Intravascular atherosclerotic imaging with combined fluorescence and optical coherence tomography probe based on a double-clad fiber combiner

Shanshan Liang
Arya Saidi
Joe Jing
Gangjun Liu
Jiawen Li
Jun Zhang
Changsen Sun
Jagat Narula
Zhongping Chen
Intravascular atherosclerotic imaging with combined fluorescence and optical coherence tomography probe based on a double-clad fiber combiner

Shanshan Liang,a,b Arya Saidi,b Joe Jing,b Gangjun Liu,b Jiawen Li,b Jun Zhang,b Changsen Sun,b Jagat Narula,c and Zhongping Chenb

aDalian University of Technology, School of Physics and Optoelectronic Engineering, Ganjingzi District, Dalian City, Liaoning Province, China
bUniversity of California, Irvine, Beckman Laser Institute, Irvine, California
cUniversity of California, Division of Cardiology, Medical Center, Irvine, Orange, California

Abstract. We developed a multimodality fluorescence and optical coherence tomography probe based on a double-clad fiber (DCF) combiner. The probe is composed of a DCF combiner, grin lens, and micromotor in the distal end. An integrated swept-source optical coherence tomography and fluorescence intensity imaging system was developed based on the combined probe for the early diagnosis of atherosclerosis. This system is capable of real-time data acquisition and processing as well as image display. For fluorescence imaging, the inflammation of atherosclerosis and necrotic core formed with the annexin V–conjugated Cy5.5 were imaged. Ex vivo imaging of New Zealand white rabbit arteries demonstrated the capability of the combined system. © 2012 Society of Photo-Optical Instrumentation Engineers (SPIE).

Keywords: optical coherence tomography; fluorescence; atherogenesis; double-clad fiber; annexin V.

Paper 12219L received Apr. 6, 2012; revised manuscript received May 16, 2012; accepted for publication May 22, 2012; published online Jun. 28, 2012.

1 Introduction

Atherosclerosis can cause serious cardiovascular diseases. The rupture of atherosclerotic plaque can lead to embolism downstream and the occurrence of acute coronary syndromes such as myocardial infarction and stroke, which cause irreversible damage to patients or even lead to their deaths. Therefore, early detection of plaque lesions is very important to prevent lethal consequences of atherosclerosis. Diagnosis of the latent vulnerability of a plaque lesion relies on both structural and tissue chemical compositions. Structurally, the thickness of the fibrous cap is a reliable indicator of plaque vulnerability. Chemically, the intralesion lipid density is a parameter that correlates with the vulnerability of the lesion. Intravascular ultrasound (IVUS) and optical coherence tomography (OCT), currently the two most commonly used modalities in clinics for diagnosing cardiovascular diseases, allow direct tomographic visualization of cross-sectional images from inside the vessel lumen. IVUS has been used clinically to diagnose atherosclerosis for more than 20 years. However, IVUS has limited resolution of 50 to 200 μm, which is not enough to resolve the thin fiber cap of the high-risk vulnerable plaque with typical thicknesses of 50 to 60 μm. On the other hand, OCT can provide cross-sectional images of tissue microstructure with a spatial resolution on the order of 5 to 10 μm. Therefore, intravascular OCT can be used to accurately assess thickness of fibrous caps and other microstructure information of vulnerable plaques. Although OCT has been used for vulnerable plaque evaluation with its high resolution, it lacks molecular specificity for identification of tissue composition in plaques. Intravascular fluorescence molecular imaging endoscopy provides biomolecular information of atherosclerosis inside the blood vessel. Combining high spatial resolution of OCT with molecular sensitivity of fluorescence imaging is capable of resolving both microstructure and biomolecular information at the same time.

In this paper, an integrated swept-source OCT and fluorescence intensity imaging system was demonstrated based on a multimodality endoscopic probe. A micromotor was used for circumferential scanning of the inner blood vessel wall. This distal scanning design eliminates the disadvantage of unstable vibration and uneven rotational speed in a proximal scanning design and can be applied to more flexible materials without the need of rotational torque transfer. The OCT and fluorescence imaging were obtained simultaneously and in real time. The capability of the integrated OCT-fluorescence imaging system was demonstrated by ex vivo imaging of specimens from New Zealand white rabbit arteries.

