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High frequency intravascular photoacoustic (IVPA) imaging for differentiating arterial wall layered structures

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ABSTRACT

Arterial wall is composed of three layers: intima, media and adventitia. Intima-media thickness (IMT) is an important prognostic indicator of atherosclerotic diseases. Although intravascular ultrasound (IVUS) imaging is a commonly used method for delineation of the layered structures, it is inferior to the optical absorption contrast offered by intravascular photoacoustic (IVPA) imaging. We introduce an integrated miniature probe that combines the capabilities of IVUS and IVPA imaging for the evaluation of arterial wall layered structures. Healthy rabbit aorta was imaged *ex vivo*. IVPA results showed superior contrast over IVUS in identifying the layered structures of arterial wall.

Keywords: intravascular photoacoustic, IVPA, intravascular ultrasound, IVUS, high frequency, layered structure

1. INTRODUCTION

Human and animal arterial walls normally display three-layer structures: intima, media and adventitia.^{1,2} Intimal thickening is considered to be an early and continuous manifestation of atherosclerosis.^{3,4} Intima-media thickness (IMT) is clinically used as a surrogate marker for the progression of atherosclerotic disease.^{1,3} The assessment of IMT was enabled by advancements in intravascular ultrasound (IVUS) and intravascular optical coherence tomography (OCT).²⁻⁷ Early studies with IVUS in normal arteries demonstrated relatively bright intimal and adventitial layers separated by a hypoechoic region, corresponding histologically to the medial layer.^{1,2} The brightness difference originates from the acoustic impedance differences of these three layers. However, due to insufficient resolution and contrast, IVUS could not accurately differentiate the boundary of intima and media, or internal elastic lamina (IEL), when intima is below the appearance threshold of 178 μm .² On the other hand, although OCT can identify IEL with superior resolution of 10-20 μm ,² the limited penetration depth and contrast of OCT may degrade its capability in detecting the boundary between media and adventitia, or external elastic lamina (EEL).

Intravascular photoacoustic (IVPA) imaging is a newly developed catheter based optical-acoustic hybrid modality, which is capable of providing optical absorption mapping of the arterial wall, offering not only morphological but also functional information.⁸⁻¹⁰ From a transient laser irradiation on biological tissues, broad band ultrasonic waves are generated and received by an ultrasonic transducer.^{8,11} Previous investigators demonstrated the capability of spectroscopic IVPA imaging in detecting lipid plaques.^{8,10} However, the application of IVPA to the assessment of layered structures has not been investigated.

For IVPA application, usually an unfocused light pulse is used, and the image resolution is determined by the ultrasonic transducer's working frequency. At certain laser energies, acoustic signal strength is determined by the light absorption coefficient (μ_a) of tissues.¹¹ Examination of the optical absorption spectra of the arterial wall at 532 nm shows that the intima and adventitia have similar μ_a values (10.04 and 13.29), but higher than that of media (5.323).^{12,13} On this basis, we hypothesize that the three-layer structures could be better resolved by IVPA imaging, with optical contrast and ultrasonic resolution. Intima and adventitia would appear brighter than media in IVPA image. The optical contrast

between layered structures is believed to be more valid than that induced by acoustic impedance, which is only a few percent.¹⁴

To test this hypothesis, an integrated 35 MHz miniature IVUS/IVPA imaging probe was developed. Healthy rabbit aorta was imaged *ex vivo* to investigate the ability of IVPA in identifying arterial layered structures.

2. MATERIALS AND METHODS

The integrated IVUS/IVPA probe is composed of parallel arranged side-firing optical probe and side-viewing ultrasonic transducer, shown in Fig. 1. For the optical part, a 200-micron-core multimode fiber is used to deliver 532 nm pulsed laser beams. At the distal end, a 45-degree polished microprism (0.25×0.25×2 mm³ Bern Optics Inc., Westfield, MA) is connected to the fiber tip and sealed inside a glass capillary tube (0.4 mm ID; 0.55 mm OD). Air is trapped inside the tube to form air/glass interface at the prism polished surface to redirect laser beams by 90 degrees, following “total internal reflection” effects. For the acoustic part, one 35 MHz miniature ultrasonic transducer is fabricated in our laboratory (0.4×0.4 mm² aperture, 59/232 μ m axial/lateral resolutions). The optical prism and ultrasonic transducer are arranged side by side with an angle of approximately 20 degrees and packaged in a polyimide tubing (Small Parts, Inc., Miramar, FL) with outer diameter of 1.2 mm.

