Intravascular photoacoustic detection of vulnerable plaque based on constituent selected imaging

Jian Zhang and Da Xing*

MOE Key Laboratory of Laser Life Science & Institute of Laser Life Science, College of Biophotonics, South China Normal University, Guangzhou 510631, China

E-mail: xingda@scnu.edu.cn

Abstract. Atherosclerosis, a disease of the large arteries, is the primary cause of heart disease and stroke. Over decades, atherosclerosis is characterized by thickening of the walls of the arteries, only advanced atherosclerotic disease could be observed. Photoacoustic imaging is a hybrid imaging technique that combines the advantages of high spatial resolution of ultrasound with contrast of optical absorption. In this paper, we present an intravascular photoacoustic (IVPA) imaging system to characterize vulnerable plaques by using the optical absorption contrast between different constituents. Epidemiological studies have revealed several important plaque constituents associated with early atherosclerosis, such as macrophage, cholesterol, lipid, calcification, and so on. We chose a section of lipid rich atherosclerosis artery and a section of normal artery as the phantom. Two IVPA images of them are given to show the difference between sick and normal. As a new method of detecting vulnerable plaque, IVPA constituents imaging will provide more details for diagnosis that offer an enticing prospect in early detecting of atherosclerosis.

1. Introduction
Atherosclerosis is a progressive disease which is the leading death world wide, because of plaque rupture causing heart disease and stroke. All of factors causing to a vulnerable plaque can be divided into morphology factors and functional factors. Traditionally angiography, diagnosis of atherosclerosis was possible only at advanced stages of disease, because they only evaluating the morphological of the large arteries. Vulnerable plaque typically has a thin fibrous cap and a lipid-rich necrotic core. At the same time, plaques can become increasingly complex because of functional changes. For example, calcification, ulceration at the luminal surface, and haemorrhage from small vessels that grow into the lesion from the media of the blood vessel wall, which can not be differentiate by the traditional methods easily [1-3].

In the past decades, a variety of diagnostic imaging techniques have been developed, such as optical coherence tomography (OCT), intravascular ultrasound (IVUS), computed tomography angiography (CTA) and magnetic resonance angiography (MRA) [4-8]. However, OCT must block blood flow, the resolution of IVUS is low, CTA has to use contrast agent containing iodine and patients suffer nuclear radiation, MRA techniques are sensitive to turbulent flow, which can cause proton spins to rapidly

* Correspondence author: Tel: +86-20-85210089, Fax: +86-20-85216052, Email: xingda@scnu.edu.cn
dephased thus causing a significant loss of signal, this can cause mis-diagnosis of stenosis. Furthermore, all of them are specific to imaging the structural characteristics.

Photoacoustic (PA) imaging is a relatively new kind of technique that has the potential to visualize constituents of the vulnerable plaques. In PA imaging, a short-pulsed laser source is used to illuminate a biological sample. The laser-generated photoacoustic signals that are excited by thermoelastic expansion resulting from a transient temperature rise on the order of 10 mk can be measured by a wide-band ultrasonic transducer; they are used to reconstruct an PA image. Therefore, PA imaging is a hybrid imaging technique that combines the advantages of high spatial resolution of ultrasound with contrast of optical absorption. Furthermore, PA imaging could provide functional information of tissues based on mapping of the differential optical absorption of tissue constituents, because of the different optical properties of different absorber [9, 10], we could differentiate the constituents from their mixture by using mult-wavelength PA imaging. In this paper, multi-wavelength PA imaging [11-13] technique and an IVPA imaging system based on IVUS imaging catheter were used to detect vulnerable plaque by constituents selected imaging.

2. Materials and methods

2.1. Animal model of atherosclerosis

A well-characterized animal model of atherosclerosis is used in the IVPA imaging experiments. Rabbits fed with high-fat diet are classical models for the study of atherosclerosis. In this study, we establish the atherosclerosis models by feeding high-fat diet plus and arterial intimal injury of the ventral aorta with balloon in a 1 year old New Zealand rabbit. After arterial intimal injury of the ventral aorta with balloon, rabbit was fed on a high-fat diet (normal rabbit feed 90%, cholesterol 2% and lard 8%) over a long period of time (6 months), The high-fat dietary regimen was utilized to induce fibro-cellular lesions comprised of inflammatory macrophage cells and lipids. For comparison, another rabbit was placed on a normal diet for the same period of time, this rabbit served as a control animal.

![Extinction spectrum of artery and fat](image)

**Figure 1.** The extinction spectrum of artery and fat.
The extinction spectroscopy [14] of artery (hard line) and fat (dash line) is shown in Figure 1, which is measured by spectrometer (Lambda 35, Perkin Elmer). According to the spectroscopy, the wavelength of laser is adjusted to 930 nm during the experiment, where the absorption of fat is higher than that of artery. A section of a lipid-rich atherosclerosis aorta obtained from a rabbit subjected to a high-fat for 6 months and a section of a normal aorta from the control sample obtained from a rabbit subjected to a normal diet for the same period of time were used in the IVPA experiment. The excised tissue was stored in saline for no more than 4 hours prior to the imaging experiments.

