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Images of Arterial Tissues Using Catheter Swept-Source Optical Coherence Tomography

Youxin Mao¹, Costel Flueraru¹, Shoude Chang¹, Dan P. Popescu², and M. G. Sowa²

¹Institute for Microstructural Sciences, National Research Council Canada,
1200 Montreal Rd, Ottawa, K1A 0R6, ON, Canada

²Institute for Biodiagnostics, National Research Council Canada,
435 Ellice Avenue, Winnipeg, MB, Canada, R3B

ABSTRACT

Optical coherence tomography images of arterial samples harvested from asymptomatic pigs and from lipid-rich Watanabe heritable hyperlipidemic rabbits were acquired using a fiber catheter-based swept-source optical coherence tomography system (OCT). A quadrature Mach-Zehnder interferometer based on multi-port fiber couplers and a semiconductor optical amplifier (SOA) were employed in the swept-source optical coherence tomography system. The improvement of signal to noise ratio as a result of incorporating the SOA into the configuration translated in an increase of the penetration depth. A fiber probe ending in a fiber ball lens was developed for the arterial imaging. The images acquired by this system offer the possibility to investigate anatomical details located under the surface of the artery such as the intima, media, and adventitia layers (from lumen side) of the blood vessel wall, as well as morphological features specific to atherosclerotic plaques such as lipid pools, fibrous caps, macrophage accumulations and calcified. This report indicates that our improved catheter-based swept source OCT is a potential tool for *in vivo* intravascular imaging.

Keywords: biomedical imaging; arterial tissue; plaque; optical coherence tomography; quadrature interferometer; optical fiber probe.

1. INTRODUCTION

Optical coherence tomography (OCT) [1,2] can image tissue structure at micrometer-scale resolution. It has the potential to become an important imaging tool for many biomedical applications. OCT relies on the interferometric measurement of coherent backscattered light to detect variations of in the refraction index that mark interfaces between different constituents of complex test samples such as biological tissues or multi-layered materials. It is analogous to ultrasound B mode imaging, except that it uses infra-red light source rather than ultrasound. OCT takes advantage of the short temporal coherence length of broadband light sources used in these systems to achieve precise optical sectioning in depth. Swept-source OCT (SS-OCT) enables a significant increase in imaging speed and sensitivity [3, 4], overcoming the limitations encountered in high-speed OCT which uses standard time-domain detection. SS-OCT is particularly important for imaging at 1300 nm. The deeper penetration of OCT imaging into tissue when using a 1.3 μm wavelength light source is an important feature for biomedical imaging when compared to the lower penetration into tissue when imaging with a 1.0 μm or shorter wavelength light source. SS-OCT could be implemented with a quadrature interferometric system based on multi-port fiber couplers, such as a 3x3 quadrature interferometer [5]. Due to its ability to obtain instantaneous complex signals with stable phase information, a 3x3 quadrature interferometer suppresses the complex conjugate artifact, thus doubling the effective imaging depth [6, 7]. Recording the phase part of the OCT signal provides additional information about the probed tissue [8, 9]. In addition, the Mach-Zehnder configuration (MZI) allows different options for distributing optical power between the reference and sample arms. An unbalanced input directs more optical power from the light source to the sample than to the reference mirror [10] while balanced detection is used to reduce the beat noise [11]. Both techniques play a role in increasing the signal-to-noise ratio (SNR) of the system. However in the case of imaging biomedical samples, the signal backscattered from tissue is much weaker than the reference signal so an attenuation of optical power in the reference arm is required in order to increase the SNR. On the other hand, directly increasing the power of the light source does not necessarily result in a SNR increase [12].