2 Materials and Methods

The diagram of an integrated swept-source OCT (SSOCT) fluorescence system is shown in Fig. 1a. The SSOCT system is similar to the one used in Ref. 9. A continuous-wave laser diode (Mespel, RS635) with a center wavelength of 635 nm and output power of 5 mW was used as the excitation source. A photomultiplier tube (PMT) (Hamamatsu, H9305-01) was used to detect fluorescence emission light. For our experiments, we used Cy5.5, a fluorescence dye with a peak excitation wavelength of around 675 nm (33% of the peak efficiency at 635 nm) and a peak emission wavelength of around 690 nm. The excitation light and the OCT beam were combined together with a wavelength division multiplexer (WDM coupler 635/1310). A double-clad fiber (DCF) combiner [Avensys Tech, (2 + 1) × 1 Pump and Signal Combiners, MMC02112A60] with one single-mode fiber port, one multimode fiber port, and one DCF port was used to deliver the OCT and fluorescence excitation light beams to the sample and collect the OCT signal and fluorescence emission light. The OCT signal and fluorescence excitation light were transported through the 8-μm core of the DCF, and the back-reflected fluorescence emission light was collected through the 105-μm inner cladding of the DCF. Fluorescence emission light back-scattered from the sample was coupled back through the multimode fiber port of the...
combiner and detected by the PMT. The use of single-mode DCF core to deliver the fluorescence excitation light improved lateral resolution of the fluorescent image.

The diagram of the dual-modality intravascular probe with outer diameter of 2.3 mm is shown in Fig. 1(b). A linear motor outside the endoscope was used to pull back the entire probe to create 3-D helical OCT scanning and achieve a 2-D superficial fluorescence intensity image. OCT and fluorescence emission signals were digitized by a two-channel, 250 M samples/s, 12-bit data acquisition card and transferred to a computer for processing. Data processing software was developed to handle OCT and fluorescence data acquisition, processing, image display, and data saving simultaneously and in real time.

To evaluate the integrated system, we imaged an excised segment of normal New Zealand white rabbit aorta injected with 0.01 mL of a model plaque material of highly saturated grease. Two model plaques were made side by side on the same piece of tissue, with one mixed with 0.1 μmol/L Cy5.5. In addition, an atherosclerosis-induced New Zealand white rabbit aorta was

Fig. 1 (a) Schematic of the optical coherence tomography (OCT)-fluorescence system. Black line denotes single-mode fiber (SMF28), red line denotes multimode fiber, and blue line denotes double-clad fiber (DCF). (b) Intravascular probe based on a DCF combiner. OCT and fluorescence excitation light are transported through the single-mode core of the DCF; the back-reflected fluorescence emission light is collected through the inner cladding of the DCF.

Fig. 2 Schematic (a) and fused fluorescence- optical coherence tomography (OCT) image (b) of normal rabbit aorta injected with 0.01 mL of model plaque material. The thickness of the plaque cap is around 128 μm as indicated in label (d). The color scale in (b) shows the relative intensity of the fluorescence signal. 3-D OCT image (c) is combined with 2-D fluorescence image (d).
Annexin V

Opt. Express

Circulation shows that the OCT image of the mimic plaque

shows the 3-D OCT image and

Circ. J.

3

Combined optical coherence tomography-fluorescence image

study on an athero-

29

–

Arterioscler. Thromb.

Vol. 17(7)

shows the schematic of the two phantom plaques


2(d)

imaged for ex vivo study. Annexin V–conjugated Cy 5.5 was

used to target the plaques and stain the tissue. The tissue was

stained for 24 h before imaging. Annexin V is an antibody

that targets apoptotic macrophages that accumulate in the necro-
tic core, a key feature of vulnerable plaques.

