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Evaluation of coronary adventitial vasa vasorum using 3D optical coherence tomography – Animal and human studies

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ABSTRACT

Objectives: This study sought to evaluate adventitial vasa vasorum (VV) in vivo with novel imaging technique of optical coherence tomography (OCT).
Methods: To verify OCT methods for quantification of VV, we first studied 2 swine carotid arteries in a model of focal angiogenesis by autologous blood injection, and compared microchannel volume (MCV) by OCT and VV by m-CT, and counts of those. In OCT images, adventitial MC was identified as signal-voiding areas which were located within 1 mm from the lumen-intima border. After manually tracing microchannel areas and the boundaries of lumen-intima and media-adventitial in all slices, we reconstructed 3D images. Moreover, we performed with OCT imaging in 8 recipients referred for evaluation of cardiac allograft vasculopathy at 1 year after heart transplantation. MCV and plaque volume (PV) were assessed with 3D images in each 10-mm-segment.
Results: In the animal study, among the 16 corresponding 1-mm-segments, there were significant correlations of count and volume between both the modalities (count $r^2 = 0.80$, $P < 0.01$; volume $r^2 = 0.50$, $P < 0.01$) and a good agreement with a systemic bias toward underestimation with m-CT. In the human study, there was a significant positive correlation between MCV and PV (segment number = 24, $r^2 = 0.63$, $P < 0.01$).
Conclusion: Our results suggest that evaluation of MCV with 3D OCT imaging might be a novel method to estimate the amount of adventitial VV in vivo, and further has the potential to provide a pathophysiological insight into a role of the VV in allograft vasculopathy.

1. Introduction

Neovascularization of the arterial wall is an important process associated with the progression and complication of atherosclerosis. It is characterized by proliferation of vasa vasorum (VV) which is a network of microvessels located in the walls of arteries and veins [1–3]. We have previously reported the role of VV in atherosclerosis using micro-computerized tomography (m-CT) which is considered one of the established tool for the imaging of VV in vitro [4,5]. Furthermore, in initial stage of atherosclerosis, VV increased in the adventitia prior to intraplaque neovascularization, which reflect advanced atherosclerosis [4]. Therefore, an assessment of coronary adventitial VV could be important to predict the progression of the coronary lesion.

Since cardiac allograft vasculopathy remains one of the leading causes of graft failure and late death among heart transplantation recipients [6–8], prevention and detection of the vasculopathy is important to improve prognosis in heart transplantation recipients. Prevalence of cardiac allograft vasculopathy was high even in first year [9,10], and progression of intimal thickness in the first year after transplantation was a significant predictor for cardiac events

Abbreviations: MC, microchannels; m-CT, micro computed tomography; MCV, microchannel volume; OCT, optical coherence tomography; PV, plaque volume; VV, vasa vasorum.

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[11]. Although a recent case report has indicated that the lesion with neovascularization detected by optical coherence tomography (OCT) shows obvious progression of the allograft vasculopathy compared to other lesions [8], the impact of neovascularization on early stage vasculopathy is not as manifest as native atherosclerosis, and methods for quantifying VV in vivo has not been established yet. OCT is an emerging tool to evaluate coronary artery lesions in vivo, and a recent study has shown that microchannels (MC) observed in OCT images are a significant predictor of plaque progression in patients with native atherosclerosis but not in those with cardiac allograft vasculopathy [12].

Although m-CT is an established tool to evaluate adventitial VV, it has the disadvantage of the limited utilization only in vitro. In this study, we sought to examine the feasibility of the in-vivo methods to evaluate adventitial microvessels with 3D OCT images. To verify the validity of OCT, we first used an animal model to compare OCT versus m-CT measurements. Subsequently, we assessed the usefulness of OCT to evaluate VV in transplant recipients with early cardiac allograft vasculopathy.

2. Methods

This study protocols was approved by the Mayo foundation institutional animal care and use committee, and the institutional review board of Mayo Clinic. We obtained the written consents for participation from all of the human subjects in this study.

2.1. Animal model

To study the correlation and agreement between VV detected by m-CT and MC by OCT, we used a model of temporal local angiogenesis in a predetermined anatomic location [13]. This model consists of a controlled injection of autologous blood in the arterial wall leading to local inflammation and proliferation of VV which peak two weeks after the injection.

Two domestic swine (mean weight 35 kgs) were sedated with a telazol/ketamine/xylazine (TKX, 2.2 mg/kg, 2.2 mg/kg, 2.2 mg/kg) mixture IM and anesthetized with Buprenex (0.01 mg/kg) IM. After intubation, anesthesia was maintained with Isoflurane 1.5–2%. 0.5 mL of autologous blood was drawn from the ear vein and then injected into 4 locations, under direct visualization, in the adventitia of the left common carotid artery, while the right carotid served as internal control.

