Intravascular confocal photoacoustic endoscope with dual-element ultrasonic transducer

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Abstract: We have developed an intravascular confocal photoacoustic (PA) endoscope with symmetrically aligned dual-element ultrasonic transducers. By combining focused laser excitation and focused acoustic collection, the intravascular confocal PA endoscope is capable of realizing resolution enhanced intravascular PA imaging with improved signal-to-noise ratio (SNR) to ameliorate the resolution reduction caused by laser scattering with increasing tissue depth. The detection sensitivity of the endoscope is improved by 5 dB compared with that of single transducer endoscope, and the transverse resolution of the system can up to 13 μm. Intravascular PA tomography of a normal vessel and an atherosclerotic vessel have been performed to demonstrate the imaging ability of the system. This intravascular confocal PA endoscope with an outer diameter of 1.2 mm supports potential for clinical applications in intravascular plaque imaging and subsequent diagnosis.

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1. Introduction

Photoacoustic (PA) imaging is a fast-growing noninvasive imaging technology utilizes ultrasonic waves excited by a pulsed laser energy source to reconstruct images of tissue internal optical absorption. In PA imaging, the tissues are irradiated with nanosecond pulsed laser, and the deeply penetrating diffused laser energy is absorbed by tissues, which subsequently undergo rapid thermoelastic expansion and further generate ultrasonic waves. Taking the advantage of diffusive photons PA imaging is capable of providing volumetric images of tissues with high optical contrast and high ultrasonic spatial resolution at sufficient imaging depths (up to centimeters) [1–5]. Meanwhile, PA imaging has been demonstrated successfully in various disease detection such as peripheral nerves, brain imaging and spatial characterization of lipid content in atherosclerosis [6–8]. Physiological indices such as hemoglobin oxygen saturation or carboxyhemoglobin saturation in the blood are also measurable by decoding multispectral PA imaging [9, 10]. Benefiting from the superiority of PA imaging, it has been widely applied in the area of biomedical imaging in the modalities of full-view tomography [11, 12], microscopy [13–15] and endoscopy [16–18].

Intravascular PA endoscopic tomography is an important application of PA imaging, which has great potential for clinical meticulous examination of blood vessels in vivo. In 2010, Emelianov et al. first introduced an external laser-irradiating and internal ultrasound-detecting intravascular PA imaging modality for differentiating healthy and sick vessels, which qualitatively demonstrating the optical absorption properties of plaque components [19, 20]. Thereafter, several groups such as Li et al., Chen et al., Jansen et al., and Song et al. developed internal laser-irradiating intravascular PA imaging modalities sequentially for atherosclerotic plaque-related research [21–24]. Recently, we designed a catheter-based multispectral intravascular PA imaging system to realize a concentration-based lipid map of the whole three-dimensional (3D) space of plaques and the detection of macrophages within atherosclerotic inflammation [25]. However, although previous studies have demonstrated the feasibility of intravascular PA imaging in plaque detection, the detection sensitivity and spatial
resolution still hinder the development of this technique in human intravascular clinical research and applications. The spatial resolution decreases rapidly as the focused light is defocused with increasing tissue depth. Therefore, we first proposed and realized symmetrically aligned dual-element ultrasonic detection in an intravascular PA endoscope to ameliorate the resolution reduction caused by laser scattering with increasing depth by improving the detection sensitivity. The spatial resolution and sensitivity of the system was examined by imaging carbon fibers, and experiments were conducted on normal and atherosclerotic vessels to demonstrate the imaging ability of the system. The confocal modality provides solutions to achieve high-sensitive intravascular PA imaging.

