Study suggests how high blood pressure might contribute to Alzheimer's

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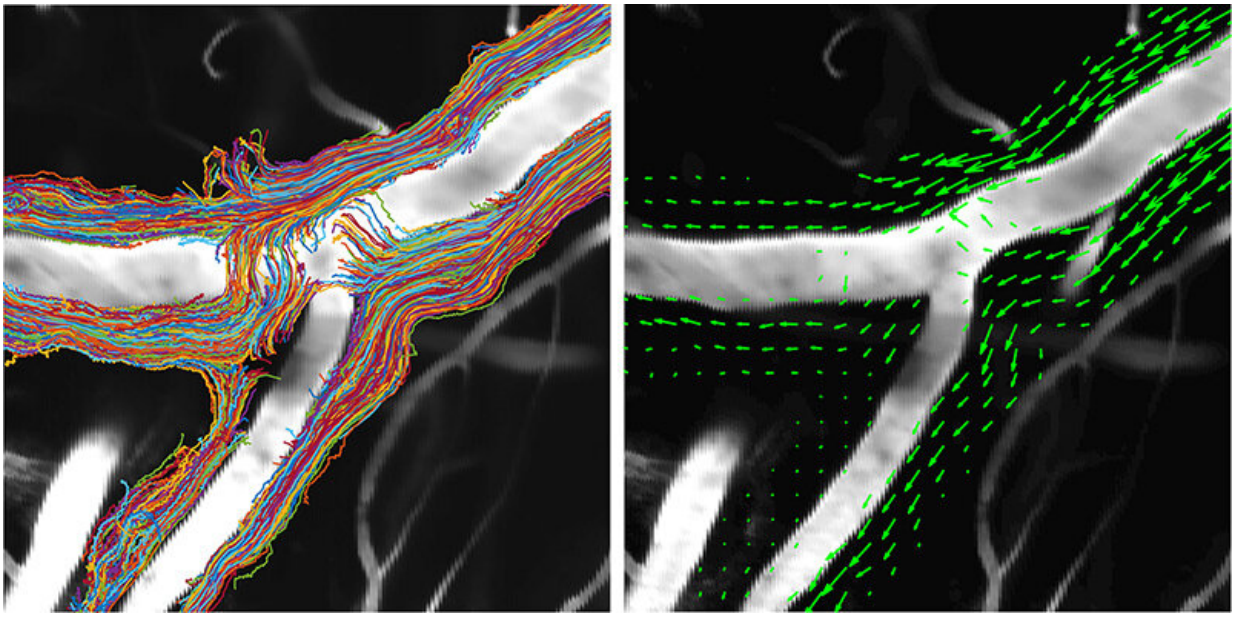


In the left panel, superimposed particle tracks reveal that cerebrospinal fluid flows through wide perivascular spaces, which are approximately as large as the adjacent artery. Averaging together hundreds of thousands of measurements produces a velocity field, shown in the green arrows in the right panel, which demonstrates that the net cerebrospinal fluid flow is in the same direction as the blood flow. Credit: University of Rochester illustration / Jeff Tithof

The brain's system for removing waste is driven primarily by the pulsations of adjoining arteries, University of Rochester neuroscientists and mechanical engineers report in a new study. They also show that

