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Multimodal intravascular photoacoustic and ultrasound imaging

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Abstract

The rupture of atherosclerotic plaques is the leading cause of death in developed countries. Early identification of vulnerable plaque is the essential step in preventing acute coronary events. Intravascular photoacoustic (IVPA) technology is able to visualize chemical composition of atherosclerotic plaque with high specificity and sensitivity. Integrated with intravascular ultrasound (IVUS) imaging, this multimodal intravascular IVPA/IVUS imaging technology is able to provide both structural and chemical compositions of arterial walls for detecting and characterizing atherosclerotic plaques. In this paper, we present representative multimodal IVPA/IVUS imaging systems and discuss current scientific innovations, potential limitations, and prospective improvements for characterization of coronary atherosclerosis.

Keywords Multimodal · Intravascular imaging · Photoacoustic · Ultrasound · Atherosclerosis · Imaging probe

1 Background

Atherosclerosis is a disease that is characterized by narrowed and hardened arteries due to the accumulation of lipids, cholesterol, fibrous constituents, monocytes, and various other inflammatory cells in the arterial wall. The leading cause of cardiovascular death is less obtrusive plaques known as “vulnerable plaques” which rupture suddenly and block blood flow by blood clot or thrombus [1–4]. Early identification of vulnerable plaque is an essential step in preventing acute coronary events. Currently, commercially available intravascular imaging technologies including IVUS imaging and intravascular optical coherence tomography (IVOCT) are widely applied in clinic settings [5–8]. The latent vulnerability of a plaque lesion is highly associated with both tissue structural and chemical composition. However, most current clinical intravascular imaging technologies only provide either structural or chemical composition which is often

insufficient for early detection of vulnerable plaque. For example, IVUS permits tomographic visualization of a cross-section segment through the vessel wall with a large imaging depth. However, it lacks the capability of plaque composition differentiation due to the limited sensitivity and specificity for soft tissue. In addition, IVUS has limited resolution to assess the thickness of the thin fibrous cap which is another key characteristic of vulnerable plaque. IVOCT based on the echo delay of light backscattered from the tissue can provide high-resolution 3D-imaging similar to that of ultrasound with micron scale resolution which is able to identify the thin fibrous cap. However, it is still insufficient due to its limited imaging depth and limited chemical specificity for identifying plaque composition. Therefore, both IVUS and IVOCT provide structural information but lack molecular contrast for plaque composition differentiation. Imaging of tissue composition is important for choosing proper interventional techniques. In order to obtain chemical information, several intravascular imaging technologies with molecular sensitivity have been developed in the past decades, which include Raman, intravascular near infrared spectroscopy (NIRS), and fluorescence imaging. However, NIRS, Raman and fluorescence imaging techniques only provide surface images and do not have the sectioning capability to generate cross-sectional images [9–14].

Intravascular photoacoustic (IVPA) imaging [15–18] is able to provide extremely high molecular contrast while maintaining the large imaging depth of ultrasound imaging.

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With multi-wavelength laser excitation, spectroscopic IVPA imaging based on unique optical absorption spectrum of different tissues can be performed to visualize lipid distribution in atherosclerotic plaques with high sensitivity and specificity. In addition, IVPA also have been used to differentiate calcified plaque, atheroma, and lipids in a healthy vessel wall. The prime benefit of photoacoustic imaging is that it provides high chemical specificity of optical and comparable penetration depth with ultrasound images. In addition, due to the usage of an ultrasonic transducer, IVPA is able to automatically incorporate IVUS imaging technology to perform multimodal imaging. Based on different laser sources and imaging probe designs, various types of multimodal imaging systems have been developed [19–25]. Each of them has its own features and limitations. This review aims to introduce the different multimodal IVPA/IVUS imaging systems and address their innovations, limitations, and strategies for improvement.

