Cardiac imaging with 3-D cellular resolution using few-mode interferometry to diagnose coronary artery disease

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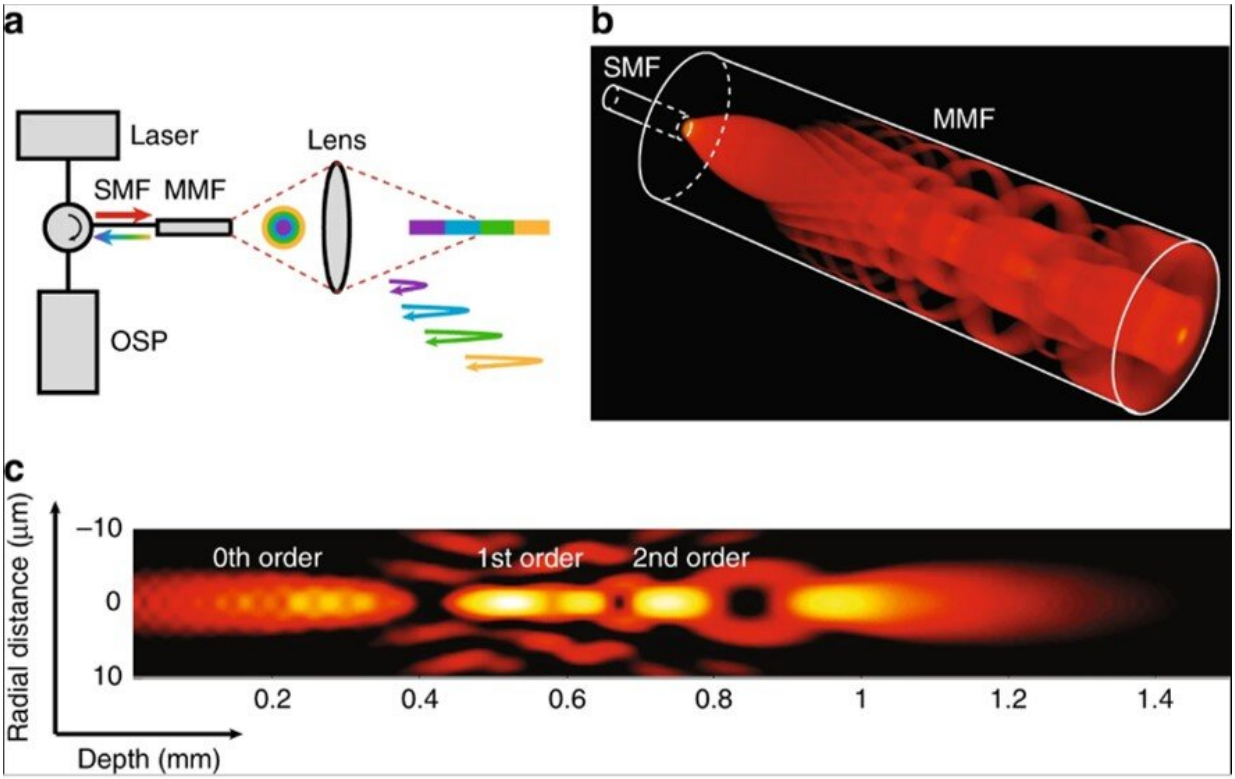


(a) The concept of using a single-mode-multimode fibre system for depth-encoded reflectometry. The color pattern corresponds to different propagation modes. SMF single-mode fibre, MMF multimode fibre, OSP optical signal processing unit. (b) 3D rendering of the intensity profile inside the multimode fibre showing the few-mode generation processes of an SMM fibre system. The lateral and axial dimensions are not drawn to scale. The SMF has a mode field diameter of 5 μm, and the MMF has a core diameter of 50 μm and a length of

