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Research Article

Photoacoustic imaging of human coronary atherosclerosis in two spectral bands

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ABSTRACT

Spectroscopic intravascular photoacoustic imaging (sIVPA) has shown promise to detect and distinguish lipids in atherosclerotic plaques. sIVPA generally utilizes one of the two high absorption bands in the lipid absorption spectrum at 1.2 μm and 1.7 μm. Specific absorption signatures of various lipid compounds within the bands in either wavelength range can potentially be used to differentiate between plaque lipids and peri-adventitial lipids. With the aim to quantify any differences between the two bands, we performed combined sIVPA imaging in both absorption bands on a vessel phantom and an atherosclerotic human coronary artery ex vivo. Lipid detection in a human atherosclerotic lesion with sIVPA required lower pulse energy at 1.7 μm than at 1.2 μm (0.4 mJ versus 1.2 mJ). The imaging depth was twice as large at 1.2 μm compared to 1.7 μm. Adequate differentiation between plaque and peri-adventitial lipids was achieved at 1.2 μm only.

1. Introduction

Myocardial infarction is a leading cause of death worldwide [1]. In the majority of cases, they are caused by the rupture of an atherosclerotic plaque and the subsequent release of its thrombogenic content into the bloodstream [2]. The presence of a lipid rich necrotic core is one of the determinants of the susceptibility of a plaque to rupture [3,4]. For that reason, the identification of necrotic core is a highly coveted imaging target. Intravascular ultrasound (IVUS) radiofrequency data analysis techniques for tissue characterization (VH-IVUS, iMap) have been developed, but their accuracy and mutual consistency are still under investigation [5–7]. Near infrared spectroscopy (NIRS) in combination with IVUS, can identify the presence but not the amount or location, relative to the lumen, of the lipid core [8–10].

Intravascular photoacoustic (IVPA) imaging has demonstrated the ability to directly image tissue components in the vessel wall, with high chemical specificity for lipid type. It utilizes differences in the absorption spectra of the vessel wall constituents to identify tissue types. Efforts have primarily concentrated on lipid detection, and started in the visible wavelength range. With the introduction of suitable light sources, focus shifted to the near-infrared wavelength range, where hemoglobin absorption is much lower, allowing for better light penetration. In this wavelength range, the absorption spectra of lipids are characterized by two prominent features around 1.2 and 1.7 μm. These absorption bands are the result of the second and first overtones of the C–H bond vibrations within the lipid molecules, respectively. The 1.2 μm absorption band has been exploited extensively to distinguish lipids from healthy vessel wall, in rabbit [11,12] as well as human [13–15] atherosclerotic arteries. In recent years, lipid detection using excitation wavelengths around 1.7 μm has seen increased interest [13,16–18]. In this wavelength range, the higher lipid absorption possibly leads to increased sensitivity using lower light intensity. However, water absorption is higher too, which could potentially offset the increased sensitivity for lipids by limiting the penetration depth (Fig. 1).

Both absorption bands each consist of several overlapping peaks as a result of C–H bond vibrations within the different structural groups ($-CH_3$, $>CH_2$, $\equiv CH$ and $>CH$ (aromatic)) of the lipid molecules [19–21]. The position and relative height of the peaks vary with the number and location of these different structural groups within the molecules and therefore provide chemical specificity. The possibility for differentiating between plaque lipids and peri-adventitial lipids, based on the specific

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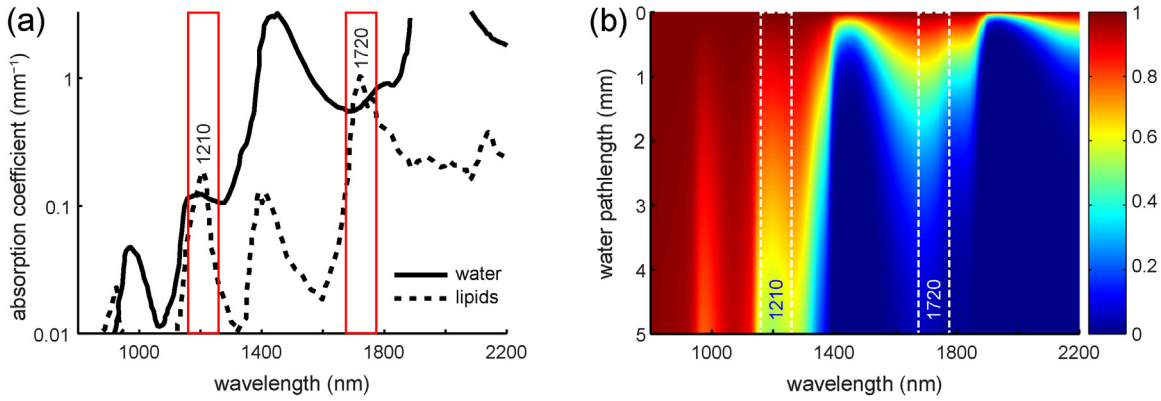

Fig. 1. (a) Lipid and water absorption in the near-infrared wavelength region, showing the two high peaks in the lipid absorption spectrum around 1210 and 1720 nm. In these two optical windows, lipid absorption exceeds water absorption. Lipid absorption at 1720 nm is 5.5 times higher than at 1210 nm; water absorption is 5 times higher. Adapted from [22]. (b) Transmission of light through water; computed based on data from http://omlc.ogi.edu/spectra/water/abs/index.html.

absorption signature of the various lipid compounds, remains to be explored.