2 Principles of intravascular photoacoustic imaging

In photoacoustic imaging, the biological tissue is irradiated by a nanosecond laser pulse. A portion of the optical energy is absorbed and converted into heat which leads to a transient pressure rise. This initial pressure acts as an acoustic source that generates an acoustic wave propagating through the tissue. An ultrasonic transducer will be used for detecting the acoustic wave to form photoacoustic images. The unique optical absorption of different tissues when excited at a specific wavelength can be used to characterize the tissue type. The goal of IVPA imaging is the chemical characterization of vessel wall components in order to identify vulnerable plaque. For intravascular application, various IVPA imaging systems have been reported with different excitation wavelengths: 461 and 532 nm were first used to image human atherosclerotic aorta by several groups [15, 26, 27]. Then 308 nm was also applied because of the contrast for calcium [28]. However, the strong absorption from blood due to the usage of a visible range to discriminate vessel wall components hindered further development. Recently, infrared sources were investigated for IVPA imaging as a result of several unique features. First, near-infrared wavelength shows lower blood absorption and exhibits a long penetration depth compared with the wavelength range of visible light. In addition, the absorption spectrum of lipids exhibits two peaks at near-infrared wavelength range due to the first overtone of CH vibration near 1720 nm and the second overtone of the CH bond stretch near 1210 nm, which can be used to map lipids in an atherosclerotic lesion. Currently, the 1210 and 1720 nm spectral bands are considered as the most suitable bands for IVPA imaging of lipid-rich plaque.

For intravascular imaging, a miniature imaging probe that contains optical components used for delivering the laser pulse onto tissue and an ultrasonic transducer for the detection of generated photoacoustic signals will be inserted into an artery to image the artery wall. The miniature imaging probe is designed such that the excitation laser beam and ultrasound detection region overlap, and the region of overlap determines the imaging range of IVPA imaging as shown in Fig. 1a. Figure 1b illustrates the principles and architecture of the multimodal IVPA/IVUS imaging system. The output laser beam from an ns-pulsed laser is coupled into the multimode fiber to deliver the optical energy from the laser source towards biological tissue through the imaging probe for photoacoustic excitation. An ultrasonic transducer housed in the imaging probe is used to receive the photoacoustic signal and perform ultrasound imaging through an ultrasound pulser/receiver. Photoacoustic and ultrasound imaging share the same ultrasonic transducer, so a short delay of $t' \mu\text{s}$ has to be set to trigger the ultrasound pulser/receiver to perform ultrasound imaging in order to separate photoacoustic and ultrasonic signals. For three-dimensional (3D) images, the imaging probe is rotated and pulled back via a 3D scanner which consists of an optical rotary joint, slip ring, motor and pull-back translation stage. The acquired photoacoustic and ultrasonic signal will be processed by a band-pass filter, demodulated for envelope detection, and then transformed into a polar coordinate for real time display.

3 Development of a multimodal IVPA/IVUS imaging system

Multimodal intravascular IVPA/IVUS imaging combines the advantages of broad imaging depth of IVUS and molecular contrast of IVPA, which will provide physicians

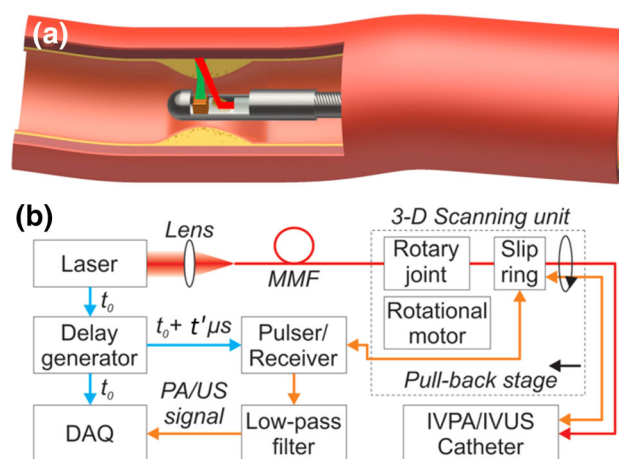


Fig. 1 **a** The schematic of IVPA imaging. **b** The setup of IVPA/IVUS system. Adapted from [24]

a new method for detecting and managing vulnerable plaque. However, there are a number of challenges for the development of this multimodal IVPA/IVUS imaging technology for clinical translation, including a high repetition nanosecond pulse laser for photoacoustic imaging, a multimodal imaging probe, imaging processing, and in vivo imaging using appropriate animal models. Recently, various multimodal imaging systems have been developed and corresponding animal experiment results have been performed to demonstrate their capability. In this paper, we will focus on technology development to introduce widely studied multimodal IVPA/IVUS imaging systems and address their advantages, limitations and possible future improvements.