3 Results and Discussion

Figure 2(a) shows the schematic of the two phantom plaques

inside the blood vessel wall. Figure 4B illustrates the fused

fluorescence-OCT image of the model plaques. The power of

OCT on the sample is around 1.5 mW. The fluorescence signal

was obtained by averaging the fluorescence signal within an

OCT a-line acquisition time. The fluorescence signal was gen-

erated from the model plaque under the tissue surface, demon-

strating that our system is capable of detecting weak signals

from deep tissue. Figure 4B shows the 3-D OCT image and

Fig. 2(b) shows that the OCT image of the mimic plaque

matches well with the 2-D fluorescence intensity image. This

experiment demonstrates that our system is capable of detecting

both OCT and fluorescence intensity signals simultaneously.

In addition, we carried out an ex vivo study on an athero-
sclerotic rabbit aorta, stained with annexin V–conjugated

Cy5.5, which contained some plaques. Figure 5 shows the

cross-sectional OCT image and the corresponding fluorescence

intensity image of the sample. From the OCT image in Fig. 4, it

is hard to distinguish the structural difference between all the

bumps, whereas the fluorescence intensity image indicates

certain regions contain phosphatidylserine (the target for

apoptotic macrophages) by detecting annexin V which was

bound to it. The phosphatidylserine in these regions is due to

formed necrotic cores or inflammation with significant macro-

phage infiltration, which are the characteristics of early-stage

vulnerable plaques.

The integration of these two techniques will help to detect

high-risk plaques at an earlier stage. OCT is capable of detecting

structural features, such as the thickness of the plaque cap and a

large lipid pool. Fluorescence intensity imaging can show the

molecular information underlying the atherosclerotic plaque,
such as inflammation or the formation of a necrotic core. We

can choose different agents to target various molecular factors

for high-vulnerability plaques. Therefore, integrating these two

modalities will provide physicians with a powerful tool to image

and diagnose vulnerable plaques and monitor therapeutic
efficacy at an earlier stage than is currently possible.

4 Conclusion

We present an integrated OCT and fluorescence intensity

imaging system that can be used in cardiology to diagnose

detect high-risk vulnerable plaques. The system is capable

of real-time OCT imaging as well as superficial fluorescence

intensity imaging simultaneous. The ex vivo experiment showed

that this integrated imaging modality can provide both structure

and molecular information that may enable diagnosing vulner-
able plaque at an earlier stage. Although significant research

remains to be done to translate this technology to clinical appli-
cations, the results reported here clearly demonstrate the poten-
tial of integrated OCT-fluorescence imaging for characterization

and diagnosis of vulnerable plaques. Furthermore, the integrated

OCT-fluorescence imaging system can also be used for imaging

and diagnosis of cancers in gastrointestinal, respiratory, and

urogenital tracts.

Acknowledgments

This work is based on the research supported by the NIH

(grants R01EB-10099, R01HL-105215, K25HL-102055, and

P41-EB2182) and the AFOSR (FA9550-08-1-0384). Shanshan

Liang is supported in part by the China Scholarship Council

(CSC) and works as a joint Ph.D. student at the Beckman

Laser Institute, University of California, Irvine.

References

1. R. P. Choudhury and E. A. Fisher, “Molecular Imaging in atherosclero-
sis, thrombosis, and vascular inflammation,” Atheroscler. Thromb


2. J. Yin et al., “Integrated intravascular optical coherence tomography


3. W. Drexler, “Ultra-high-resolution optical coherence tomography,”


4. Y. Liu et al., “Assessment by optical coherence tomography of stent

struts across side branch: comparison of bare-metal stents and drugelut-

5. H. C. Yang et al., “A dual-modality probe utilizing intravascular ultra-

sound and optical coherence tomography for intravascular imaging


57(12), 2839–2843 (2010).


imaging of atherosclerosis: toward coronary arterial visualization of


7. H. Yoo et al., “Intra-arterial catheter for simultaneous microstructural


8. A. R. Tumlinson et al., “Miniature endoscope for simultaneous optical

cohere tomography and laser-induced fluorescence measurement,”


9. J. Su et al., “In vivo three-dimensional microelectromechanical

endoscopic swept source optical coherence tomography,” Opt. Express


10. K. Ohtsuki et al., “Detection of monocyte chemoattractant protein-1

receptor expression in experimental atherosclerotic lesions,” Circulation