2.1.1. OCT studies

Two weeks after the injection [13], we performed in-vivo OCT studies under the same anesthetic procedures as described above. Guiding catheter (7Fr) was inserted from a right femoral artery and placed in a proximal common carotid artery. After angiographic identification of the carotid artery, an over-the-wire OCT catheter (Dragonfly, St Jude Medical, St. Paul, MN) was introduced and placed 5 mm beyond the carotid bifurcation. Then, OCT images were recorded over 50 mm in the left and right common carotid arteries with C7-XR OCT Intravascular Imaging System (St Jude Medical, St Paul, MN), using automatic pull-back at a speed of 20 mm/s and 100 frames/sec, and high-speed (6 mL/s, total = 30 mL) injection of iodinated contrast to clear the lumen from blood. OCT images were saved as a DICOM files for offline analysis.

The 3-D reconstruction and analysis was performed with the ANALYZE software 11.0 (Biomedical Imaging Resource, Rochester, Minnesota), which was demonstrated as the useful modality of 3D volumetric analysis of IVUS images [14]. DICOM file of OCT images was loaded as red channel data with 8 bit matrix of 20*20*200 μm cubic voxels. MC areas and lumen-intima borders are traced in every cross-sectional OCT image slices separated by a distance of 200 μm. Adventitial MC was defined as signal-voiding tubular or layer structures with major diameters from 50 to 300 μm [15], which were observed in at least 2 consecutive slices, and located within 1 mm from the lumen-intima border (Fig. 1A and B). After volume rendering process, which provides a variety of display representation of 3-D image data sets, 3D pattern of MC was determined visually (Fig. 1C). Then, volumetric analysis of MC and lumen was performed in every 1 mm segment consisted of 5 OCT image slices.

2.1.2. Micro-CT studies

Following the OCT imaging, the swine were euthanized with 100 mg/kg IV injection of pentobarbital and the carotid arteries were cannulated at their bifurcation. The vessels were cleared of blood with an infusion of heparinized Ringer's Lactate via an injection pump under a controlled pressure of 100 mmHg. Subsequently a radiopaque, lead-containing, liquid, low-viscosity polymer (Microfil® MX-122, Flow Tech; Carver MA) was infused until the compound flowed freely from the distal end of the vessel. As we reported previously, m-CT images were obtained after dehydration with alcohol and embedding into paraffin wax [4,16–19].

The areas of VV and vessel lumen were determined as previously reported (Fig. 1D and E) [16,17,20]. Micro-CT images were reconstructed into 3-D images at 20 μm cubic voxel resolution with the ANALYZE software (Fig. 1F) [16,17,20]. We calculated VV volume and lumen volume, and average number of VV, in each 1-mm-segment. Each 1-mm-segment contained 50 slices, because a slice interval was 20 μm. Image analysis of m-CT was performed by a support of Mr. Andrew J Vercnocke, a medical imaging analyst at Physiological Imaging Research Lab.

To confirm the proliferation of VV, we compared VV volume between the left (injected blood) and the right carotid arteries (control) which were reconstructed from same slice levels as the left carotid arteries.

2.1.3. Comparison of MC by OCT with VV by m-CT

Finally, to verify the evaluation with 3D OCT, we matched the segments obtained from both methods. After volume rendering and 3D reconstruction of OCT and mCT images, anatomical characteristics of VV including bifurcation was evaluated visually and used to match the corresponding image slices (expressed in yellow, Fig. 1C). Cross-sectional slices corresponding for anatomical landmark, bifurcation of VV, were determined and volumetric analysis was evaluated in every 1 mm segments. The correlation and agreement of the counts and volumes between MC detected by OCT and VV detected by m-CT were evaluated.

2.2. OCT study in transplant patients

2.2.1. Patients

From September 28, 2011 and June 7, 2012, we enrolled 11 transplant patients who were referred for annual coronary angiography one year after transplantation, and OCT imaging for the assessment of cardiac allograft vasculopathy. After exclusion of 3 recipients because of poor images, we analyzed the remaining 8 patients. The patient characteristics were collected from the medical records.

2.2.2. Image acquisition and analysis

OCT images in the mid segment of left descending artery were performed as previously described [21]. OCT images were recorded over 50 mm which were divided into five 10-mm-segments of 50 slices each from the most distal slice. We excluded the segments