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Research article

All-optical extravascular laser-ultrasound and photoacoustic imaging of calcified atherosclerotic plaque in excised carotid artery

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ABSTRACT

Photoacoustic (PA) imaging may be advantageous as a safe, non-invasive imaging modality to image the carotid artery. However, calcification that accompanies atherosclerotic plaque is difficult to detect with PA due to the non-distinct optical absorption spectrum of hydroxyapatite. We propose reflection-mode all-optical laser-ultrasound (LUS) imaging to obtain high-resolution, non-contact, non-ionizing images of the carotid artery wall and calcification. All-optical LUS allows for flexible acquisition geometry and user-dependent data acquisition for high repeatability. We apply all-optical techniques to image an excised human carotid artery. Internal layers of the artery wall, enlargement of the vessel, and calcification are observed with higher resolution and reduced artifacts with nonconfocal LUS compared to confocal LUS. Validation with histology and X-ray computed tomography (CT) demonstrates the potential for LUS as a method for non-invasive imaging in the carotid artery.

1. Introduction

Stroke is currently the second leading cause of death and morbidity worldwide [1]. These cerebrovascular events result from atherosclerotic plaque deposits rupturing and forming blood clots that occlude blood flow to the brain. Therefore, both understanding and preventing carotid atherosclerotic disease is of substantial interest [2]. Certain characteristics of plaque deposits can contribute to rupture vulnerability [3,4]. Accepted factors include a thin, fibrous cap (<100 μm [3]), spotty calcification [5,6], positive remodeling, a large lipid core (>40% plaque volume) [3], and intraplaque neovascularizations [4]. Biomedical imaging of the carotid artery is therefore of primary importance for determining disease risk, preparing for surgical intervention, and monitoring treatment outcomes. Favorable characteristics of carotid imaging include accurate, high resolution, repeatable, and operator-independent capabilities that facilitate diagnosis and treatment in a rapid time window with minimal risk [2]. Furthermore, imaging that is practical for screening and allows for longitudinal studies to better understand cardiovascular disease is desirable [6].

Calcification, in particular, not only contributes to plaque vulnerability, but is also a concern for many additional cardiovascular diseases and conditions. Examples include calcification of vascular implants (valves [7], grafts [8], and stents [9]), post surgery calcification [10], and vascular calcification in hemodialysis patients [11,12].

A range of imaging modalities are currently used to assess vulnerable characteristics of atherosclerotic plaque in the carotid artery (Table 1). Each modality has advantages and limitations depending on the clinical requirement. In general, intravascular modalities offer superior resolution compared to non-invasive imaging due to proximity to the target and/or contrast enhancement. Nonetheless, non-invasive modalities are often the first line of assessment, and in some cases a combination of non-invasive modalities are used exclusively for diagnosis [2]. Ultrasound (US), computed tomography (CT), and magnetic resonance imaging (MRI) are capable of imaging several characteristics of atherosclerotic plaque non-invasively, including calcification. Magnetic resonance imaging (MRI) has the ability to image a range of components with sub-millimeter resolution, but the high cost, low signal-to-noise, and motion artifact will likely limit MRI for widespread plaque screening [13]. In CT, calcifications may be masked by radiopaque contrast in the vessel lumen [14], and CT cannot differentiate between intimal and medial calcification

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Table 1
Imaging modalities used to detect various characteristics of vulnerable atherosclerotic plaque in the carotid artery: magnetic resonance imaging (MRI), ultrasound (US), intravascular US (IVUS), contrast enhanced US (CEUS), optical coherence tomography (OCT), computed tomography angiography (CTA), multi detector CT (MDCT), and positron emission tomography (PET). This table is modified from Ibrahimi et al. [6].

Plaque feature	Imaging modality
Thin cap	IVUS, OCT, MRI
Positive remodeling	MRI, CTA, IVUS
Large lipid core	US, MDCT
Plaque composition	US, MDCT
Neovascularization	CEUS
Intraplaque hemorrhage	MRI
Inflammation	PET
Calcification	US, CT, MRI, IVUS

[15,11], the former of which has been shown to destabilize plaque [16]. "Blooming" artifacts are also common to CT images of calcification and cause significant overestimation of calcified plaque (average of 400% for multi detector CT of the coronary artery) [17]. Additionally, CT uses ionizing X-ray radiation that is undesirable for screening. A recent study of calcification in thyroid nodules found that ultrasound is more sensitive to calcification than CT [18]. Nonetheless, CT is currently the gold-standard for calcification detection [11,12]. Calcification has strong acoustic contrast compared to soft tissue, and the relative low-cost and safety of US are desirable for plaque screening. However, operator skill is known to cause inter-operator variability in US imaging [19] whereas CT and MRI use fixed, remote acquisition geometries that are well-suited to follow-up studies.