* Linda.mao@nrc-cnrc.gc.ca; phone 1 613 993-7331; fax 1 613 954 3338; <http://ims-ism.nrc-cnrc.gc.ca/>

The ability of OCT to image vascular tissues has been previously demonstrated [13-17]. However, OCT images of the arterial wall are limited to depths of ~ 1 mm even when using Fourier domain methods. The limited imaging depth into the vascular wall is one of the most serious limitations for the routine clinical use of OCT for diagnostics intravascular imaging. Further improvement of the SNR of OCT is needed in order to increase the imaging depth into tissue. Adding an optical amplifier into the path of the backscattered light in the sample arm of an SS-OCT system with a balanced Michelson interferometer [18] and a 2x2 MZI configuration [19, 20] has been proposed. Unfortunately, in these configurations the noise level is also amplified together with the signal leading to only a modest (~ 2 dB) SNR improvement. Recently we reported [21] that the cross-beat noise between the reference power and the spontaneous emission power of the optical amplifier is suppressed in a swept-source optical coherence tomography system using a quadrature interferometer when using a semiconductor optical amplifier to amplify the weak signal from the sample. In this configuration, a 14 dB increase of the SNR is obtained when compared to the system without the optical amplifier. Overall, an improvement was demonstrated in recording the signal coming from deeper regions within the samples.

In this paper, a fiber catheter-based SS-OCT system with a quadrature interferometer using a semiconductor optical amplifier (SOA) for the amplification of the weak light in the sample arm is demonstrated. Healthy porcine left-descending coronary tissues and lipid-rich arterial plaque from WHHLMI rabbits are visualized and characterized with this system. Preliminary results show that normal arterial structures and plaques with fibrous cap, macrophage accumulations and calcifications are measurable with our OCT system, which is able to image features located as deep as 1.7 mm from the lumen surface.

2. METHOD

Fig. 1. Schematic diagram of our fiber catheter-based SS-OCT system using a balanced compound 3x3 and 2x2 quadrature MZI interferometer and a SOA for sample signal amplification.

Fig. 1 shows a schematic diagram of our fiber catheter based SS-OCT system. The system uses a balanced compound 3x3 and 2x2 quadrature MZI interferometer and a SOA for sample signal amplification. The swept source (HSL2000-HL, Santec) used in the system had a central wavelength of 1320 nm and a full scan wavelength range of 110 nm, which was linearly swept on the optical frequency scale with a linearity of 0.2%. The axial resolution of the OCT system is determined by the bandwidth of the swept-source therefore, a 5 μ m axial resolution in tissue with 1.3 optical refraction index is estimated. The average output power and coherence length of the swept source was 12 dBm and 10 mm, respectively. A repetition scan rate of 20 kHz was used in our system and the related duty cycle was 68%. The output light from the swept laser source was launched into the first coupler and divided by two fiber circulators with 90% of the available power directed toward the sample arm while the rest of the light was guided into the reference arm. The reference arm ended with a fiber collimator and a mirror. Light was focused onto the sample through a lensed single mode fiber located at the end of the sample arm. A galvanometer (Blue Hill Optical technologies) scanned the tip of the fiber probe along the sample surface, with a 20-Hz frequency and a travel length up to 4 mm, corresponding to OCT images which were 900 transverse pixels (A-scans) wide. The total optical power illuminating the sample was approximately 10 dBm. The weak light back-scattered from the sample was fed into a SOA (Covega) whose gain could be adjusted by a variable attenuator connected along the sample arm after the SOA. The SOA had the same center

wavelength and bandwidth as the swept source. Its gain could be varied from 15 dB to 35 dB. The amplified reflected sample signal was combined with the returning light from the reference mirror through the output couplers using compound the 3x3 and 2x2 optical couplers together with two fiber attenuators in order to implement a complex dual-channel balanced detection scheme. The two outputs were digitized using a data acquisition card (DAQ) (Alazartech, Montreal) with 14-bit resolution and a sampling speed of 100 MS/s. The swept source generated a start trigger signal that was used to initiate the function generator for the galvo scanner and initiate the data acquisition process for each A-scan. Because the swept source was linearly swept with wave-number k , A-scans data with resolved complex conjugate artifact were obtained by a direct inverse Fourier transformation (IFT) from DAQ sampled data without any re-sampling process. The optical power in the system was optimized to ensure high sensitivity imaging.

In an OCT system, the light exiting the sample arm will be directed toward a sample. Based on the interaction of this light with the sample, imaging depth into a tissue sample ranges from 0.5 mm to 3 mm when the system uses near infrared wavelengths of light. For example, penetration depths range from 0.7 mm in human skin to 3.0 mm in liver respectively at 1300 nm, a conventional wavelength used in OCT systems. Thus, when designing an optical probe for OCT the working distance should be in the range of 0.4 mm to 1.2 mm depending on the tissues to be tested [22, 23]. The proper depth of field is also in the range of 0.4 - 1.5 mm in the air and this parameter keeps the spot size in the range of 18 to 35 μm at the 1300 nm wavelength according to the tradeoff existent between the depth of field and the size of beam spot for a Gaussian beam. The quality of the probing beam is crucial for the performance of an OCT imaging system. Ideal characteristics of a fiber-optic probe include a clean Gaussian beam intensity profile, an appropriate intensity-distance shape, high flexibility, and low optical aberration and loss.