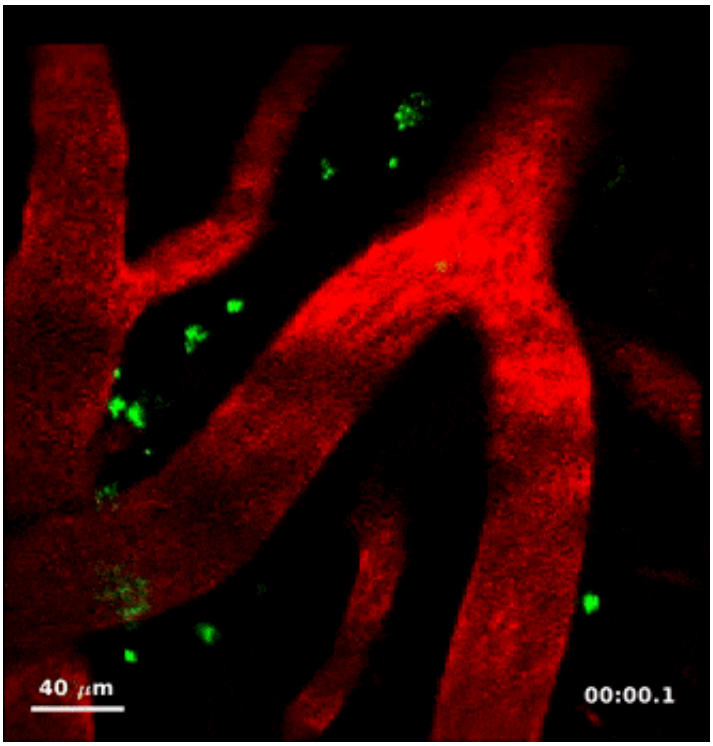
changes in the pulsations caused by high blood pressure slow the removal of waste, reducing its efficiency.

This might explain the association between high blood pressure and Alzheimer' disease, the researchers say. Alzheimer's, the most common cause of dementia among older adults, is characterized by abnormal clumps and tangled bundles of fibers in the brain.

The study, reported in *Nature Communications*, builds upon groundbreaking discoveries about the brain's waste removal system by Maiken Nedergaard, co-director of the University's Center for Translational Neuromedicine. Nedergaard and her colleagues were the first to describe how cerebrospinal fluid is pumped into brain tissue and flushes away waste. Subsequent research by her team has shown that this glymphatic waste removal system is more active while we sleep and can be damaged by stroke and trauma.

This latest research shows "in much greater depth and much greater precision than before" how the glymphatic system functions in the perivascular spaces that surround arteries in the outer brain membrane, says Douglas Kelley, an assistant professor of mechanical engineering and an expert in fluid dynamics. His lab is collaborating with Nedergaard's team as part of a $3.2 million National Institute on Aging grant.

For this study, Humberto Mestre, a Ph.D. student in Nedergaard's lab, injected minute particles in the cerebrospinal fluid of mice, and then used two-photon microscopy to create videos showing the particles as they moved through the perivascular spaces.



Credit: University of Rochester

Jeff Tithof, a postdoctoral researcher working with Kelley, then used an automated particle tracking code developed by the Kelley lab that can follow a dot from frame to frame of a video, and after a few frames estimate its velocity and acceleration. From a typical video spanning "tens of minutes," the code could track more than 20,000 individual particles and derive about a million total measurements to quantify their movements, which show up as "comet tails" behind each of the tracked dots in the videos.

By analyzing videos from experiments involving multiple mice, "we were able to gather a really rich data set of what's actually happening with this flow," Kelley says.

The researchers found that:

- The flow of cerebrospinal fluid is synchronized with the heartbeat, as seen in the animation below. "One of the main points of this paper is that this flow is mostly – and maybe purely—driven by the flexing of the artery wall," Kelley says.
- When high blood pressure was induced in the mice, the flow slowed down and was not as efficient. Artery walls are muscular; they have to flex harder in order to hold the same shape when there's more pressure inside, and they get stiffer," Kelley says. "And that changes the waveform of the flexing of the artery wall ."

"That's highly interesting because early onset high blood pressure is known to be a risk factor for Alzheimer's in humans," Kelley says. "There are still a few steps between what we did and chronic high blood pressure. But it may be that high blood pressure—by reducing the pumping of cerebrospinal fluid so that waste isn't cleared out as well—is the mechanism that leads to Alzheimer's."

The findings should resolve a debate among researchers about whether the flow of cerebrospinal fluid in the glymphatic system is in the same direction as arterial blood flow, as demonstrated by this paper, is opposite, or is random molecular diffusion, Kelley says. "This is going to quell a lot of those debates."

More information: Humberto Mestre et al. Flow of cerebrospinal fluid is driven by arterial pulsations and is reduced in hypertension, *Nature Communications* (2018). DOI: 10.1038/s41467-018-07318-3

Provided by University of Rochester