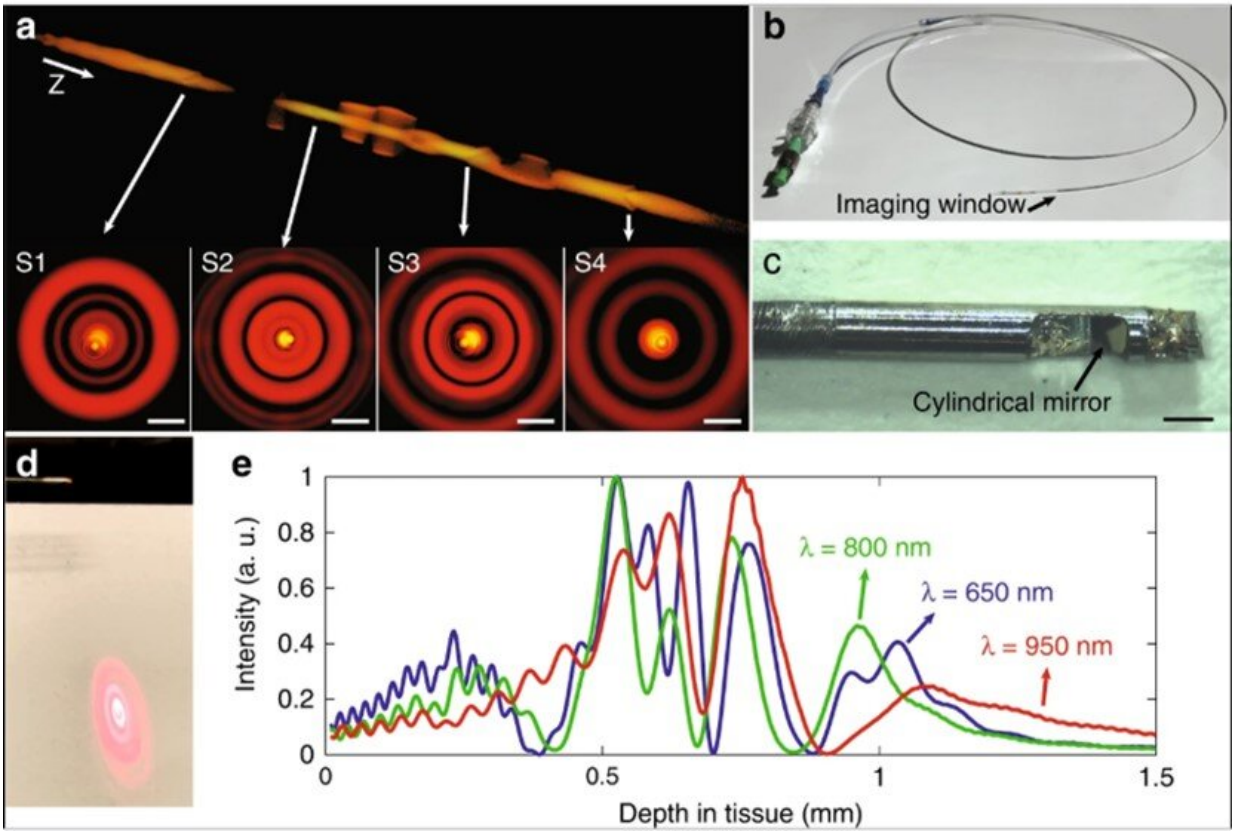
1.2 mm. A system wavelength of 800 nm is assumed. (c) Simulations of the focused field intensity distribution in the image space. The length of the spacer is 1.6 mm, and the objective has a focal distance of approximately 0.5 mm. We assume a refractive index of 1.34 in the image space. The focused field intensity distribution is normalized by the peak intensity and displayed on the dB scale with a dynamic range of 16 dB. Credit: Light: Science & Applications, doi: 10.1038/s41377-019-0211-5

A new imaging technique developed by Biwei Yin and interdisciplinary researchers at the Massachusetts General Hospital and Harvard Medical School in the U.S., provides resolution at the subcellular-level to image the heart's vascular system. As a result, heart researchers can study and diagnose human coronary artery disease with greater precision. Conventionally, cardiologists employ intravascular optical coherence tomography (OCT) to assess the buildup of coronary plaque, which can narrow arteries to cause coronary artery disease.

The OCT technique is, however, limited by a lateral resolution of only 30 microns (μm) therefore researchers are unable to obtain images at the subcellular level to understand the disease. The newly developed few-mode interferometry intravascular imaging system contains a resolution of three microns to provide images of cellular and subcellular structures in the artery wall. The enhanced view can provide detailed information on individual crystals, smooth muscle cells and inflammatory cells with greater precision during disease diagnosis. The research work is now published on *Light: Science & Applications*.

