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Integrated intravascular optical coherence tomography (OCT) - ultrasound (US) catheter for characterization of atherosclerotic plaques *in vivo**

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Abstract—A miniature integrated intravascular optical coherence tomography (OCT) – ultrasound (US) catheter for real-time imaging of atherosclerotic plaques has been developed, providing high resolution and deep tissue penetration at the same time. This catheter, with an outer diameter of 1.18mm, is suitable for imaging in human coronary arteries. The first *in vivo* 3D imaging of atherosclerotic microstructure in a rabbit abdominal aorta obtained by an integrated OCT-US catheter is presented. In addition, *in vitro* imaging of cadaver coronary arteries were conducted to demonstrate the imaging capabilities of this integrated catheter to classify different atherosclerotic plaque types.

I. Introduction

Heart attack is a major cause of death in developed country. In the United States alone, 7.9 million individual suffers from heart attack in 2011[1]. With aging population, these numbers are still increasing. Heart attacks are mainly(86%) due to rupture of a vulnerable atherosclerotic plaque in a coronary artery[2].

Pathological studies have revealed a prototypic vulnerable plaque, thin-cap fibroatheroma(TCFA). It is characterized by:1)a large lipid pool, 2) an overlying thin fibrous cap(<65um)[3-4]. Recently, imaging technologies for analyzing the risk of plaque ruptures are advanced quickly[4-5]. However, no technology to date has demonstrated the ability to identify all of the characteristic features of TCFA. For over 20 years, intravascular ultrasound (IVUS) imaging has been a commonly used diagnostic tool to visualize plaque and predict proneness of a plaque to rupture. "Positively remodeling" and "high eccentricity" have been introduced as markers for potential high-risk plaque[6-7]. Yet none of these factors are optimally predictive of TCFA, due to intrinsically limited resolution of IVUS [8-9]. Lately, OCT is translated from an imaging technique to a clinical utility. With its superior axial(5~15um) and lateral resolution, Optical coherence tomography (OCT) provides an innovative insight for vulnerable plaque research[3]. More recently, a study has verified the feasibility of the combined use of separately acquired IVUS and OCT data for diagnosing vulnerable plaque in patients. The results revealed that neither modality alone is adequate for identifying vulnerable plaques. Contrarily, the combined use of OCT and IVUS, providing accurate imaging of entire artery wall[4], is a practicable tool for diagnosing vulnerable plaques.

We propose that simultaneous IVUS-OCT imaging with a single integrated probe is more sensitive and precise in evaluating vulnerable plaque. Integrated IVUS-OCT system provides high resolution for imaging the thickness of the fibrous cap and deep penetration for imaging the whole lipid pool at the same time. By identifying these two major characteristics of a vulnerable plaque, the integrated system permits accurate identification of patients with high-risk of sudden heart attack. Additionally, in the integrated system, under the guidance of IVUS, minimal dose of OCT flushing agent is needed , while it diminishes side effect caused by the flushing agent . Meanwhile, operation time and cost will be highly reduced compared to using IVUS catheter and OCT catheter separately. In previous research[10-12], our group has developed an integrated IVUS-OCT imaging system and several probe designs. *In vivo* 2D healthy rabbit imaging and a pilot *in vitro* imaging of cadaver coronary artery with calcified plaque were conducted. However, translation this technique to clinical applications still requires: 1) development of a catheter for potential human experiment. 2) validating the accuracy of discriminating atherosclerotic plaque types by this system. In this paper, *in vitro* imaging of cadaver coronary arteries with calcified and lipid atherosclerotic plaques, two foremost types of plaques, were conducted to demonstrate the capability of IVUS-OCT system imaging and classification of different plaque type. *In vivo* 3D imaging of atherosclerotic microstructure in a rabbit abdominal aorta is also reported for assessment of our catheter and procedure designs, paving our road for porcine experiment and human pilot study.

II. Material and Methods

A. Imaging probe and system design

We developed a miniature integrated optical coherence tomography–ultrasound probe, which is small enough for

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TABLE I. Specifications of the integrated IVUS-OCT catheter

	Criterion	Solution	Notes
General dimensions	Total Usable Length	140cm	135cm~140cm is standard length for intracoronary catheter.
	Intracoronary Usable Length	>15cm	This enables that possible evaluation length by our catheter is 15cm.
Rotation transmission	Transmit rotation at polar-axial direction	Torque coil	It is necessary for rotational scanning of imaging probe.
	Be flexible at radial direction	Torque coil	During clinical procedure, catheter is inserted via a femoral artery and turned into heart through a sharp bend. Catheter should be able to transmit rotation even at this position.
Catheter distal end Fig.1	X-ray detectable	2 metal bands	It facility the detection of precise position of this catheter.
	6F guide catheter compatibility	0.40mm inner diameter channel	6F guide catheter is standard catheter for percutaneous coronary intervention (PCI) procedure.

imaging in coronary artery. More detail about probe design and the integrated system setup can be found in Yin *et al[11]*.

