Medical Xpress

Ultrasound reveals the human brain vasculature down to the microscopic scale

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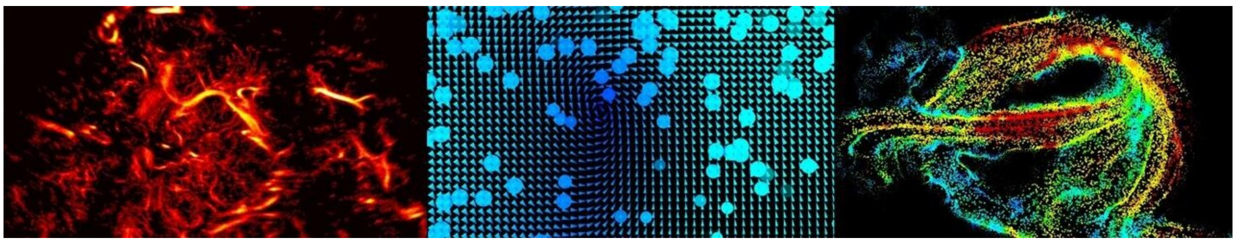

Ultrasound Localization Microscopy gives details of the brain vasculature down to the microscopic scale. Credit: Alexandre Dizeux/ Physics for Medecine

Mapping the cerebral vascular network in human patients, at unprecedented scales: This *tour de force* has been achieved by the French laboratory Physics for Medicine Paris (ESPCI Paris-PSL, Inserm, CNRS). In a study published on the front page of *Nature Biomedical Engineering*, the research team details its method—ultrasound localization microscopy, which combines ultrafast sonography and contrast agents. The researchers have addressed several technical challenges to apply the method to human patients. The resulting images are spectacular, and carry vast amounts of information on cerebral blood flows as well as their dynamics. Ultrasound localization microscopy opens new horizons for a better understanding and an earlier diagnosis of cerebrovascular diseases such as stroke or aneurysm, and neurodegenerative disorders like Alzheimer's disease.

The blood vessels of the brain constitute an extremely complex network, which supplies neurons with oxygen and nutrients. Hence, vascular activity and neuronal activity are intimately linked, and vascular dysfunctions are the underlying cause of many neurologic disorders. Diagnosing and treating these diseases is made difficult by a lack of knowledge on the functions of small blood vessels, due to the limitation of existing cerebrovascular imaging methods. CT-angiography (computed tomography) or MR-angiography (magnetic resonance) combined with injected contrast agents are the two most common methods used in hospitals. They capture large arteries of a few tenths of a millimeter in diameter but fail to detect smaller, micron-diameter capillaries. Moreover, these two angiographies do not provide dynamic information at the different spatial scales of the vascular network. The solution proposed by the laboratory Physics for Medicine Paris promises to fill this gap by offering dynamic images of the blood flows across the whole vascular network (from larger arteries to small capillaries), through a non-invasive, non-ionizing, bedside and low-cost technology.

Ultrasound micro-angiography

For fifteen years, the team of Mickael Tanter has developed ultrafast sonography, a technique acquiring thousands of ultrasound images per second. Inspired by optical FPALM microscopy (the discoverers fo which were awarded the Nobel Prize in Chemistry in 2014), the team has associated ultrafast sonography with contrast agents: microbubbles, made of a biocompatible gas and injected intravenously, circulate across the entire brain vascular network. These micron-sized bubbles are then imaged using an ultrasound probe placed against the head at the temple. By determining the position of millions of microbubbles within a few seconds, the researchers are able to retrieve the anatomy of the vascular network down to the micron scale, while collecting quantitative information on the local dynamic components of blood flows. So far, this had never been achieved by any other non-invasive medical imaging modality. This new method has been coined ultrasound localization microscopy (ULM).

Imaging human patients: a technical tour de force yielding unique images

The technique had been validated in 2015 on small animals, but imaging an adult human patient remained a major challenge. Firstly, the ultrasound signal is perturbed as it travels through the skull bone, leading to a severely degraded image quality. Methods to measure and then correct these perturbations have therefore been applied during signal processing to restore an optimal image quality. Secondly, it was necessary to develop motion correction algorithms, since any macroscopic movement of the brain hinders the ability to localize a microbubble with a micron-scale accuracy. Charlie Demené, associate professor at ESPCI Paris, details the key points of his work:

"The stars have aligned, so to speak, to make this world premiere in human subjects possible, through the conjoined implementation of several techniques. The first technique is ultrafast imaging, which provides a tremendous amount of data in a very short time, and enables us to discriminate the acoustic signature of each individual microbubble. Then, ultrasound localization overrides the resolution limits inherent to wave physics: the image of a tiny object is a blurry spot which is larger than the actual object. This is what we call the spatial resolution limit. But if this object is isolated, we can reasonably assume that its exact location is the center of the blurry spot. In our case, the microbubbles circulating in the blood stream play the role of isolated objects, and allow us to recover the exact location of each blood vessel. Finally, recording the echo of each microbubble gives access to the history of the wave coming from this micron-sized object, and hence enables to recover what occurred during the propagation of the wave through the skull in order to correct its perturbations."

With these new developments, the researchers have achieved ultrasound localization microscopy in human patients at the clinical neurosciences center of the University of Geneva (Switzerland), in collaboration with Prof. Fabienne Perren. For instance, in a patient with an aneurysm, the team has been able to capture the finest details of a turbulent blood flow in the area of the aneurysm, located in depth in the middle of the brain.

A powerful tool for patient management

These new vascular imaging performances open new horizons for a better understanding of the link between the cerebral vasculature and brain diseases. Visualizing and quantifying cerebral blood flows, which were so far unseen for lack of a sufficient resolution and sensitivity, could have a major impact by providing new insights on the relationships between vascular and neuronal activity, and, from a clinical perspective, by offering a better and an earlier diagnosis of cerebrovascular diseases and hence opening the possibility to develop more efficient treatments.

Ultrasound localization microscopy will be widely accessible to patients and easier to use by clinicians, compared to current techniques. ultrasound technology is more cost-effective, less cumbersome and can be operated at bedside.

More information: Transcranial ultrafast ultrasound localization microscopy of brain vasculature in patients, *Nature Biomedical Engineering* (2021). DOI: 10.1038/s41551-021-00697-x , dx.doi.org/10.1038/s41551-021-00697-x

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