Optical coherence topography (OCT) is a mainstream imaging method used to obtain cross-sectional reflectance mainly in clinical settings to image a range of human tissues including luminal organs within the body . Intravascular OCT (IVOCT) is of interest to access coronary plaque structure and guide percutaneous coronary intervention (PCI) during

coronary artery disease; a leading cause of mortality in the world. Bioengineers and cardiologists have recently demonstrated advanced IVOCT techniques, such as multimodal IVOCT to combine the conventional form with additional imaging and sensing modes, such as fluorescence and near-infra-red spectroscopy. Additional innovations include polarization-sensitive IVOCT to measure tissue birefringence and provide imaging contrast, as well as heartbeat IVOCT to densely image coronary arteries in vivo without introducing motion artefacts. The most challenging technical barrier to increase the lateral resolution of an OCT system includes adjusting the depth of focus (DOF) for cross-sectional imaging. Preceding studies that achieved increased DOF, have a form factor or complexity to prevent intraluminal clinical applications for coronary imaging.

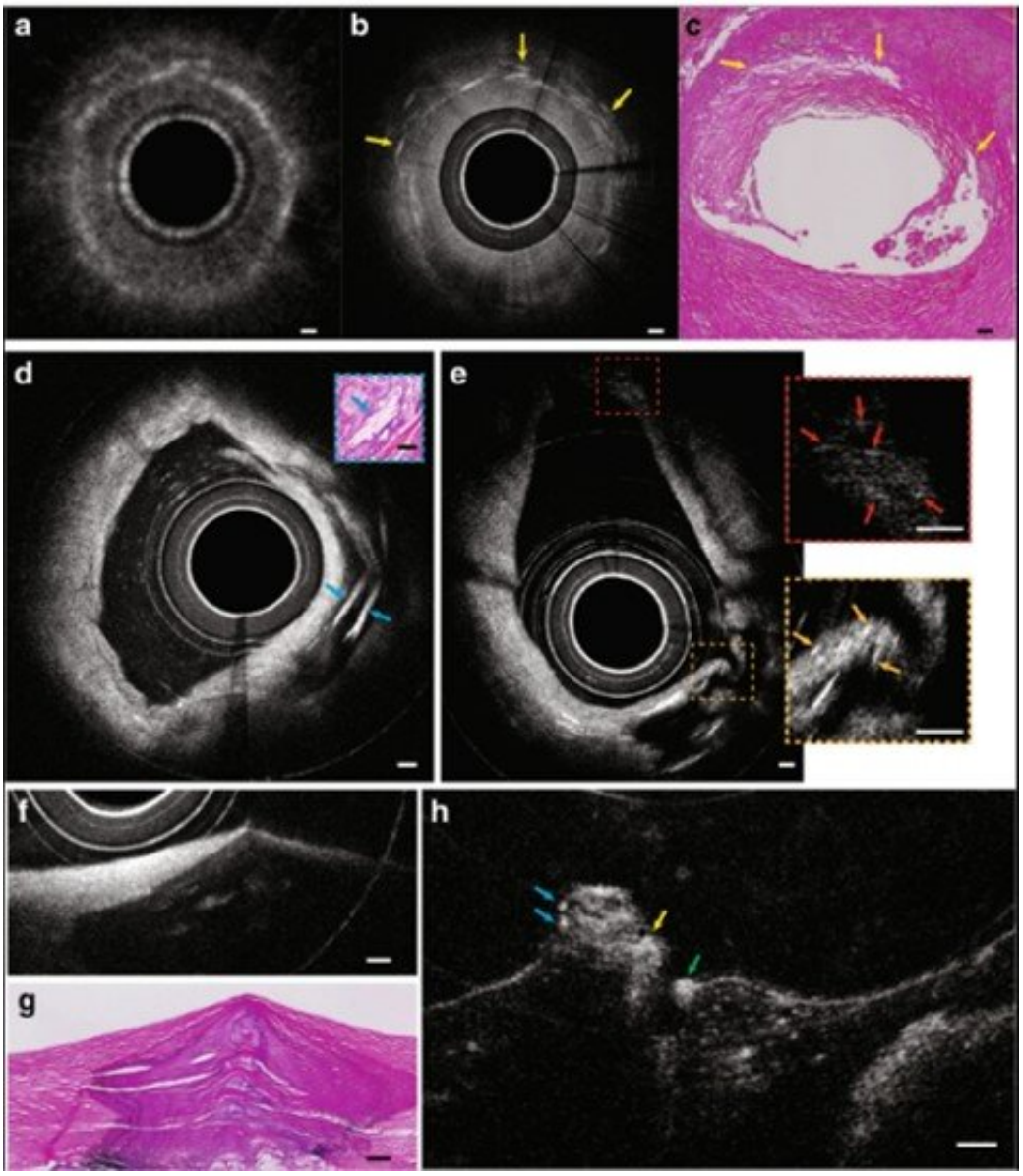


(a) Simulation of the aberrated beam field intensity when scatterers are positioned at the center of the beam path. Four scatterers were modelled, denoted as S1–S4. The scatterers had a diameter of 2 μm and a refractive index of 1.5. 3D rendering of the beam field and the transverse intensity distributions show that the aberration introduced by an individual scatterer is confined within each mode. Z indicates the beam propagation direction. Scale bar: 10 μm. (b) Photograph of the completed 2.6-F rapid guidewire exchange coronary catheter. (c) A photograph of the distal end of the catheter, taken using a microscope. The fibre probe had a diameter of 500 μm and a rigid length of less than 4 mm. Scale