2. Methods and materials

Figure 1(a) shows a schematic of the intravascular confocal PA endoscope, which consists of a nickel tube, a single mode fiber (SMF) (S630-HP, Thorlabs), a customized gradient index (Grin) lens, a prism, and a dual-element transducer. The length and outer diameter of the nickel tube are 20 mm and 1.2 mm, respectively. A custom-made Grin lens with a diameter of 0.5 mm and a focus distance of 5 mm is used to focus the laser from the SMF to the prism (Right Angle Prism, Edmund). The inclined plane of the prism is purposely tilted at an angle of 60° to reflect the focused laser beam to top of the transducers. Following the widely used method to evaluate the surface laser fluence in optical-resolution PA imaging [26], the output laser energy from the endoscope is limited to ~400 nJ per pulse, corresponding to a fluence of ~12 mJ/cm² per pulse at the tissue surface (assuring the optical focus is 1 mm below vessel), which is below the 20 mJ/cm² safety standard of the American National Standard Institute (ANSI) safety standard. A window is opened at the side of the tube to allow the delivery of the laser beam for PA excitation and acoustic reception. The transducer elements with dimensions of 1.1 mm × 0.3 mm are symmetrically placed on both sides of the reflected laser to form an acoustic focus with focal length of ~2.5 mm and an angle of about 148°, in accordance with the length from the center to the vessel wall. Each element of the transducer has a coaxial cable with an outer diameter of 200 μm, the end of which is combined with bayonet nut connectors (BNC). The laser beam is focused into the acoustic focus area to improve the detection sensitivity. Figure 1(b) shows a photograph of the intravascular confocal PA endoscope with an outer diameter of 1.2 mm.

Fig. 1. (a) Architecture of the endoscopic probe. Transducer elements with an angle of about 148° are symmetrically placed on both sides of the reflected laser. (b) Photograph of the intravascular confocal PA endoscope.

A schematic of the whole imaging system is shown in Fig. 2(a). According to the absorption spectrum, the blood has a strong optical absorption in the range 400-600 nm, water-rich tissue greatly absorbs the energy of light from 900 nm to far-infrared range. Light in a narrow range of 600-900 nm can effectively avoid the strong absorption, which is known as an optical window for biomedical imaging, and the lipid absorption band reach its peaks between 750 and 760 nm [25], therefore, an optical parametric oscillator (OPO) laser (VIBRANT B 532I, OPOTEK) delivers 10-ns laser pulses at a wavelength of 750 nm was used to excite PA signals with a
repetition rate of 10 Hz. The laser beam is focused by a convex lens, which passes through a 50-\(\mu\)m pinhole for spatial filtering and finally focuses into the SMF using an objective lens (NA 0.1; Working distance (WD) 37.5 mm). The optical and electric slip ring (Fig. 2(b)) is used to connect the rotary fiber with the stationary fibre channel (FC) connector. The Grin-lens is used to focus the laser. A photodiode is used to monitor and calibrate the intensity and stability of the laser beam. The laser is reflected by the prism to irradiate the sample, and then PA signals are generated due to thermal expansion. The generated PA waves are detected by the dual-element focused ultrasound transducer. The PA signal is first amplified by 20 dB with an amplifier (ZFL-500, Mini circuits), then digitized and collected by a high-speed data acquisition card (NI 5124, National Instruments, USA) at a sampling rate of 100 MHz, and finally stored in the computer. The acquired PA data are post-processed for image display. All the processes mentioned above are controlled by a Labview program on the computer.

![Schematic diagram of the system.](image)

**Fig. 2.** (a) Schematic diagram of the system. PBS, polarizing beam splitter; POL, plan objective lens; AMP, amplifier; DAQ, data acquisition system; NDF neutral density filter; PD, photodiode. (b) Photograph of the optical and electric slip ring.