Fig. 2. Scanning electron micrographs of fiber ball lenses used in a forward-view (a) and a side-view (b) probes with a measured beam profile image (c).

The probe in the OCT sample arm used to acquire OCT images in this study was a ball lens fiber. Fig. 2 shows typical scanning electron micrographs of the fiber ball lenses fabricated in our laboratory used in a forward-view (a) and a side-view (b) probes with a ball size of 0.3 mm. The ball lens has about 1 mm working distance and a 28- μm spot size, which determined the lateral resolution of the OCT images. This spot size corresponds to a 0.9-mm depth of field. When side-view fiber ball lens probes are used, fiber beam rotators could be attached to the tip of the fiber lenses. Thus, the output beam can be reflected to 90 degrees by a 45-degree polished face on the ball lens, as shown in Fig. 2 (b). To further examine the beam quality of the ball lens, beam profile images and normalized intensity distributions with Gaussian-fitted results in the x and y directions were measured. Fig. 2 (c) shows a typical measured beam profile image of the fiber ball lens fabricated in our laboratory. The measured beam profiles match Gaussian distributions very well. The circular shapes in the beam profile images, such as the one shown in Fig. 2 (c), indicate high x and y symmetry of the beam profiles through the whole range of the depth of field. The fiber lens tip together with a tubing system for protection and a connected linearly scanning or 360 degrees rotating motor could be built as an endoscope or a needle probe to be used in the biomedical optical imaging system for *in situ* and *in vivo* minimally invasive diagnostic and/or guided surgery and treatment applications.

3. IMAGING RESULTS

The first class of tissues tested in this study was porcine arterial samples from healthy pigs. Segments of coronary left descending artery from three porcine specimens were snap-frozen and stored at -80°C after they were harvested. After a short period of thawing at the room temperature the arterial samples were cut open to expose their luminal surface to the OCT beam as shown in Fig. 3. The catheter was used in the forward view geometry with the arterial sample placed in a

horizontal position with the lumen exposed to the probing beam. The ultra-small fiber ball lens probe was covered with a plastic shield for protection. The acquisition of images was conducted at room temperature in two directions: parallel and perpendicular to the direction of the blood flow.

Fig. 3. A pig coronary left descending arterial piece cut along the direction of blood flow with the lumen surface facing up. A portion of the OCT fiber ball lens probe is displayed during the acquisition of an OCT image. The forward-view ball lens fiber is protected by a plastic tube.

Fig. 4. OCT images (B-scans) of the porcine arterial tissue acquired using a forward-view ball lens probe while scanning (a) along the blood flow and (c) perpendicular to the blood flow with image size of $2 \times 3 \text{ mm}^2$. Differences in texture are observed between the two images. (b) and (d) are the corresponding histology sections.

Fig. 4 (a) shows an example of an OCT image (B-scans) of a porcine artery. The image acquisition was performed with the fiber probe scanned parallel to the direction of blood flow. The axial and lateral dimensions of the image are 500 x 900 pixels respectively which correspond to an image size of 2 x 3 mm². The image size was calibrated using a one-mm glass slice and an assumed arterial refractive index of 1.3. The three layers of the vessel wall anatomy were visualized: tunica intima (TI), tunica media (TM), and adventitia. The tunica intima is a thin layer inside the blood vessel that also contains the endothelial layer. The tunica media follows the tunica intima and consist of elongated muscle cells and elastin fibers. The outer layers contain vessels of adventitia (VA) and tunica adventitia (TA). They are largely composed of collagen fibers with the role to protect and to anchor the vessel to the surrounding structures. Readable signal is obtained from depths of 1.5 mm into the sample. These structures were distinguishable in a standard histological preparation of the sample as shown in Fig. 4 (b). Fine circular muscles in the tunica media layer were also well visualized in the OCT image acquired with the probe scanned perpendicular to the direction of blood flow, Fig. 4 (c). The features observed in the OCT image were confirmed by a comparison to the histology of the sample, as shown in Fig. 4. (d).