bar: 500 μm. (d) Photograph of the ring pattern of the light transmitted through the catheter's fibre probe optics, corresponding to multiple propagation modes. The screen was positioned at a small angle with respect to the beam propagation direction, showing that the cylindrical mirror directs the beam at an ~8° angle normal to the sheath to reduce specular reflection. (e) Simulation of the normalized on-axis field intensity distribution with respect to depth for the center wavelength and the two ends of the spectra, showing that the chromatic focal shift effect mitigated the field intensity discontinuity. Credit: Light: Science & Applications, doi: 10.1038/s41377-019-0211-5

In the present work, Yin et al. described a few-mode interferometry -based intravascular imaging system with extended DOF for cross-sectional imaging at cellular resolution, across a depth range of more than 1 mm. The technology allowed them to observe cellular and sub-cellular structures of intact human-coronary-sized arteries ex vivo and in vivo through a flexible, submillimeter diameter catheter. The researchers used low coherence interferometry that resolved pathlength delay to decode the information carried by each mode travelling at a different optical pathlength in the experimental setup.

Multiple propagation modes could simultaneously interrogate a sample at different depths to transmit the depth-encoded signal through a common channel for processing. The process increased the acquisition capacity of the reflectometry system without additional illumination and detection

channels. To visualize the effects, Yin et al. simulated the focused beam field at different depths along the center of the beam path, where scattering particles introduced aberration into the beam field as field disturbance. The self-healing (self-reconstructing) property of the propagation process suggested the independence of each mode in the scattering media.