Herein, we present laser-ultrasound (LUS) imaging as a candidate for non-invasive imaging of the carotid artery and associated calcification. Like US, LUS provides improved details of the artery wall and the location of calcification within the artery wall compared to CT, while achieving operator-independent, highly repeatable data acquisition capabilities. As LUS uses non-ionizing radiation, it may also be suitable for screening and longitudinal studies. Further, the achievable pulse-width and lateral resolution are improved with all-optical systems compared to piezoelectric transducers, and the quantitative nature of optical detectors open up the potential to create quantitative maps of acoustic properties in the tissue with non-ionizing radiation.

1.1. Photoacoustic and laser-ultrasound imaging

PA imaging maps optical absorption properties of tissue up to centimeters deep, overcoming the diffusion-limited imaging depths of purely optical imaging modalities, such as OCT. A nanosecond-pulse of light rapidly becomes diffuse upon propagating through highly scattering biological tissue. Chromophores in the path of the diffuse beam absorb the light, causing thermoelastic expansion and the generation of pressure waves originating at the location where the majority of light is absorbed (Fig. 1(a)). Detection and localization of these acoustic sources create a PA map of optical absorption.

PA imaging has proven sensitive to the optical absorption contrast of both lipids and hemoglobin in the carotid artery. PA systems have demonstrated imaging depths of 2 cm in tissue phantoms [20] and 3.5 cm *in vivo* with intrinsic contrast [21]. Further, Dima et al. [22] showed that PA imaging of the carotid artery is possible *in vivo* at depths of 2 cm using both linear and curved transducer arrays. Deep-tissue imaging of the carotid artery primarily utilizes the intrinsic contrast of hemoglobin to image the vessel structure. Hemoglobin is a strong optical absorber in the optical window (~600 to 900 nm), where light is weakly absorbed by skin. Near-infrared light is preferred for PA imaging of lipids [23], however, near-infrared is strongly absorbed by skin and subcutaneous fat. Therefore, non-invasive light delivery for lipid plaque detection may not be possible. Light delivery through the pharynx is a promising approach for non-invasive imaging of lipid pools in the carotid artery wall closest to the pharynx [24], but intravascular light delivery may be required for illumination of the wall closest to the skin surface.

Detecting calcification is not straightforward with PA, as the optical spectrum is not unique in the visible and near-infrared wavelength range [25]. It is known that US is sensitive to calcification, yet enhanced resolution and reduced inter-operator variability are desirable for reliably detecting calcification deposits. In contrast to transducer-based US, LUS uses the photoacoustic effect at the tissue surface (Fig. 1(b)) to create broadband, highly repeatable acoustic sources without the need for contact with the sample or a coupling agent.

LUS images of acoustic reflectivity [26,27] and speed-of-sound [28,29] have been demonstrated, both of which are complemented by combining with PA imaging. Furthermore, the information

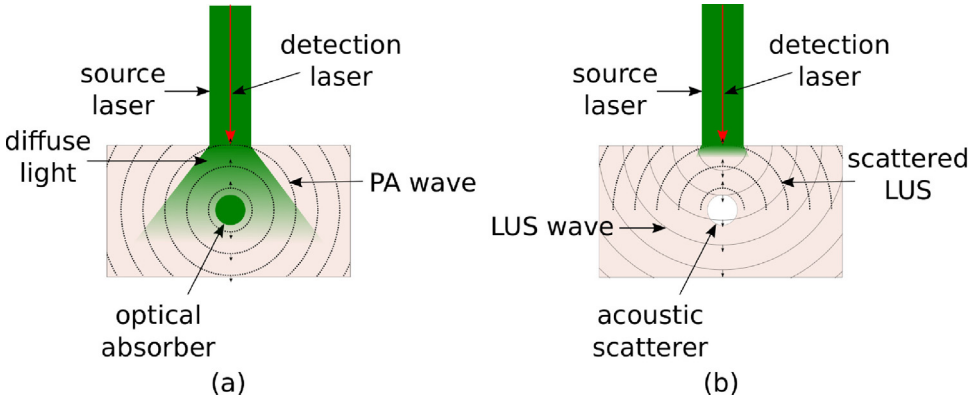

Fig. 1. Diagram of (a) photoacoustic (PA), and (b) laser-ultrasound (LUS) generation, wave propagation, and optical detection. In (a) light propagates deep in tissue. A PA wave is generated upon absorption by an optical absorber. The PA wave propagates to the surface, and the resulting surface displacement is recorded by an optical detector. Strong absorption of light occurs at the surface of tissue to generate an LUS wave in (b). The LUS wave is scattered/reflected back to the surface by acoustic inhomogeneities, where it is detected. Arrows indicate the direction of propagation of the wavefronts.