Fig 5. An opened aorta from a Watanabe heritable hyperlipidemic (WHHLM) rabbit being scanned along the direction of blood flow with the forward ball lens fiber probe protected by the plastic tube. The luminal surface is facing the probing beam.

Another sample used in this study is shown in Fig. 5 and corresponds to part of the descending aorta from a 9-month old rabbit breed that develops spontaneous plaques. The atherosclerosis-prone Watanabe heritable hyper-lipidemic (WHHL-MI) rabbits are a suitable animal model to study familial hypercholesterolemia and atherosclerosis [24]. Arteries in these rabbits develop atheromatous plaques similar to those in humans. The arterial sample was cut along the blood flow with the lumen facing the OCT probe. There are fatty deposits on the lumen surface that show as white regions in the picture. The motion of the OCT probe head ensures the scanning width necessary to obtain a B-scan that is about 3 mm wide.

Fig. 6 (a) shows an OCT image collected from an un-opened descending aorta acquired from a WHHL-MI rabbit. The sample is scanned by the beam of the swept-source OCT system while placed on a microscope slide. The OCT image collected from the samples was acquired by scanning the probing beam in the direction perpendicular to the blood flow. There are several structures of the artery that are seen very clearly in this image. First of all, there is a portion of the lumen imaged through the upper tissue of the collapsed artery. The anatomical composition of the top-side is labelled in the image; the serosa (SR), vaso-vasorum (VV), tunica adventitia (TA), tunica media (TM) and tunica intima (TI). The vaso-vasorum is a network of vessels that feed the artery with nutrients and can be seen penetrating the adventitia.

(a)

(b)

(c)

Fig. 6. OCT image ($2 \times 3 \text{ mm}^2$) of a descending aorta; for an un-opened piece (a) and opened pieces (b, c) from a WHHLMI rabbit. The images were acquired with our SS-OCT system and clearly show several anatomical features in detail: lipid cores (LC), fibrous caps (FC), calcified regions (CR), fat tissues (FT), muscle cells (MC).

Fig. 6 (b) and (c) show OCT images of an opened segment of aorta (obtained after cutting the aorta along the direction of blood flow in order to expose the lumen to the probing beam) in two locations. The images have the same dimensions as the image shown in Fig. 4. In Fig. 6 (b) and (c), details such as lipid cores (LC) with macrophage accumulations and non-uniform reflectance coefficients within their volume are evident. Thin fibrous caps (FC), which strongly scatter light, cover the lipid cores. The fibrous cap thickness was defined as the minimum distance from the lumen of the vessel to the upper border of the lipid pool. This quantity is important because it is a major determinant of plaque vulnerability

in lipid-rich plaques. The thickness of the fibrous cap could be measured from the acquired OCT images. A few calcified regions (CR), characterized themselves by uniform and low reflectance, were also clearly discernable. Some fat tissue (FT) was identified beneath the calcified regions as pointy high reflectance coefficients. The fat tissue (FT) with pointy high reflectance coefficients were less dense than the lipid cores (LC) with macrophage accumulation. The regions with uniform reflectance correspond to bundles of smooth muscle cells (MC), which can be viewed up to depths of 1.7 mm even through the upper fat tissue and calcified regions. The results obtained from OCT images of WHHLM arteries acquired with our QSS-OCT were in agreement with the histological sections obtained from this type of samples and shown in the Fig. 4 of ref. [24].

4. CONCLUSION

Identification of lipid-rich cores and measuring the thicknesses of their corresponding fibrous caps are important for quantifying the vulnerability of arterial plaques. We demonstrated an OCT setup, based on a catheterized SS-OCT system with a quadrature Mach-Zehnder interferometer and a semiconductor optical amplifier for weak sample signal amplification, which can quantify these clinical aspects. The images acquired with this system offer the possibility to investigate micro-morphologies and clinical conditions located on and under the luminal surface of the artery wall. The results show that catheter-based swept source OCT with sample signal amplification is an effective imaging modality suitable for real-time diagnosis and with high potential for *in vivo* applications.

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