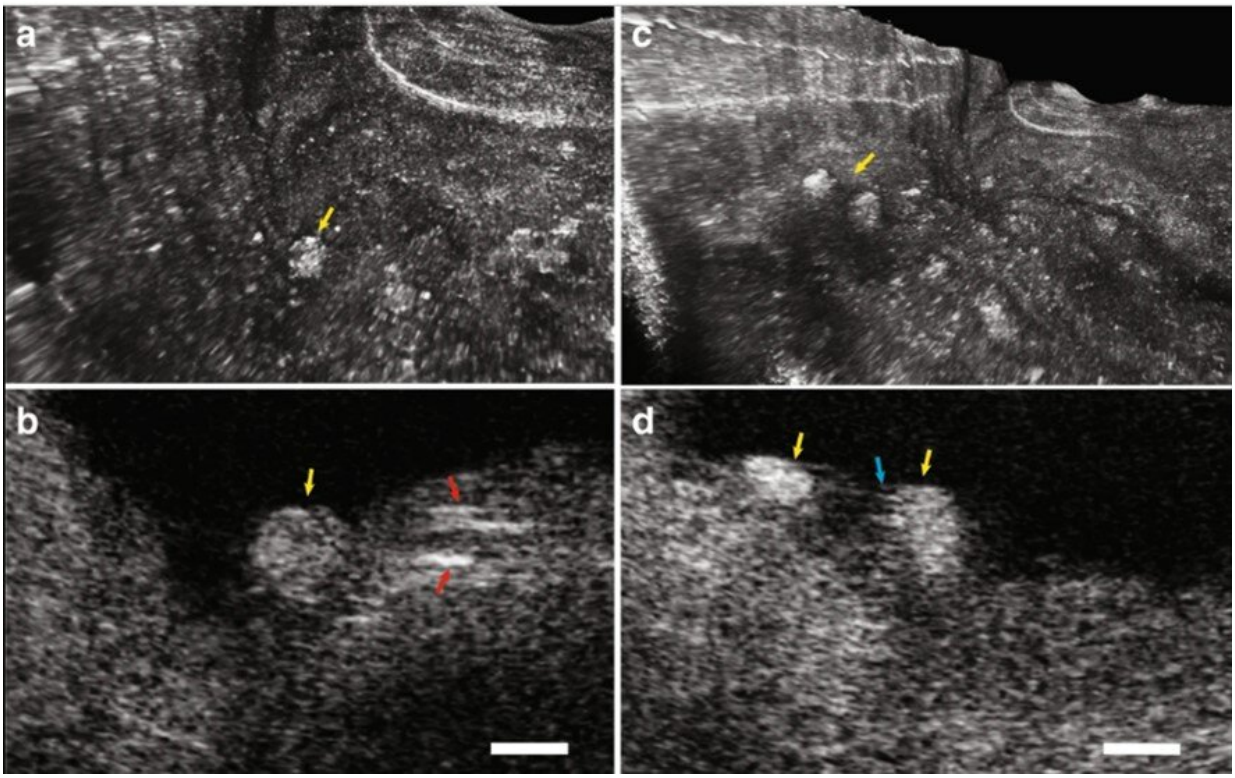
(a–c) IVOCT, IVFMI, and histology images showing a cross-section of the artery containing deposits of cholesterol crystals. In the standard IVOCT image (a), the

highly scattering structures would be considered macrophage accumulations using current IVOCT criteria21, while the IVFMI image (b) demonstrates that these features were crystals, a finding that is consistent with the corresponding histology. (d) A cross-section of an artery that had multiple cholesterol crystals characterised by reflections from their top and bottom surfaces. (e) Image showing that IVFMI could resolve small crystals at distances close to the sheath (a couple hundred microns) and far from the sheath (~1 mm) simultaneously. (f, g) IVFMI and corresponding histology images of a calcific nodule, respectively. (h) was approximately 1.3 mm away longitudinally from (g), where thrombus was observed over the calcific nodule. The blue arrows are features that are consistent with leucocytes, the yellow arrow is suggestive of thrombus, and the green arrow shows a cell that is likely a monocyte/macrophage. A Gaussian blur filter with a radius of 2 μm was applied to the cross-sectional IVFMI images. Scale bars for all images are 100 μm. Credit: Light: Science & Applications, doi: 10.1038/s41377-019-0211-5

Based on the concept, the research team created an intravascular few-mode interferometry (IVFMI) imaging device with a supercontinuum laser as the light source. They used a low-coherence interferometer as the optical signal processing unit, a catheter for depth encoding and backscattering signal detection, as well as optomechanics for scanning. Using the setup, the researchers conducted a helical scan of the lumen wall for three-dimensional (3-D) reconstruction of the artery. Using a catheter inside an artery they acquired cross-sectional images at 17 frames per second. With an almost 1000-fold improvement in volumetric resolution, the research team resolved cellular and subcellular structures using IVFMI (intravascular few-mode interferometry) in contrast to the conventional IVOCT (Intravascular OCT) method.

For example, when the scientists compared standard IVOCT and IVFMI images corresponding to the same cross-section of a human cadaver coronary artery, they could clearly distinguish densely packed crystals