4 Development of a high-speed nanosecond pulsed laser with lipid contrast

The nanosecond pulsed laser is one of the most important components for IVPA imaging. The pulse energy of the laser correlates with the sensitivity, and the repetition rate determines the imaging speed [15, 27]. Previous studies reported the usage of the 532 nm nanosecond pulse laser to image vascular tissues and identify tissue composition [15, 27]. Currently, a high-repetition-rate laser source with high-pulse-energy operated at 532 nm is commercially available. However, a number of limitations (such as the inability of providing clear lipid contrast and short penetration depth) have hindered the application of the 532 nm nanosecond pulse laser source for characterization of vulnerable plaque. Although excitation at 532 nm enables the identification of intima, media, and adventitia in the vascular wall [27], it is not sensitive to other tissue compositions, such as lipids. Lipid is considered a major hallmark of atherosclerosis. The extent of intra-lesion lipid density is strongly correlated with the vulnerability of plaque to rupture. Therefore, the wavelength that is able to provide the best lipid contrast should be used for IVPA imaging. To provide that contrast, two wavelengths, 1210 and 1720 nm, have been demonstrated as the optimal wavelength ranges for characterization of lipid components. Several groups [19–21, 23–25, 29–32] have reported a multimodal IVPA/IVUS imaging system based on the excitation wavelengths of 1210 and 1720 nm. According to the absorption spectrum of lipids, 1720 nm is considered as an optimal wavelength for IVPA imaging because of the high absorption coefficient (optical absorption coefficient value of lipids at 1720 nm is almost six times higher than the value at 1210 nm) (Fig. 2) and longer penetration depth. In addition, optical scattering from blood is also weaker at 1720 nm compared with 1210 nm. Consequently, 1720 nm is considered as the best appropriate wavelength for IVPA

imaging for now. The advantage of the 1720 nm band for IVPA imaging of lipids was also confirmed by Wang et al., who reported a threefold enhancement of the IVPA signal from excitation at 1720 nm versus excitation at 1210 nm and have demonstrated that IVPA has the capability of imaging lipids through luminal blood using the 1720 nm wavelength [31]. Therefore, most nanosecond pulse lasers focus on an excitation wavelength of 1720 nm for IVPA imaging. Hui et al. [32] demonstrated a potassium titanyl phosphate (KTP)-based optical parametric oscillator operated at 1724 nm with a repetition rate of 500 Hz, but it is still too slow for real time intravascular imaging. A commercial laser source which operates at ~ 1720 nm with a relatively high repetition rate produced by Elforlight Ltd. is available right now. It has output pulse energy of 80 μJ /pulse with a repetition rate of 5 kHz. Min et al. demonstrated the possibility of characterization of lipids by using this laser [25]. However, they had to apply heavy water to enhance the sensitivity due to the low excitation efficiency caused by low laser pulse energy. Although a high repetition rate was demonstrated, the pulse energy was insufficient for effective in vivo characterization of lipid components. A desired light source for in vivo applications which requires 5 kHz or a higher repetition rate with enough pulse energy remains a challenge.

5 Multimodal IVPA/IVUS imaging system

Limited by the development of a tunable laser, current in vivo multimodal IVPA/IVUS imaging system mainly focuses on imaging lipid components using one single wavelength. Based on different imaging probe designs, the current widely used multimodal imaging systems can be divided into three groups.

