomes," says Alicia García Culebras, a researcher at the Complutense University of Madrid.

"These findings reinforce the clinical relevance of circadian immun regulation in stroke," adds Patricia Calleja, neurologist at the Stroke Unit of *Hospital 12 de Octubre*.

The authors conclude that incorporating both the time of day and the circadian regulation of the immune system into treatment decisions could improve the effectiveness of future therapies. In addition, blood biomarkers linked to immunothrombosis may help support personalized medicine approaches based on individual patient characteristics and on the biological moment at which a stroke occurs.

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- *Vázquez-Reyes S., García-Culebras A., Di G., De Castro-Millán F. J., Díaz-Benito B., Nieto-Vaquero C., Ruiz-Sanchez A., et al., Moro M. A. Circadian Control of Neutrophils Drives Collateral Perfusion and Stroke Outcome. Circulation Research. Publicado online. https://doi.org/10.1161/CIRCRESAHA.125.326438*

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