### 3. Results

#### 3.1 Enhancements of the PA signals

As a first demonstration of the performance of the system, we tested the detection sensitivity of the system by irradiating a normal vessel. New Zealand white rabbits were euthanized with an overdose of pentobarbital (3%, 120 mg/kg), the thoracic vessels were harvested and further detected with intravascular endoscope. The vessel was fixed in a hollow gelatin phantom, and the endoscope was inserted into the vessel lumen to detect the PA signals by single-element and dual-element ultrasonic transducers, separately. The results are shown in Figs. 3(a) and (b). The signal-to-noise ratio (SNR), which was defined as the ratio of the signal peak value to the root-mean-square value of the noise, of the PA signal detected by the single-element transducer was \(\sim 23\) dB, and that detected by the dual-element transducer was improved to \(\sim 28\) dB. An obvious amplitude enhancement of the PA signal was observed, which is because the receiving area of the dual-element transducer was double that of the single-element transducer. Meanwhile, the coherent superposition of PA signals from the symmetrically aligned dual-element ultrasound transducer with the same sound path also contributed to the enhancement of PA signals. As shown in Fig. 3(b), the amplitude enhancement of PA signal is slightly lower than the theoretical result of 6 dB. Two factors take the main role. First, due to the limitation of machining process, unavoidable size difference exists between the two single-element ultrasonic transducers. Second, the slight difference between the two sound paths of PA signal from laser point to transducer elements leads to a phase delay between PA signals. These factors result in the SNR enhancing without the maximum coherent superposition, which made the SNR gap between theoretical and experimental results. Then, an experiment was conducted to detect the frequency of the transducer by using pulse-echo measurement from a metal plane. Figure 3(c) gives the corresponding spectrum of the
dual-element transducer, showing a center frequency of 19 MHz and a –6 dB bandwidth of 58%. Finally, we calculated the signal-to-noise (SNR) of PA signals versus the radial position by irradiating a vessel. In Fig. 3(d), the SNR is presented (laser energy, 400 nJ/pulse).

3.2 Resolution evaluation of the system
To investigate the imaging resolution of the intravascular confocal PA endoscope, we employed an approximately 7-μm carbon fiber immersed in a hollow gelatin phantom as a target and acquired depth-resolved PA B-scan images with 1600 A-lines. The endoscope driven by a rotary motor was rotated in the hollow gelatin. Figure 4(a) shows a PA B-scan image of the carbon fiber at a radial position of about 2.5 mm, and Fig. 4(b) shows an enlarged view of the dashed box in Fig. 4(a). In Fig. 4(d), the transverse point spread function (PSF) for the target located at the focal point is presented, corresponding to the dashed line 1 in Fig. 4(b). The transverse resolution defined as the full-width half-maximum (FWHM) of the PSF was 13 μm at best.

Fig. 4. (a) PA B-scan image of the carbon fiber. (b) Enlarged view of the dashed box in (a). (c) PA B-scan image of carbon fibers with different locations and angles. (d) Transverse point spread function (PSF) for the target located at the focal point cut along dashed line 1. (e) Hilbert-transformed signal of PA A-line signal cut along dashed line 2. (f) The transverse resolution varies with depth.
The radial resolution was determined by ultrasonic center frequency rather than laser spot size. In our system, the radial resolution was measured by using an approximately 7-μm diameter carbon fiber. A Hilbert-transformed signal of the PA carbon fiber A-line signal is presented in Fig. 4(e), corresponding to dashed line 2 in Fig. 4(b). Owing to the small diameter of the carbon fiber, the FWHM of the envelope of the radial spread profile could be regarded as the radial resolution of the system. The radial resolution based on the FWHM of the profile was estimated to be 127 μm, which coincided well with the theoretical radial resolution of 124 μm estimated by the equation $R_a = 0.88(\frac{v_s}{\Delta f})$, where $v_s$ is the speed of sound and $\Delta f$ is the bandwidth of the transducer.

Then, seven carbon fibers were employed as the targets and inserted in gelatin with different angles and locations to estimate the transverse resolution variation with depth. Figure 4(c) shows a PA image of carbon fibers with different locations. As seen from Fig. 4(f), the transverse resolution deteriorates as the targets are moved away from the focus.

### 3.3 Imaging of normal and atherosclerotic vessels by the system

To validate the imaging ability of the intravascular confocal PA endoscope with enhanced PA signal, experiments were conducted to image a normal vessel in the New Zealand white (NZW) rabbit model by using single-element and dual-element transducer respectively, as shown in Figs. 5(a) and 5(b). The PA signal amplitude of the normal vessel along the dashed line were presented in Figs. 5(e) and 5(f). An obvious amplitude enhancement of PA signals received by dual-element transducer was observed compared with that of single-element transducer. Experimental results demonstrated the priority of confocal PA endoscope in intravascular PA imaging.