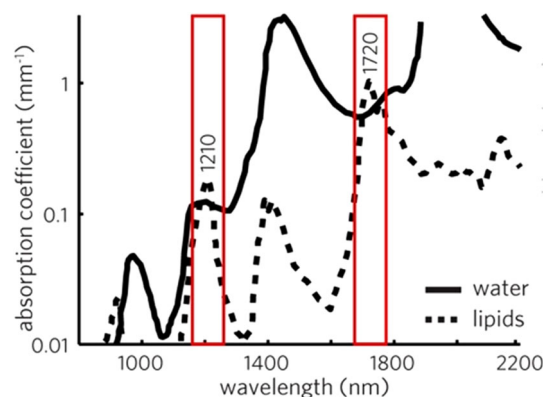


Fig. 2 Lipid and water absorption spectrum around 1210 and 1720 nm. Adapted from [33]

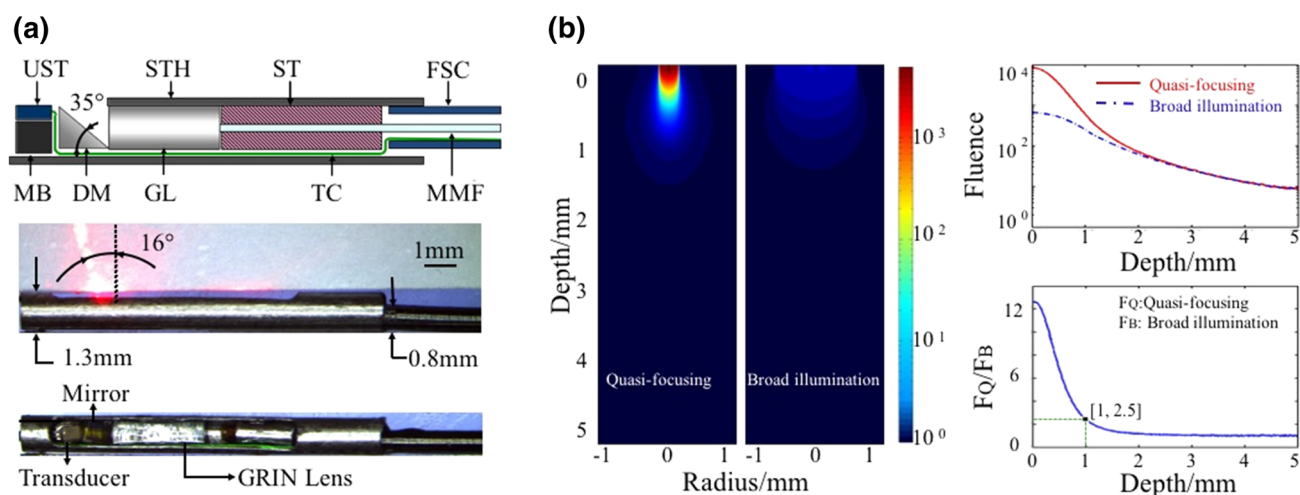


Fig. 4 **a** The schematic of the quasi-focusing IVPA/IVUS imaging probe. **b** Monte Carlo simulation of photon transport in a numerical plaque phantom for quasi-focusing and broad illumination schemes. Adapted from [23]

is distally aligned from the fiber tip and ultrasonic transducer to reflect both laser and acoustic beams towards the vessel wall. The innovation is that the ultrasonic wave and optical illumination beam share the same path which contributes to optimal overlap between the laser and acoustic beams with enhanced sensitivity through the entire imaging range. However, the current minimum size of the ring-shaped ultrasonic transducer is limited to ~ 2 mm due to the traditional fabrication method, which makes it

difficult for in vivo IVPA imaging. In addition, the side lobe effect is significant in the ring-shaped ultrasonic transducer which should be carefully considered in this coaxial imaging probe design.