These considerations outline tradeoffs in terms of sensitivity, imaging depth, and possibly chemical specificity connected to the choice of IVPA wavelength. In this paper, we present spectroscopic IVPA (sIVPA) imaging of a lipid containing vessel phantom and an atherosclerotic human coronary artery ex vivo at 1.2 μm and 1.7 μm, providing a direct comparison between the wavelength ranges. In the phantom, we acquired high-resolution spectra of cholesterol, cholesterol oleate and cholesterol linoleate, representative of plaque lipids, and peri-adventitial tissue. The resulting spectra were used to determine a limited number of wavelengths that maximize the difference between plaque and peri-adventitial lipids. At these wavelengths, we obtained co-registered sIVPA/IVUS images of the vessel phantom that we used to detect the plaque and peri-adventitial lipids alternatively. With two wavelengths per spectral range only, the lipid detection capability in each range was examined using both the phantom data and the ex vivo data of a diseased human coronary artery specimen.

2. Methods

2.1. Phantom design

To determine the capacity for lipid detection and differentiation at 1.2 and 1.7 μm, we made a cylindrical vessel mimicking phantom (Fig. 1a). The phantom consisted of 10% (by weight) poly-vinyl-alcohol (PVA) crystals in demineralized water that formed an acoustically transparent gel after 2 freeze/thaw cycles. It had a central lumen with a diameter of 3 mm and four 5 mm deep cylindrical cavities with a diameter of 1.5 mm, located at 500 μm from the lumen. We filled three cavities with cholesterol, cholesterol oleate and cholesterol linoleate (Sigma Aldrich Co., C8667, C9253 and C0289, resp.). These are the three most abundantly present lipids in atherosclerotic lesions [23,24], and are assumed to be representative of plaque lipids. The fourth cavity was filled with peri-adventitial tissue that was obtained from a human coronary artery specimen, see description below. In peri-adventitial tissue, lipids are deposited as a mixture of fatty acids [25].

2.2. Human artery acquisition and handling

A human coronary artery was collected at autopsy from the Department of Pathology of the Erasmus Medical Center (MC), after obtaining consent from the relatives and approval of the research protocol by the Medical Ethics Committee of the Erasmus MC (MEC-2007-081). The coronary artery was frozen within 4 h at −80 °C and stored. It was thawed and measured three months later.

2.3. Combined intravascular photoacoustic and ultrasound imaging system

All co-registered sIVPA/IVUS images were acquired using a combined IVPA/IVUS imaging system described previously [14]. The excitation light for photoacoustic imaging was supplied by a tunable laser (OPOTEK Vibrant B/355-II) with a pulse duration of 5 ns and a repetition rate of 10 Hz. The laser was coupled to the custom-built catheter by a tapered multimode fiber (Oxford Electronics, Four Marks, UK; input diameter 1 mm; output diameter 360 μm).

The hybrid IVPA/IVUS catheter prototype we used is similar to those used earlier [14], but with a different transducer. It comprised a 400 μm diameter core optical fiber (Pioneer Optics, Bloomfield, CT) to deliver the light pulses to the vessel wall. The fiber tip was polished under a 34° angle covered by a quartz cap to maintain an air–glass interface deflecting the beam by total reflection. An ultrasound transducer was placed distal from the fiber tip to transmit and receive ultrasound waves. The 0.4 by 0.4 mm lead magnesium niobate-lead titanate (PMN-PT) single crystal ultrasound transducer was designed and custom built by the Department of Biomedical Engineering of the University of Southern California [26] and had a center frequency of 44.5 MHz and a −6 dB fractional bandwidth of 45%. The separation between fiber tip and transducer center was approximately 1 mm; the optical and acoustical beam overlapped between 0.5 and 4.5 mm from the transducer, with an angle of 22°. The catheter tip assembly had an outer diameter of 1 mm.

The catheter was rotated using a motorized rotary stage (Steinmeyer GmbH & Co. KG). For pulse echo imaging, an arbitrary waveform generator (Tabor Electronics WW2571A) transmitted a Gaussian-modulated cosine wave which was transmitted to the probe through a custom-built expander and limiter. Received US and PA signals were band pass filtered (13–60 MHz 5th order Butterworth, custom built), amplified by a 43 dB amplifier (Miteq AU1263) and digitized at a sample frequency of 350 MS s^{-1} by a 12-bit data acquisition card (Acqiris DP310).

2.4. Phantom measurements

Using the dual modality imaging system described above, we imaged the lipid containing vessel phantom in a water bath, with the combined IVPA/IVUS catheter positioned in the lumen. We first acquired a cross sectional IVUS image to locate the lipid inclusions.