![Fig. 5.](image-url)

Fig. 5. (a) PA imaging of a normal vessel by using single-element transducer. (b) PA imaging of a normal vessel by using dual-element transducer. (c) PA imaging of a normal vessel. (d) PA imaging of an atherosclerotic plaque. (e)-(f) Distribution of the PA amplitude (dots) along the dashed line in (a)-(b). (h) Bright-field optical image of a normal vessel stained with oil red, targeting lipids. (i) Bright-field optical image of an atherosclerotic vessel stained with oil red, targeting lipids.

Thus, after verification of photoacoustic signal enhancement, experiments were performed to distinguish normal and atherosclerotic vessels in the New Zealand white (NZW) rabbit model. A New Zealand white rabbit was fed a high-cholesterol diet (97% normal chow, 2% lard, and 1% cholesterol) for 3 months to develop advanced atherosclerosis in the thoracic aorta. Control vessel samples were obtained from another rabbit maintained on a normal diet. Normal and atherosclerotic vessel samples were fixed in the transparent gelatin, and then we inserted the endoscope into the samples and performed endoscopic imaging. PA images of normal and atherosclerotic vessels are shown in Figs. 5(c) and 5(d). The structure, thickness and components of vessels were reflected in PA images. Figure 5(d) highlights the amplitude...
and location of PA signals, corresponding to the spatial distribution of lipid content in Fig. 5(i). Based on the difference in the optical absorption coefficients between the normal vessel and atherosclerotic vessel, lipid-rich regions with higher optical absorption lead to higher PA signals, which is the principle of detecting lipid plaques by intravascular PA endoscope. Clearly, the thickness of the plaque area was in the range from ~500 μm to ~750 μm, which was thicker than that of the normal vessel. After the PA images were obtained, the normal and atherosclerotic vessel samples were stained with oil red, a lipid-sensitive stain, and imaged using a stereo microscope, as shown in Figs. 5(h) and 5(i). Figure 5(i) shows that the plaques in the atherosclerotic vessel are lipid-rich, whereas no lipid is observed in the normal vessel in Fig. 5(h). The force applied to the tissue section in experiments resulted in the shape changing of the atherosclerotic vessel, thus images in Figs. 5(d) and (i) are not well matched. These results show that the intravascular confocal PA endoscope can distinguish normal and atherosclerotic vessels.

4. Discussion and conclusions

We first proposed and designed an intravascular confocal PA endoscope based on a symmetrically aligned dual-element transducer. The endoscope has an outer diameter as small as 1.2 mm and achieves an optical transverse resolution of 13 μm. The signal strength is quite different depending on the radial position of the sample and the spatial resolution decreases rapidly as the focused light is defocused with increasing tissue depth. To address this issue, we designed a dual-element transducer to receive the ultrasound with coherent superposition to ameliorate the resolution reduction. Furthermore, multi-element phased-controlled array transducer would be designed to improve the detection sensitivity of the PA signals in the future, but some challenges are still worth to overcome, mainly including: (1) Accurately aligning the dual-element transducer, the Grin lens and the prism inside the 1.2 mm diameter tube; (2) Improving the machining process to manufacture the dual-element transducer with more precise dimensions. Meanwhile, the PA imaging speed is restricted by the low repetition rate of the laser. Therefore, a higher repetition rate laser source [8] maybe the key technical improvement to promote clinical applications in intravascular photoacoustic imaging.

In conclusion, an intravascular confocal PA endoscope with a symmetrically aligned dual-element transducer was developed and tested. Reconstructed PA images of normal and atherosclerotic vessels were obtained ex vivo to verify the imaging ability of the system. This study shows that the intravascular confocal PA endoscope can provide higher sensitivity for better imaging of tissue and has great potential for detecting atherosclerotic plaque in vivo.

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