Another coaxial imaging probe was reported by Cao et al. (Fig. 6) [20]. In this study, an ultrasonic transducer and multimode fiber are housed parallel to each other. The multimode fiber's end is polished to 45 degrees to reflect the ultrasonic wave, and both optical beam and ultrasonic

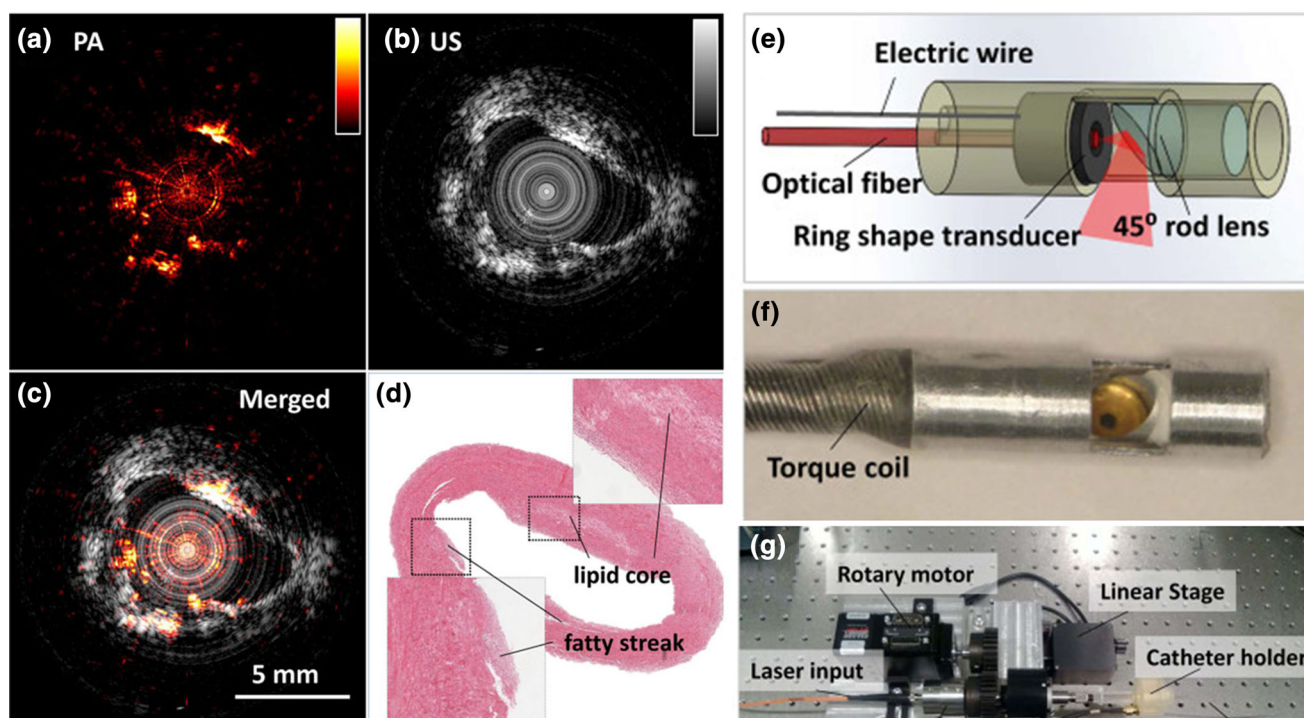


Fig. 5 **a** IVPA and **b** IVUS imaging of an atherosclerotic artery. **c** Combined PA/US image. **d** Histology. **e** Schematic and **f** photograph of the IVPA probe. **g** Photograph of the scanning assembly. Adapted from [21]

beam are reflected by a mirror towards the tissue. Compared with the above confocal design, this design utilizes multi-reflection to achieve a coaxial optical beam and acoustic beam instead of using a ring-shaped ultrasonic transducer so it does not have the problem of a side lobe effect caused by a ring-shaped ultrasonic transducer. The coaxial design enables an improved imaging depth and sensitivity. However, there are several limitations to this design. Firstly, the complexity of the housing makes it difficult to fabricate a probe small enough to be compatible with clinical requirements. In addition, it also applies broad illumination so it has a limited resolution for IVPA images. Finally, ultrasonic and generated photoacoustic signals will experience significant attenuation from the multi-reflections which will decrease the sensitivity.