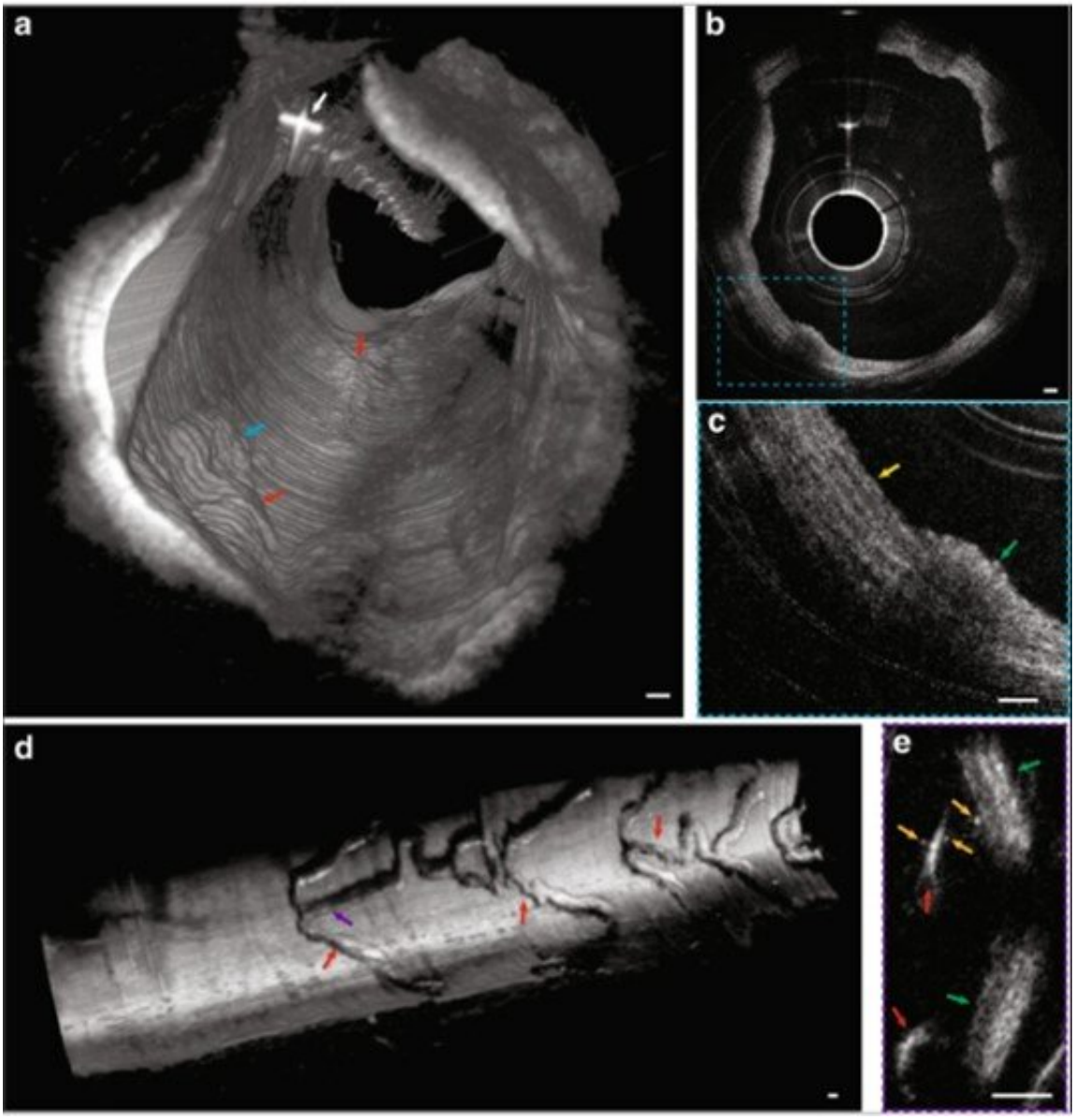
using IVFMI only. In contrast, images obtained using the standard IVOCT technique were blurred and globular, making it more likely to characterize them erroneously as macrophage accumulations. Similarly, the research team observed smooth muscle cells using the IVFMI catheter, which could not be resolved using the conventional IVOCT method.



3-D reconstruction and corresponding cross-sectional images of IVFMI data obtained from a human cadaver coronary artery. The lumen shows individual macrophages residing on the surface of a fibroatheromatous plaque. (a, b) 3D rendering and cross-sectional images showing an individual cell (yellow arrows) that appears to be transmigrating through the endothelium towards a deposit of intimal crystals (red arrows). (c, d) 3D rendering and cross-sectional images showing two macrophages tethered to the endothelial surface, polarised towards one another with extended pseudopodia (blue arrow). Scale bars: 50 μm. Credit: Light: Science & Applications, doi: 10.1038/s41377-019-0211-5.

