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In vivo detection of atherosclerotic plaque using non-contact and label-free near-infrared hyperspectral imaging

Hideo Chihara [a], Naoya Oishi [b, c, *], Akira Ishii [a], Toshihiro Munemitsu [d], Daisuke Arai [a], Hiroyuki Ikeda [a], Susumu Miyamoto [a]

[a] Department of Neurosurgery, Kyoto University Graduate School of Medicine, 54 Shogoin Kawahara-cho, Sakyo-ku, Kyoto, 606-8507, Japan
[b] Human Brain Research Center, Kyoto University Graduate School of Medicine, 54 Shogoin Kawahara-cho, Sakyo-ku, Kyoto, 606-8507, Japan
[c] Department of Psychiatry, Kyoto University Graduate School of Medicine, 54 Shogoin Kawahara-cho, Sakyo-ku, Kyoto, 606-8507, Japan
[d] Department of Neurosurgery, Shiga Medical Center for Adults, 5-4-30 Moriyama, Moriyama-shi, Shiga, 524-8524, Japan

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ABSTRACT

Background and aims: Detecting detailed atherosclerotic plaques is important to reduce risk factors during surgery. However, there are few methods to evaluate them during surgery. The aim of this study was to establish an *in vivo*, non-contact, and label-free imaging method for identifying atherosclerotic plaque lesions from outside vessels with a diffuse-reflectance near-infrared (NIR) hyperspectral imaging (HSI) system.

Methods: NIR spectra between 1000 and 2350 nm were measured using an NIR HSI imaging system outside the exposed abdominal aorta in five Watanabe Heritable Hyperlipidemic (WHHL) rabbits *in vivo*. Preprocessed data were input to a supervised machine learning algorithm called a support vector machine (SVM) to create pixel-based images that can predict atherosclerotic plaques within a vessel. The images were compared with histological findings.

Results: Absorbance was significantly higher in plaques than in normal arteries at 1000–1380, 1580–1810, and 1880–2320 nm. Overall predictive performance showed a sensitivity of 0.814 ± 0.017, a specificity of 0.836 ± 0.020, and an accuracy of 0.827 ± 0.008. The area under the receiver operating characteristic curve was 0.905 (95% confidence interval = 0.904–0.906).

Conclusions: The NIR HSI system combined with a machine learning algorithm enabled accurate detection of atherosclerotic plaques within an internal vessel with high spatial resolution from outside the vessel. The findings indicate that the NIR HSI system can provide non-contact, label-free, and precise localization of atherosclerotic plaques during vascular surgery.

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1. Introduction

Unstable atherosclerotic plaque is one of the major factors predicting embolism of stenotic arterial lesions. It is also a risk factor for embolization during carotid endarterectomy [1,2]. Therefore, evaluation of atherosclerotic lesions is important [3]. The properties and distribution of atherosclerotic plaques are clinically evaluated by preoperative plaque imaging, such as magnetic resonance imaging (MRI), ultrasonography (US), and computed tomography (CT). These non-invasive methods can evaluate hemorrhage, lipid core, or calcification in the atherosclerotic plaque and show the distribution of lesions. However, these methods cannot always provide accurate information about atherosclerotic lesions clinically because of their low spatial resolution. Therefore, other invasive methods, such as radiocontrast angiography and indocyanine green (ICG) video-angiography, that enable real-time and high spatial resolution imaging are often applied during vascular surgery. They can be used to diagnose the possibility of plaques as contrast defects. Radiocontrast angiography was previously considered the gold standard intraoperative method. However, it can cause embolization or arterial dissection because it needs an arterial puncture and injection of contrast agents [4]. In

* Corresponding author. Human Brain Research Center, Kyoto University Graduate School of Medicine, 54 Shogoin Kawahara-cho, Sakyo-ku, Kyoto, 606-8507, Japan.
E-mail addresses: dollmaster213@yahoo.co.jp, hchihara@yahoo.ne.jp (H. Chihara), noishi@kuhp.kyoto-u.ac.jp (N. Oishi), ishiiakira@gmail.com (A. Ishii), evzwnb5150@gmail.com (T. Munemitsu), adaisuke1981@gmail.com (D. Arai), rocky@kuhp.kyoto-u.ac.jp (H. Ikeda), miy@kuhp.kyoto-u.ac.jp (S. Miyamoto).

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addition, it only visualizes atherosclerotic lesions as defects. ICG video-angiography is a useful method with a cyanine dye with a peak spectral absorption approximately at 800 nm [5]. It suggests the plaque distribution as defects in the vascular site of the surgical field. Thus, it helps us understand the localization of plaques. However, the contrast deficits do not always correspond to atherosclerotic plaques. Furthermore, ICG hypersensitivity can occur as a complication because it requires intravenous administration of ICG [6]. Despite these methods, perioperative cerebral ischemic infarctions sometimes occur without any abnormalities seen with these methods [7,8]. Therefore, a method that can evaluate more detailed atherosclerotic lesions without any contrast agents needs to be developed.