6 Spectroscopic IVPA imaging system

Spectroscopic IVPA imaging [22, 23] has the capability of identifying the key lipid components of human atherosclerotic plaque based on the intrinsic contrast in optical absorption between tissue types. Several groups [22, 23, 35] demonstrated the spectroscopic IVPA imaging system based on a tunable pulse laser which operated at around 1210 and 1720 nm and had the capability of distinguishing different lipid components (Fig. 7a). With 6 or 3 wavelengths at around 1720 or 1210 nm, the atherosclerotic plaque and peri-adventitial lipids could be detected and distinguished, respectively. However, the atherosclerotic plaque and peri-adventitial lipids could be detected but could not be differentiated when only 2 wavelengths were used. In addition, the imaging speed was

extremely slow due to the utilization of a low repetition rate of the tunable laser (10 Hz). Li et al. reported high-speed spectroscopic imaging in 2015 (Fig. 7b). In their study, an ns-pulsed tunable laser with a repetition rate of 1 kHz was used for spectroscopic IVPA imaging. In consideration of the wavelength tuning and stabilization time (~ 1 s), it would take around 6 s to obtain a spectroscopic B-scan IVPA image with five different wavelengths, which was ~ 10 times faster than previously reported spectroscopic IVPA imaging systems. However, this imaging speed was still too low for translation to in vivo imaging.

7 Discussion

The multimodal IVPA/IVUS imaging system is able to provide both structural and chemical compositions simultaneously which demonstrates the capability to characterize vulnerable plaque. However, the current IVPA/IVUS imaging systems still operate at a low imaging speed with long imaging acquisition time, relatively big imaging probes, insufficient sensitivity, and limited imaging depth. For clinical translation of this imaging technology, continuing improvements are required on the following aspects.

1. Develop a high-repetition-rate with high-pulse-energy nanosecond laser centered at an optimal wavelength for lipid contrast. The main technical barrier hindering the imaging speed of IVPA is the shortage of appropriate laser sources. Therefore, the successful development of such lasers will allow high-speed multimodal IVUS/IVPA imaging for clinical

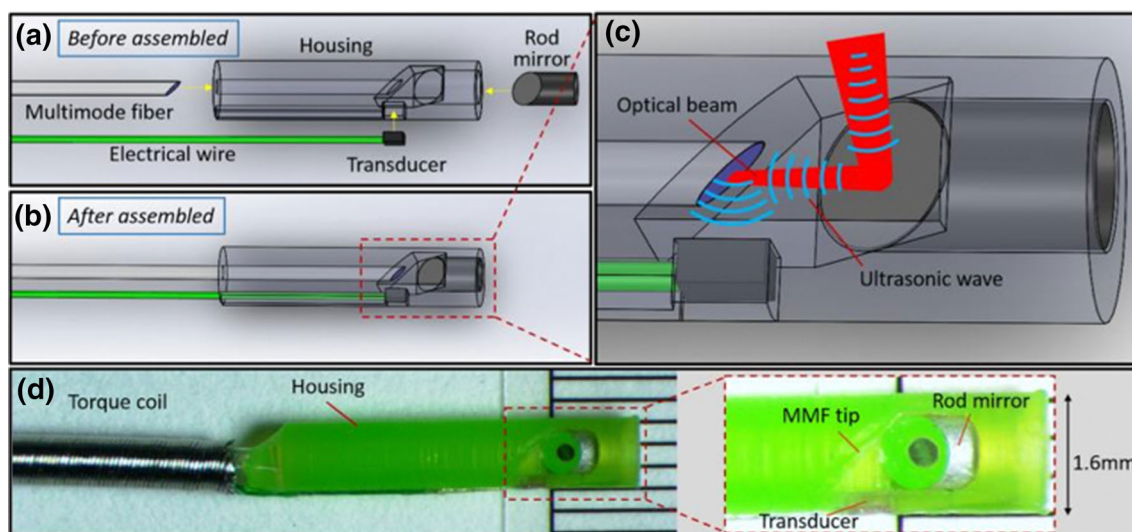


Fig. 6 **a** Key components of the collinear probe before assembly. **b** Assembled IVPA imaging probe. **c** Zoom-in view of the probe tip. **d** Photo of the probe. Adapted from [20]