Figure. 1 Schematic of the integrated IVUS/IVPA probe: top view (a) and front view (b). Light beam is in green and acoustic beam in gray

A pulsed Q-switched Nd:YAG laser (532 nm, 3-5 ns pulse width, 10 Hz repetition rate, Continuum, Inc., Santa Clare, CA) is used as the excitation source. The free space laser output is coupled by a 4 × objective lens into an optical fiber then delivered to the prism at the distal end of the probe. The integrated probe is inserted into sample lumen and internally illuminates the sample with the surface fluence energy around 10 mJ/cm². The circumferential scanning was achieved by rotating a water tank with sample inside using a stepper motor, while probe was kept immobile. A PR5900 pulser/receiver (Olympus NDT, Inc., Kennewick, WA) is used to generate US pulses and receiving both US and IVPA waves. Received signals are digitized and processed in computer. For each IVPA scan, 1000 A-lines are acquired and averaged by every two A-lines. US scan is then followed with the same scanning pattern at the same cross section. Co-registration between IVUS and IVPA is ensured by the precision of motor stepping. The scanning procedure is controlled by a custom LabVIEW program (National Instruments, Austin, TX) and synchronized by the laser trigger signals.

A section of healthy rabbit abdominal aorta was harvested and preserved in phosphate buffer. During the experiment, the specimen was immersed and supported by a sponge to stand in a water tank. Only the part of sample above the sponge was imaged. Imaged sections were pinpointed for Hematoxylin-Eosin (H&E) stained histology examination.

3. RESULTS AND DISCUSSION

IVUS and IVPA images of a rabbit aorta are shown in Fig. 2. Both images could see through the vessel wall. However, the layered structures in the IVUS image looks more ambiguous than that in IVPA image. The IVPA imaging depth could be demonstrated up to 4 mm at 12~2 o'clock in Fig. 2 (b). In order to demonstrate the accuracy of IVPA in evaluating IMT, one Region of Interest (ROI), which is marked by a blue dashed square in Fig. 2 (a), (b) and (d), was selected for further analysis. The close-up images of ROI are shown in Fig. 3 with a field of view of 1×1 mm². In IVPA image (Fig. 3 (b)), the boundaries of intima, media and adventitia (IEL and EEL), are legibly delineated with optical contrast. The delineation of EEL and measurement of IMT, which is around 558 μ m, matches well with the histological results. On the other hand, IEL and EEL in IVUS image (Fig. 3 (a)) are difficult to distinguish, especially in the lower

part, due to the inferior acoustic contrast. A rough brightness comparison of adventitia and media areas in IVPA image reveals that adventitia is 10~15 dB higher than media, while the number is 5~10 dB in IVUS, which indicates that the contrast in IVPA is around 5~10 dB higher than that in IVUS. The optical contrast enables IVPA to distinguish the boundaries of the three layers more effectively than IVUS.

Figure. 2 Cross-sectional IVUS (a), IVPA (b) and fused (c) images of a healthy rabbit aorta at 35 MHz; and Hematoxylin-Eosin (H&E) stained histology image (d); ROI: Region Of Interest

Figure. 3 Close-up images of IVUS (a), IVPA (b) and H&E (c) at ROI in Fig. 2. A, Adventitia; M, Media; I, Intima; EEL, External Elastic Lamina; IEL, Internal Elastic Lamina

The improved contrast of IVPA in differentiating layered structures could be more beneficial for diagnosing atherosclerosis at an early stage, where intima is not significantly thickened and under the detection threshold of IVUS. However, IVUS is still valuable to provide anatomical information of thickened intima and plaque. Moreover, since blood has strong absorption at 532 nm, which requires saline flushing, IVUS could serve as guidance before flushing.

4. CONCLUSION

In summary, we introduced the IVPA for differentiating the arterial wall layered structures by using a miniature integrated IVUS/IVPA probe, which could internally illuminate the vessel wall and provide IVUS and IVPA imaging simultaneously. Compared to IVUS image, IVPA offered better delineation of intima, media and adventitia layers and possessed the potential for IMT measurement.

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