B. Catheter design

To suit the necessities of clinical procedures, our catheter (including the probe and outer sheath, Fig.1) satisfies the above criteria, TABLE I.

C. Rabbit model

Six male New Zealand White rabbits were fed by a high-cholesterol diet(0.5% cholesterol 6% peanut oil). After 1 week on diet, deendothelialization procedure was performed in all rabbits. The rabbits were anesthetized and incubated during the surgical procedures. A Fogarty arterial catheter was inserted via a femoral artery in the groin area and advanced into the aorta, inflated to 8 atm and pull back to the abdominal aorta. Experiments followed the guidance of UC Irvine institutive review board approved protocol. After 12-16 weeks of diet, plaque formation is mature. This plaque produced by balloon deendothelization and special diet is similar to human atherosclerosis.

During imaging procedure, anesthetized was induced to the rabbit for imaging. A 6-F guiding catheter was inserted into the aorta and led the IVUS-OCT catheter to the imaging position. OCT and US imaging were performed simultaneous with an automatic pullback device(Newport inc. linear stage)at a rate of 0.2mm/s for 50 seconds. After imaging, the

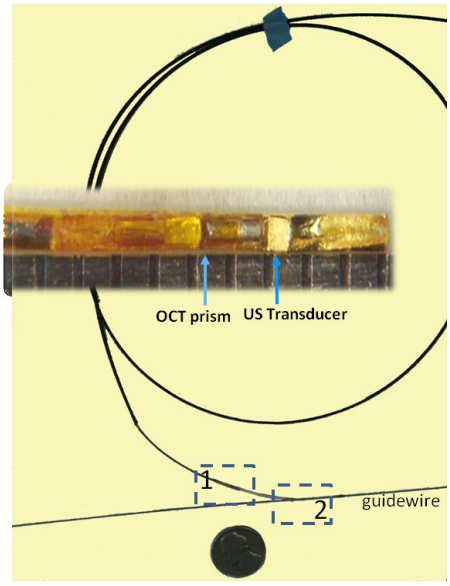

Figure 1. Photograph of IVUS-OCT catheter sheath. Compared to a U.S. dime. Box1: Integrated IVUS-OCT imaging window. Box2: Radiopaque Markers. Inset: photo of integrated IVUS-OCT probe tip(OD<0.75mm 2.3F).

length of IVUS-OCT catheter inside rabbit was measured. Exact position of imaging was found out by re-inserting the catheter to previous position and illuminating visible light, and then marked with a pin. This vascular ring (1.5mm around the pin) was excised for histology and fixed in 10% buffered formalin.

D. Coronary artery specimens from cadaver

To demonstrate the capability of IVUS-OCT system imaging and classification of different plaque type, *in vitro* experiments of cadaver coronary artery samples were conducted. A total of 8 specimens of coronary arteries from 4 cadavers will be imaged. We used formalin to fix the samples for 12 hours. After formalin fixation, the specimens were imaged in phosphate buffered saline (PBS), less than 72 hours from obtaining the sample. Plaque types are classified based on optical scattering contrast [3].

III. Result and Discussion

A. In vivo imaging of atherosclerosis microstructure in rabbit model

3D in vivo imaging of the normal rabbit abdominal aorta was performed using this integrated catheter. OCT and US images of a rabbit abdominal aorta with lipid plaque are shown in Fig.2. Fig.2 (a) and 2(b) is the US and OCT images with contrast agent flushing. The plaque can be identified in both Fig.2(a) and 2(b). In the ultrasound image, the low acoustic signal region as pointed by the arrow indicates the location of the plaque. This miniature acoustic shadow is caused by acoustic impedance difference between the fibrous cap and the lipid pool. Yet the boundary between lipid pool and cap is