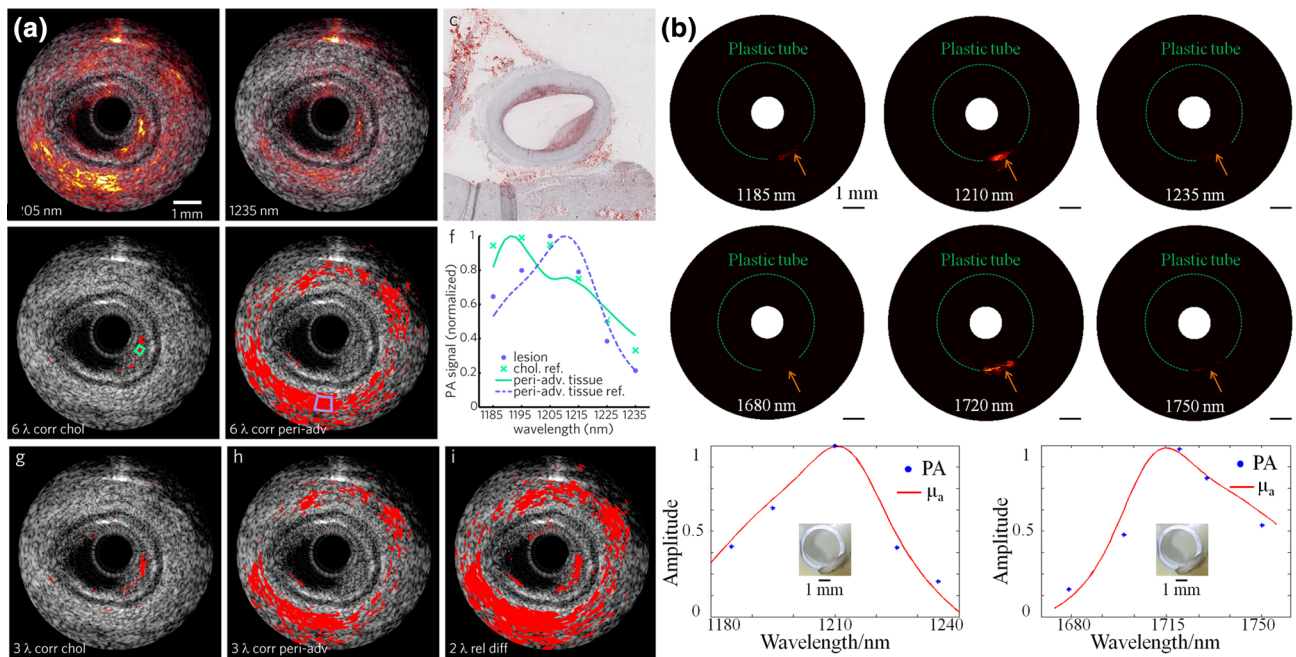


Fig. 7 **a** Lipid detection atherosclerotic human coronary artery with different wavelengths. **b** Spectroscopic photoacoustic B-scan images from a porcine aorta segment at both spectral bands and comparison between spectroscopic results and the absorption spectrum of lipid.

The arrows indicate the position of the adipose tissue, while the dashed green circles show the contour of the plastic tube. Blue dots: PA signals at different wavelength. μ_a : absorption spectrum of lipid. Adapted from [22, 23]. (Color figure online)