2.2. Experimental setup of multi-wavelength IVPA imaging
The setup for multi-wavelength intravascular photoacoustic imaging system is shown in Figure 2. A tunable pulsed Nd:YAG pumped optical parametric oscillator laser source (Vibrant B 532I, Opotek, USA) operating at the wavelength range of $\lambda = 690 – 960$ nm with a pulse wide of 10 ns and a pulse repetition rate of 10 Hz, was used to provided the optical illumination for photoacoustic imaging. The sample was immersed in a custom-built water tank, and a single element, 2.5 F, 0.83-mm diameter; 40 MHz IVUS imaging catheter (Atlantis SR Plus, Boston Scientific Inc.) was used to detect the photoacoustic waves generated by optical excitation. A revolving detection was driven by a computer-controlled stepper motor to rotate the phantom with a step size of 1.8 deg. The photoacoustic signals detected by the transducer were amplified by a low-noise preamplifier (ZFL-500LN, Min-circuit) and an amplifier (Ha2, Precision Acoustics LTD) before being fed to a digital oscilloscope (TDS 3032, Tektronix), which digitized the photoacoustic signals. Finally, a computer acquired the signals and stored the data for image reconstruction. A modified back-projection algorithm was employed to reconstruct the artery images from the photoacoustic signals.

![Figure 2. Schematic of the multi-wavelength IVPA imaging system.](image)

3. Results
Experiment was taken to demonstrate the ability of the IVPA imaging system. A black thermoplastic pipe with the diameter of 6 mm was used as a phantom. During the experiment; the phantom is irradiated by 532nm laser from outside while the detector is placed inside the lumen of it. The IVPA image (a) and cross-section photograph (b) is shown in Fig.3. It can be seen that IPVA image visualize the morphology of black tube, as well as, its unified optical absorption property.
Figure 3. Photoacoustic image (a) and photography (b) of a black tube cross-section using IVPA imaging

The IVPA images and the histological cross-sectional images of the control normal aorta (a, b) and atherosclerotic aorta (c, d) covering a field of view of 8 mm are presented in Figure 4.

Figure 4. IVPA images and the histology of the cross-section of the normal control aorta (a, b) and aorta containing plaques (c, d).

The histological cross-sectional images of the atherosclerotic aorta (d), the normal aorta (b) shows a thin wall, at the same time, the difference can be seen clearly from the IVPA images. Figure 4(a) shows a uniform thin wall while the IVPA image morphology of Figure 4(b) shows a different
character, the left region of it is thicker than the right region, which matched well with its histological cross-sectional image.

4. Discussion and Conclusions

IVPA images of atherosclerotic aorta (Figure. 4 (c)) indicate the presence of plaques and are clearly different from the IVPA images of normal aorta (Figure. 4 (a)). There are significant spatial and spectral variations in the energy of the photoacoustic signal within the plaque-rich. Figure. 4(a) shows uniform photoacoustic signal intensity, while the photoacoustic signal intensity of left region is stronger than the right region in the Figure. 4(c). As we know the intensity of photoacoustic signal associate with two factories, the intensity of laser pulse and the extinction coefficient of absorber at the wavelength. In our experiment, the laser beam intensity per pulse is limited to 1 mJ/cm² and keeps the same in the two experiments. This energy is well below the maximum permissible exposure of 20 mJ/cm² specified by the American National Standards Institute (ANSI-Z136.1). Therefore, the different absorption ability of the normal aorta and atherosclerotic aorta is the reason of signal intensity uneven. Laser of 930 nm is chosen in the experiment, where the extinction coefficient of fat is bigger than artery, as we can see in the spectroscopy of Figure. 1. The whole aorta wall of the normal aorta is uniform, and its photoacoustic signal is uniform. Yet, the left region of atherosclerotic aorta is lipid rich, where shows a strong absorption and produces strong photoacoustic signals at the wavelength of 930 nm.

![Image of extinction spectrum](image)

Figure 5. The extinction spectrum of cholesterol, hydroxylapatite and thrombus.

Furthermore, we measured the extinction spectrum of cholesterol, hydroxylapatite and thrombus presented in the Figure. 5, all of them are the constituents of the vulnerable atherosclerotic, which show quite different optical absorption. IVPA imaging utilizing the variation in the optical absorption may play a major role in the detection of vulnerable plaque by mult-wavelength.

The results of IVPA photoacoustic imaging of a lipid rich atherosclerotic artery at wavelength 930 nm indicated the potential to detect a vulnerable plaque by using mult-wavelength constituent selected imaging. However, more studies and significant understanding of the imaging technique are required to confirm the ability.

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