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Biomedical engineering

Microbubbles map hidden signs of heart disease

Elisa E. Konofagou

Cardiovascular disease claims more lives each year than do the two next-deadliest diseases combined. An ultrasound technique that tracks tiny gas-filled bubbles could pave the way towards improved early detection.

Roughly every 34 seconds in the United States, someone has a coronary event — an attack brought on by a disease affecting the coronary arteries, which supply blood to the heart muscle. Around every 83 seconds, such an event results in death. One of the main reasons for this death toll is the poor performance of tools that are used to detect a narrowing of the arteries at a time when pharmacological interventions can still reverse it. If people survive a coronary event, this deficiency also makes it challenging to work out the severity of the injury and the potential future outcomes, which could be determined by mapping blood flowing through the part of the heart muscle that remains viable. Writing in *Nature Biomedical Engineering*, Yan *et al.*[1] report the efficacy of a real-time, quantitative method that could overcome these problems — using machinery that can be wheeled into any emergency department.

Yan and colleagues' breakthrough means that a cardiologist or physician can quickly determine the status of different areas of a person's heart muscle (myocardium), and without subjecting the person to stress testing[2]. The method the authors used is based on ultrasound localization microscopy[3–5], which is a super-resolution imaging technique that surpasses the resolution limit of conventional ultrasound imaging with the help of gas-filled bubbles that are just a micrometre in diameter. These microbubbles are injected into a person's bloodstream, and then tracked as they move through the small blood vessels that perfuse the myocardium with oxygenated blood (Fig. 1). This technique is especially useful in the heart, because the thick muscle walls can be penetrated by ultrasound only with low-frequency signals that otherwise offer very low spatial resolution.

Although ultrasound localization microscopy has been reported previously, and its application to the myocardium is not new[3–5], Yan *et al.* have now shown its clinical applicability unambiguously. By using it for people who are diagnosed with heart disease, and in a clinical environment, the team confirmed that the results of the method are consistent with those of other, more-invasive clinical-imaging methods, such as coronary angiography, which is based on computed tomography.

This task is not trivial. The required resolution is on the order of tens of micrometres, and the imaging must be undertaken while the myocardium moves and stretches by centimetres over the course of a heartbeat. This can result in artefacts that make tracking small vessels extremely challenging — and quantifying the flow through them even more so. However, Yan *et al.* found that they were able to circumvent these difficulties by tracking the microbubbles with hundreds of images per second, which made the method extremely sensitive, thereby reducing the number of tracking errors.

The endeavour is made even more challenging by the fact that it uses the most conventional form of cardiac ultrasound imaging, known as transthoracic echocardiography. Transthoracic echocardiography is safer than some other forms of cardiac imaging used in the clinic, but it has drawbacks. Perhaps the biggest problem is that the probe is placed between a person's ribs to obtain an 'acoustic window' — a way for ultrasound to penetrate the myocardium unhindered. But this can produce artefacts that compromise the image quality so much that the ultrasound probe might need to be inserted into the person's throat instead.

These artefacts typically result from the ultrasound signal reflecting off the cardiac muscle, and then bouncing off the ribs before returning to the probe. This creates imaging noise that motion-tracking algorithms can mistake for direct reflections from the myocardium, resulting in inaccurate information about the underlying structure. Yan *et al.* successfully reduced these artefacts, achieving a spatial resolution of 13–16 micrometres in a controlled environment, and hundreds of micrometres in a moving heart. This resolution enabled the authors to distinguish blood vessels that were hundreds of micrometres apart

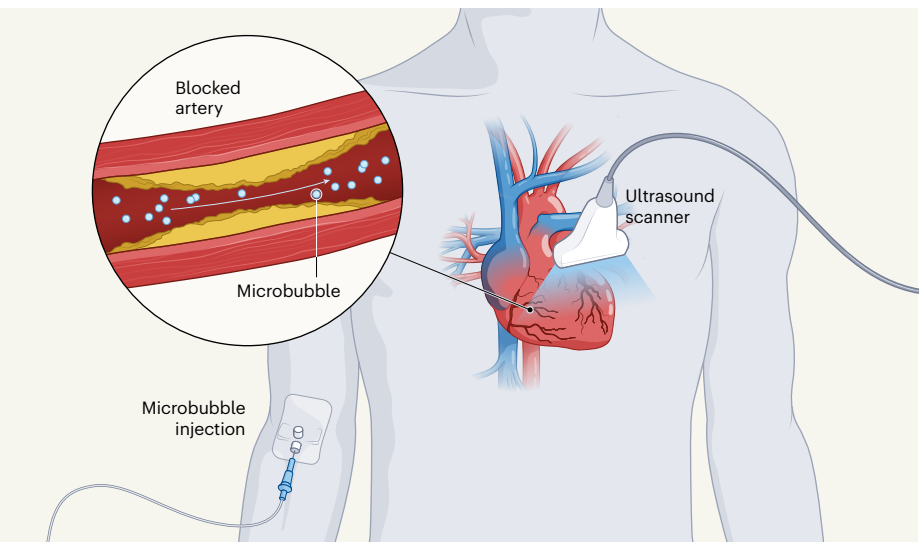

Figure 1 | Super-resolution imaging of blood flow through the heart muscle. Yan *et al.*[1] showed that ultrasound can be used to determine the health of a person's heart muscle (myocardium) by tracking the flow of gas-filled microbubbles through the small blood vessels that perfuse the myocardium with oxygenated blood. The authors developed a way of distinguishing mobile structures from static structures, which increased the sensitivity of the method enough to enable them to verify its efficacy in clinical tests on people diagnosed with heart disease.

in a beating heart. They did so by developing techniques to separate static structures from moving structures, such that the erroneous signals could be distinguished from the actual signals (from moving microbubbles).

The current state-of-the-art approach to assessing the perfusion of blood through the myocardium uses positron emission tomography (PET) to measure the flow rates when the body is under stress and at rest. However, PET both exposes people to radiation and is prohibitively expensive in certain countries. It also requires access to a cyclotron that can synthesize the radioisotope agents used. Therefore, the technique can be used only in well-equipped medical centres and not at the point of care or in emergency departments. In these settings, echocardiography is the most accessible approach, owing to its low cost, its portability and its ability to work in real time.

Now, because of Yan and colleagues' breakthrough, sensitivity can be added to this list of advantages. In clinical settings, echocardiography is currently considered less quantitative than PET, and its effectiveness varies between operators. Ultrasound alone does not offer the sensitivity required to quantify myocardial perfusion but, with the authors' approach, ultrasound localization microscopy can now be used reliably to visualize small blood vessels in the myocardium, to map their flow rates and to assess the viability of the myocardium.

Although the authors' work provides an initial confirmation of the clinical feasibility of the method, there are still practical hurdles to overcome. For example, the microbubbles need to be administered intravenously for each imaging session, which could limit the number of sessions that can be performed for a single person. The number of artefacts could also be increased for people with large amounts of subcutaneous fat. And the technique currently works only during the myocardium's passive phase (diastole), whereas the active phase (systole) is equally, if not more important, for assessing cardiac function.

"The authors could distinguish blood vessels that were hundreds of micrometres apart in a beating heart."

Finally, microbubbles contain gas that might attenuate the intensity of the ultrasound signal, which could in turn complicate the imaging of deeper myocardial regions. A larger clinical study that involves several participants would potentially address these limitations, while also uncovering further capabilities of the technique. In the meantime, Yan and colleagues' study offers an exciting glimpse of the future of myocardial imaging.

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