translation. The desired laser has to satisfy several requirements. (1) Center wavelength: ~ 1720 nm. A wavelength of 1720 nm has been demonstrated as the optimal wavelength for lipid characterization due to its high contrast of lipid components and its capability of imaging lipid components through blood. (2) Repetition rate: ≥ 5 kHz. Assuming a resolution of ~ 200 μm and 5-mm vessel lumen, 200 A-lines (larger than $2 * 5 * \pi/0.2$) are enough for a circular scan, according to the Nyquist theorem, so the laser with such a repetition rate enables real time imaging with a frame rate higher than 25 fps. (3) Pulse energy: > 1 mJ. Pulse energy of 0.4 mJ at the probe tip has proven to be enough to identify lipids from normal tissue. Considering the energy loss from the optical path coupling, fiber optic rotary joint and imaging probe, 1 mJ is required from the laser output. In addition, assuming a 200- μm diameter illumination area with 0.4 mJ pulse energy, the fluence is around 0.8 J/cm^2 , which is below the ANSI safety standard (1 J/cm^2) regarding the wavelength of ~ 1720 nm [36]. (4) High wavelength sweeping rate. In order to obtain truly high-speed spectroscopic IVPA imaging, a tunable laser source that can operate not only at a high repetition rate but also at a high wavelength sweeping rate is essential for in vivo spectroscopic imaging.

2. Further improvement of the imaging probe

Each type of imaging probes has unique features

and limitations. For clinical translation, the imaging probe needs to be further improved. The desired parameters for a multimodal intravascular imaging probe include the following. (1) Small size: < 1 -mm outer diameter and < 5 -mm rigid length to ensure a smooth advance through the branching points of the tortuous cardiovascular system. A big probe will cause severe non-uniform rotation distortion (NURD) and make it hard to advance when going through the branching points of the cardiovascular system. The 0.9-mm diameter is the smallest IVPA probe to date [23]. However, the outer diameter with the sheath will be larger than 1 mm. A potential solution is to apply a GRIN fiber instead of GRIN lens which has better flexibility and a stable connection when operating at a high scanning speed while performing quasi-focusing illumination. (2) High-speed scanning: the imaging procedure time should be shortened in synchrony with each cardiac cycle. Currently, 25 frames per second is the reported fastest imaging speed for IVPA imaging. However, heavy water has to be applied due to limited pulse energy [19]. Therefore, the development of a high-repetition-rate with high-pulse-energy nanosecond laser will facilitate high-speed in vivo intravascular imaging. At the same time, scanning speed of the imaging probe needs to be synchronized. In order to increase the scanning speed further, a potential method is to apply a MEMS motor to rotate a mirror to perform

cross-sectional imaging [37]. The unique feature of this mirror-rotating design allows more steady rotation and a higher frame rate than the traditional probe-rotating method. (3) High sensitivity: probe sensitivity can be improved by optimizing the overlap between optical and acoustic beams (such as coaxial design) and applying a quasi-focusing illumination scheme and high-performance ultrasonic transducer (such as the PMN-PT single crystal composite ultrasonic transducer) [38] which show significantly improved performance by increasing the effective electromechanical coupling coefficient.

3. Imaging processing

For spectroscopic IVPA imaging, minimization of the number of wavelengths is necessary for enhancing imaging speed. Therefore, the corresponding algorithm needs to be further developed to minimize the required maximal number of wavelengths. In addition, the small size of the ultrasonic transducer causes a limited effective imaging range so an advanced signal processing algorithm, such as chirp coded excitation [39], also needs to be implemented which could potentially compensate for the lost imaging depth from reduced aperture size. Finally, the compensation for laser energy attenuation and acoustic attenuation when penetrating deeper into tissue should be considered.

8 Summary

In summary, the multimodal IVPA/IVUS imaging system is undergoing rapid development towards becoming a clinically viable technology. IVPA can differentiate between plaque components by using the distinct differences in the optical absorption spectra of different tissues with ultrasound imaging depth. Integrated with IVUS, this multimodal imaging provides both structure and chemical compositions of arterial walls. In the future, with further improvement, this multimodal imaging will provide clinicians with a powerful tool for diagnosing vulnerable plaques, monitoring the progression of plaque, and evaluating the efficacy of interventional treatment.

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Compliance with ethical standards

Conflict of interest Dr. Zhongping Chen has a financial interest in OCT Medical Imaging, Inc., which, however, did not support this work.

Ethical approval All methods were carried out in accordance with the Guide for Care and Use of Laboratory Animals.

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