The IVFMI cross-section of an artery also resolved cholesterol crystals that are typically difficult to image using conventional methods due to their notable reflections. As a result of the extended DOF enabled with the IVFMI setup, the researchers resolved microstructures residing a few hundred microns to millimeters away from the catheters sheath, simultaneously in one circumferential scan.

Since inflammatory cells drive the development of atherosclerotic plaques, Yin et al. represented intimal smooth muscle cells and macrophages undergoing diapedesis using IVFMI. The images showed fine detail of the intraluminal mass, including the presence of bright cells such as leucocytes embedded in the fibrin mesh to form what appeared to be a thrombus. The researchers used the IVFMI data obtained from a cadaver coronary lumen wall for 3-D reconstructions and also developed 3-D reconstructions of IVFMI data obtained from a living rabbit aorta with atherosclerotic plaque. They detected the plaque from the normal artery wall by observing the raised surface morphology, which projected into the lumen (inside space of a tubular structure such as an artery).



IVFMI images of rabbit arteries acquired in vivo. (a) 3D reconstruction of atherosclerotic rabbit aorta. The white arrow indicates the guide wire. The blue and red arrows indicate atherosclerotic plaque regions. (b) Cross-sectional image of the lumen wall that contains normal aortic media tissue and the atheromatous lesion indicated by the blue arrow in (a). (c) Magnified image corresponding to the blue dashed region in (b). The yellow arrow demarcates a region containing smooth muscle cells embedded in a collagen network in a portion of the normal aortic wall, while the green arrow indicates an atherosclerotic plaque. (d) 3D reconstruction of a stent implanted in the iliac artery. The purple and red arrows indicate stent struts. (e) A cross-sectional image corresponding to the location

indicated by the purple arrow in (d). Orange arrows highlight tiny, punctate, highly scattering features that are consistent with platelets around the stent strut (red arrow), with the green arrows indicating the artery wall. A Gaussian blur filter with a radius of 2 μm was applied to the cross-sectional IVFMI images. Scale bar: 100 μm. Credit: Light: Science & Applications, doi: 10.1038/s41377-019-0211-5.

Using cross-sectional images, the team observed a network of collagen and smooth muscle cells in the normal media with improved clarity. They also obtained 3-D reconstructed IVFMI data at a segment of the lumen wall implanted with a stent an hour prior to imaging. The IVFMI process visualized microstructural detail of the stent struts with unprecedented detail for intravascular imaging. Yin et al. observed small, high-reflectivity, micron-sized dots surrounding some of the stent struts and could even identify the fine-detail of microstructural platelets in the images.

In this way, Biwei Yin and colleagues developed and demonstrated a technique to overcome the problems of implementing few-mode interferometry, to increase the depth of focus (DOF) by more than an order of magnitude. The optical configuration technology has a small footprint, depth-encoding capability and transmission stability, with important applications in depth-resolved endomicroscopy. The results confirmed the potential of the new technology to acquire images with a good signal-to-noise ratio and show well-defined disease-relevant cellular and subcellular microstructures within human cadaver coronary arteries ex vivo and rabbit arteries in vivo.

The device is physically and mechanically identical to coronary catheters used for conventional IVOCT imaging in the clinic. These findings indicate the possibility of translating the new IVFMI technique for

clinical imaging to view cellular coronary pathology in humans at the cardiac catheterization lab. The technique can be used to view cellular imaging beyond intravascular imaging to include luminal organs such as the gastrointestinal tract and pulmonary tracts to increase clinical diagnostic accuracy.

More information: 1. 3D cellular-resolution imaging in arteries using few-mode interferometry www.nature.com/articles/s41377-019-0211-5 Biwei Yin et al. 21 November 2019, *Light: Science & Applications*.

2. Simultaneous micromanipulation in multiple planes using a self-reconstructing light beam www.nature.com/articles/nature01007 V. Garcés-Chávez et al. 12 September 2002, *Nature*.

3. Heartbeat OCT and Motion-Free 3D In Vivo Coronary Artery Microscopy imaging.onlinejacc.org/content/9/5/622.abstract Tianshi Wang et al. 5 May 2016, Journal of American College of Cardiology (JACC): *Cardiovascular Imaging*.