The major atherosclerotic plaque models with spontaneous hyperlipidemia are apolipoprotein E-deficient (ApoE$^{-/-}$) mice and Watanabe Heritable Hyperlipidemic (WHHL) rabbits. Whereas the main apolipoprotein of mice is composed of B48, B100 is the main apolipoprotein in rabbits and humans. Therefore, the models have different lipid metabolic pathways [9]. In addition, the atherosclerosis that occurs in *ApoE−/−* mice is extremely lipid-rich, and macrophage-derived foam cells stand out, with a very scarce fiber component [10–12]. Such lesions differ from the atherosclerosis seen in humans, which shows a variety of lesions, including smooth muscle cells and collagen fibers covering the fibrous layers of lipid and foam cells [13]. In addition, the diameter of the aorta in mice is too small compared to that of the human carotid artery, which is one of the final clinical targets. The atherosclerosis of the WHHL rabbit shows a variety of lesions by age, as in humans [14]. Therefore, the WHHL rabbit seems a more suitable animal model for studying atherosclerotic plaques, especially for future applications of imaging methods and findings to humans.

Near infrared (NIR) spectroscopy with a micro-catheter has been used to identify vulnerable plaques in coronary artery regions [15,16]. NIR spectroscopy is a well-accepted method in biological science that enables chemical analyses without damaging the investigated materials. In addition, NIR light has two desirable properties for biomedical imaging. The first one is tissue permeability. The NIR spectral region, and specifically the 650–950 nm window, offers attractive characteristics for optical imaging, compared to the visible light range, due to lower light absorption by water in this wavelength band [17,18]. This enables practical photo detection even after propagation through several centimeters in tissue, for example human breast and brain [19–22]. The NIR window is also used for near infrared fluorescence molecular imaging, which offers high spatial resolution and good sensitivity of investigational targets. Macrophage-mediated inflammation [23], endothelial adhesion molecule activity [24], and thrombin activity [25,26] have been investigated by the *in vivo* NIR fluorescence imaging approach. However, a probe needs to be administered, and its safety in humans has not yet been verified. Therefore, a method without probes is desirable. The second one is that NIR has a unique spectral absorption pattern in each material. Several wavelengths identify characteristic components of human atherosclerotic plaques [27,28]. However, spectral interference caused by oxy-hemoglobin and deoxy-hemoglobin, which cannot be avoided in the evaluation of vessels, was mainly expected in the 700–1000 nm. In addition, wavelengths over 2350 nm allow detailed information about lipids [29,30]. However, these wavelengths have low tissue penetration, and thus have no suitability for examinations through the vessel wall. On the other hand, wavelengths of 1000–2350 nm included cholesterol to 1200 and 1700 nm in the prior studies [27,28]. Furthermore, absorption peaks of vessel protein components, which are mainly collagen and other matrix proteins, have been shown in the vicinity of 2200 nm [28]. Characterization of human advanced atherosclerotic plaque using these wavelengths has already been done in clinical catheter intervention for coronary arteries [16]. However, the method has a potential risk of embolic complications and is, hence, not suitable during vascular surgery. Consequently, the distinguishing wavelengths, which have both tissue permeability for an examination from outside vessels and discriminability of components of atherosclerotic plaques, can be suitable.

Hyperspectral imaging (HSI) is a newer spectroscopic technique integrated with image information, providing both spatial and spectral data. HSI has been widely used for the quality assessment of agricultural products [31] and the evaluation of pharmaceutical materials [32]. Because HSI has more information than panchromatic or multispectral imaging, it can improve the accuracy of plaque identification. Previous reports showed the effectiveness of HSI for the identification of cholesterol crystals in plaques of ex vivo atherosclerotic mice aorta, using coherent anti-Stokes Raman scattering HSI with wavelengths in the range of 2650–3050 nm [29,30]. In addition, the combination of a supervised machine-learning method, such as a support vector machine (SVM), which is widely used because of its remarkable performance in classification with multiple parameters [33–35], can be effective because the HSI contains considerable spectral information.

The aim of this study was to establish an *in vivo*, noncontact, and label-free imaging method for identifying atherosclerotic plaque lesions from outside vessels with the NIR HSI system and SVM.

2. Materials and methods

2.1. Animals

WHHL rabbits were used for the study as a suitable animal model for human familial hypercholesterolemia and atherosclerosis [36] (7–8 months of age; n = 5, male). We selected only male WHHL rabbits because a tough operation was needed in a female WHHL rabbit which has a large amount of accumulated intraperitoneal fat. In WHHL rabbits, aortic plaque formation is observed in all individuals more than five months old, and lesion occupancy reaches 30–40% at the age of 7–8 months [36].

Anesthesia was induced by venous injection of 12.5 mg/kg pentobarbital and continued by inhalation of 1.0–1.5% isoflurane. Local anesthesia was added in the abdominal wall by xylocaine for relief during NIR image data measurement. The abdominal aorta proximal to the renal artery branch level was exposed and measured by the NIR HSI system (Compovision, Sumitomo Electric Industries, Osaka, Japan). After measurement, WHHL rabbits were euthanized with an overdose injection of pentobarbital, and their aortas were excised for histological examination.

All experiments conformed to a protocol approved by the Standing Committee on Animals of Kyoto University.

2.2. Spectrum detection system

The HSI system consists of an NIR spectroscopic camera, which has a spectroscope and a two-dimensional NIR detecting chip (indium gallium arsenic detector). The NIR detecting chip has 215 wavelengths, which range from 1000 to 2350 nm (spectral resolution 6.27 nm). The camera takes 100–320 frames per second. The system is without peer with respect to the measurement speed over a wide area; it can measure the two-dimensional NIR spectra of a 15 × 20 cm^2 (approximately 100,000-pixel) sample in five seconds or less [32,37].

A schematic diagram of the experimental design is shown in Fig. 1. Diffuse-reflectance spectra in the 1000–2350 nm region of each pixel in a target were measured by the HSI system. Since images with high spatial resolution were needed in the study, the

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