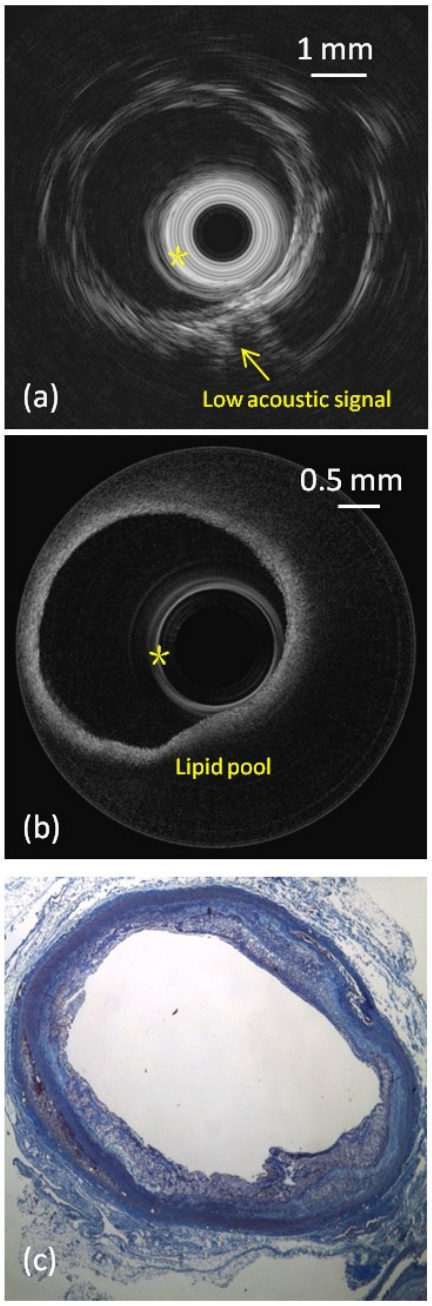

Figure 2. *In vivo* imaging of rabbit abdominal aorta with Dual –modality IVUS-OCT system. Ultrasound(a) and OCT(b) images of atherosclerosis microstructure, obtained by a integrated IVUS-OCT cathter simotanously, in a rabbit with contrast agent flushing. The corespoding Trichrome-stained histology is (c).

very obscure, due to limited resolution of ultrasound. In OCT image, at the same position, there is an obvious homogenous, diffusely bordered structure, which indicates this position is a lipid plaque. On the other hand, OCT images alone cannot give a full picture of the artery wall three-layer structure. The penetration depths of OCT and ultrasound are 1mm and 4 mm, respectively. As we proposed, OCT provides high resolution for imaging the thickness of the fibrous cap, and IVUS provides deep penetration depth for imaging the whole lipid pool. Artifact circles in ultrasound images, * in Fig.2.(a), are due to ultrasound pulse. Artifact circle in OCT images, * in Fig.2(b), is caused by a high back reflection from the interface between prism and GRIN lens.

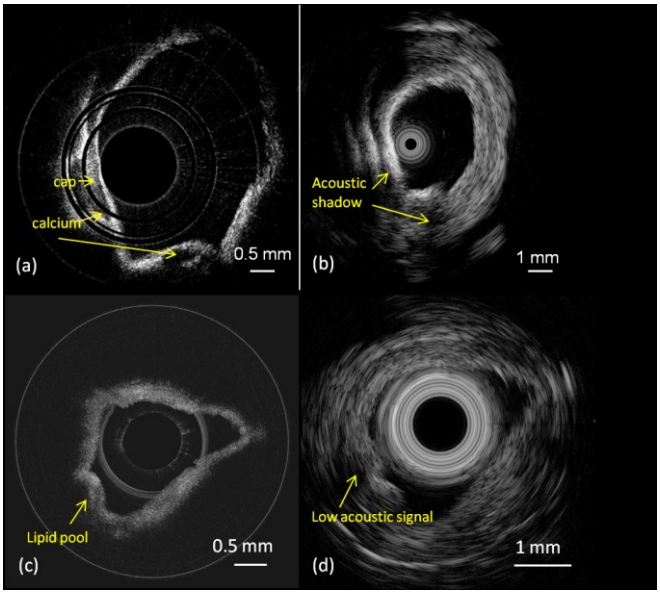

Figure 3. OCT (a), ultrasound (b) images of a human coronary artery specimen with calcified plaques. OCT (c), ultrasound (d) images of a human coronary artery specimen with a lipid plaque. The corresponding histology slides are still under process.

B. In vitro imaging of Coronary artery specimens from cadaver

OCT and IVUS images of calcified plaque and lipid plaque, Fig.3, illustrate the capability to identify different plaque types by our imaging catheter and system. Fig.3(a) and Fig.3(b) obtained by an integrated IVUS-OCT catheter simultaneously [11] demonstrate the characteristics of calcified plaque. In Fig.2(a), signal poor regions with sharp boundaries indicates calcified plaques. At the same spatial location in IVUS image (b), acoustic shadows verify that these plaques are calcified ones. These acoustic shadows are caused by huge acoustic impedance difference between calcified caps and surrounding tissues. In contrast, in lipid plaque shown by Fig.3(c) arrowhead, there is low organelle density and thus low reflective index fluctuation leading to low scatter power with diffuse boundary. Moreover, as this figure illustrates, the cap of this plaque is more than 100um, over thin-cap's criterion of 65um. It means that this plaque is not a thin-cap fibroatheroma, a prototypic of vulnerable plaque. The type of plaque is hard to be identified by IVUS image, Fig. 3(d), due to limited resolution of IVUS.

IV. CONCLUSION

We have successfully developed a miniature integrated OCT-US catheter with an outer diameter of 1.18mm which is

suitable for in vivo coronary imaging. Both *in vivo* imaging of atherosclerotic microstructure in rabbit and *in vitro* imaging of different types atherosclerotic plaques in human coronary artery specimens, verifies the feasibility of our system for intravascular imaging. The results of these experiments hold promise for this integrated system to be used in clinical studies, providing high resolution and high penetration depth for better assessment of atherosclerotic vulnerable plaque.

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