Contrast Intravascular Ultrasound for Vasa Vasorum Imaging

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Intravascular ultrasound (IVUS) is an established clinical tool for assessing coronary artery atherosclerosis. Its use has contributed to an improved understanding of the natural history of atherosclerosis and, increasingly, IVUS data are used as an endpoint in therapeutic trials. For diagnostic purposes, it is employed as an adjunct to angiography to provide additional insight into the extent and severity of atherosclerosis and frequently reveals the presence of angiographically occult lesions. Such “nonculprit” lesions are now recognized to be responsible for a high proportion of ensuing cardiac events resulting in either fatalities or requiring further interventional treatment. A significant issue in cardiology is, therefore, to develop imaging methods to identify specific atherosclerotic lesions that are vulnerable to rupture. Candidate markers of lesion vulnerability currently under investigation include plaque volume, mechanical integrity and composition. More recently, there is a growing recognition of the significance of vasa vasorum in plaque development and instability. Neovascular vasa vasorum are part of an apparent positive feedback loop of inflammation and angiogenesis (Moulton et al 2003) and are associated with intraplaque hemorrhage and, thereby, to rupture.

While the ultrasound imaging has been successful in detecting carotid artery vasa vasorum (Feinstein 2004), there are at present no established in vivo methods of imaging vasa vasorum in coronary arteries. IVUS is one candidate imaging modality for accomplishing this. Due to high levels of relative tissue-catheter motion, it is unlikely that conventional high frequency microvascular flow imaging methods will be effective. There have been several reports of extra-luminal image enhancement following the bolus injection of contrast agent, which has been attributed to the presence of vasa vasorum (Kakadiaris et al 2006). The basis of this approach is to compare post-contrast injection images with a baseline image derived from a single point in the cardiac cycle, which is potentially susceptible to acyclical catheter-vessel motion or non-uniform rotation of the transducer element. This motivates the development of contrast IVUS detection techniques based on bubble-specific signatures, which are dominant at lower ultrasound frequencies.

To this end, we are investigating the use of nonlinear contrast intravascular ultrasound techniques for vasa vasorum imaging. A prototype nonlinear IVUS contrast imaging system has been developed which employs mechanically scanned single element transducers (Frijlink et al 2006; Goertz et al 2006a). Conventional commercial catheters as well as catheters modified to incorporate custom dual frequency transducer elements have been assessed. The system has been evaluated at transmit frequencies in the 20 to 40 MHz range in second harmonic (H) and subharmonic (SH) imaging modes. The feasibility of improving contrast-to-tissue ratio (CTR) in H40 and SH20 modes relative to fundamental imaging was demonstrated in phantom experiments using both free and targeted microbubbles. The contrast agents employed include experimental micron to submicron sized lipid encapsulated agents as well as the commercial agent Definity™

(Bristol-Myers Squibb Medical Imaging). These agents have been shown to be capable of exhibiting a rich variety of nonlinear behaviours in the IVUS frequency range.

The feasibility of using nonlinear contrast IVUS imaging to detect the vasa vasorum was investigated in atherosclerotic rabbit aortas (Goertz et al 2006b; Goertz et al 2007) using both H40 and SH15 imaging modes. Following the bolus injection of Definity™, a significant enhancement was observed within the adventia. An example image is shown in Figure 1 below. Histology confirmed the presence of microvessels in the enhanced regions, indicating the potential of nonlinear contrast IVUS as a new technique for imaging vasa vasorum.

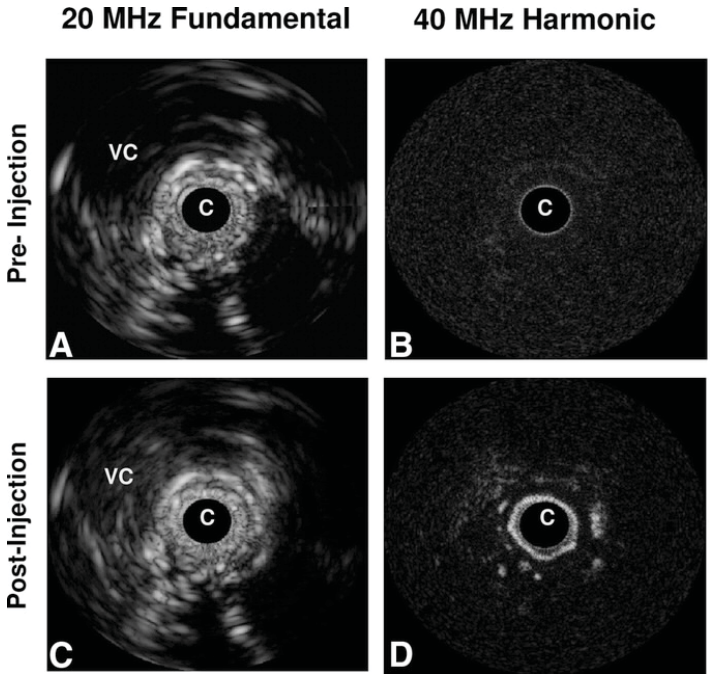

Figure 1. In vivo results in an atherosclerotic rabbit aorta using decanted Definity. A, Fundamental mode before agent injection, where “C” is the catheter and “VC” is the vena cava. B, Fundamental mode 10 seconds after injection where changes in adventitial enhancement are not evident, except for in a region at 4 o'clock and within the vena cava. C, Harmonic mode before injection shows the tissue signals to be largely suppressed. D, At 10 seconds after injection, the harmonic mode shows significant adventitial enhancement, consistent with the detection of adventitial microvessels. Scale of images is 12 mm across. The dynamic range of the fundamental and harmonic images are 40 and 25 dB, respectively.

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Figure 1.