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● *Original Contribution*

CONTRAST-ENHANCED INTRAVASCULAR ULTRASOUND PULSE SEQUENCES FOR BANDWIDTH-LIMITED TRANSDUCERS

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Abstract—We demonstrate two methods for vasa vasorum imaging using contrast-enhanced intravascular ultrasound, which can be performed using commercial catheters. Plaque neovascularization was recognized as an independent marker of coronary artery plaque vulnerability. IVUS-based methods to image the microvessels available to date require high bandwidth (−6 dB relative frequency bandwidth >70%), which are not routinely available commercially. We explored the potential of ultraharmonic imaging and chirp reversal imaging for vasa vasorum imaging. *In vitro* recordings were performed on a tissue-mimicking phantom using a commercial ultrasound contrast agent and a transducer with a center frequency of 34 MHz and a −6 dB relative bandwidth of 56%. Acoustic peak pressures <500 kPa were used. A tissue-mimicking phantom with channels down to 200 μm in diameter was successfully imaged by the two contrast detection sequences while the smallest channel stayed invisible in conventional intravascular ultrasound images. Ultraharmonic imaging provided the best contrast agent detection. (E-mail: d.maresca@erasmusmc.nl) © **2013 World Federation for Ultrasound in Medicine & Biology.**

Key Words: **Intravascular ultrasound, Ultrasound contrast agents, Ultrasound contrast imaging, Ultraharmonic, Pulse inversion, Coded excitation, Chirp, Vasa vasorum.**

INTRODUCTION

The identification of vulnerable coronary atherosclerotic plaques remains a central issue in cardiac imaging (Fayad et al. 2012). As with malignant tumors, intraplaque formation of new microvessels is critical to the progression of atherosclerosis and may constitute an independent marker of vulnerability (Barger et al. 1984, Hellings et al. 2010), a hypothesis recently supported by a 3-D micro-computed tomographic study of *ex vivo* coronary arteries (Gössl et al. 2010). There is a clear role in both studies of atherosclerosis and diagnostic imaging for methods capable of detecting and visualizing the microvascular networks within the arterial wall, also referred to as "vasa vasorum" (VV). VV diameters reported in human diseased arteries range from 2–200 μm (Sluimer and Daemen 2009); however, the clinical tools to image coronary artery VV *in vivo* do not exist. Intravascular ultrasound (IVUS) is an established minimally invasive diagnostic tool that provides high-resolution intravascular images of the vessel wall and atherosclerotic plaques (Bom et al. 1972, de Korte et al. 2011). It has been shown that IVUS combined with an ultrasound contrast agent (UCA) has the capacity to detect VV in the arterial wall (Goertz et al. 2006a, 2007; Vavuranakis et al. 2008). Pulse inversion schemes proved to be efficient in cancelling fundamental signals and therefore detecting subharmonic or second harmonic responses from UCAs (Goertz et al. 2006b; Hope Simpson et al. 1999). In a step toward harmonic IVUS imaging of VV, an IVUS transducer having two frequency peaks at 22 and 40 MHz was designed (Frijlink et al. 2006; Goertz et al. 2006a, 2007; Vos et al. 2005). Despite a good sensitivity, this transducer suffered from a lower spatial resolution than conventional clinical IVUS because of the narrow bandwidth of the two frequency peaks (two-way 30%, −6 dB relative bandwidth) and is not produced commercially. Alternatively, harmonic IVUS imaging could be performed with single-frequency peak IVUS transducers presenting a −6 dB relative frequency

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bandwidth of 70% or more (Yuan et al. 2008). Such a frequency bandwidth allows one to transmit at the inferior or superior limit of the −6 dB frequency bandwidth and receive the response of UCA at the second harmonic frequency or the subharmonic frequency with adequate sensitivity. These broadband IVUS transducers have not progressed beyond the prototype stage to date, and they remain far from application in routine clinical devices.

In this study, we investigated the performance of two contrast-enhanced intravascular ultrasound pulse sequences for VV imaging functioning with conventional IVUS transducer bandwidths (<60%), chirp reversal IVUS imaging (Maresca et al. 2012) and ultraharmonic IVUS imaging. Chirp reversal capitalizes on the asymmetric resonant response of UCAs to upsweep and downsweep chirp excitations. Ultraharmonic imaging presents two advantages over subharmonic imaging. First, a 40% −6 dB relative bandwidth is sufficient to capture it, whereas the second harmonic or subharmonic require 70%. In addition, the lateral resolution of ultraharmonic imaging is expected to be superior to subharmonic and fundamental imaging (Goertz et al. 2005). Like the subharmonic response, the ultraharmonic response is a UCA-specific response that is not generated by tissue, thus providing a contrast signal more specific than second harmonic imaging (Kate et al. 2012; Pasovic et al. 2011; Tang et al. 2010). Both IVUS contrast detection methods were evaluated in a tissue-mimicking phantom including channels perfused with a commercial ultrasound contrast agent.

MATERIALS AND METHODS

Tissue-mimicking phantom for IVUS vasa vasorum imaging

To mimic a coronary artery cross section with intra-wall vascularization, we manufactured a tissue-mimicking phantom (Culjat et al. 2010) with five through cavities; a central lumen 3 mm in diameter and four side channels of diameters equal to 2 mm, 1 mm, 500 μm and 200 μm. Human VV vessel diameters, which range from a few hundred micrometers down to a single red blood cell dimension (Sluimer and Daemen 2009), were simulated in our phantom by the 200 μm channel. All side channels were situated at a distance of 500 μm from the central lumen border, and the total phantom diameter was equal to 2 cm (Fig. 1). The phantom material was made of 10% w/w polyvinyl alcohol gel mixed with 0.5% w/w silicon carbide particles less than 15 μm in size (SiC, K-800, MTN-Giethoorn) and 0.5% w/w silicon dioxide particles ranging 1–5 μm to account for scattering and attenuation. The mixture underwent three freeze thaw cycles to reach tissue mimicking mechanical properties (Hansen et al. 2010).

IVUS imaging system overview

The IVUS imaging system used in this study was similar to the one described in Maresca et al. (2012). A mechanically rotated unfocused single element IVUS transducer (PMN-PT single-crystal, 0.5 × 0.5 mm^2, center frequency 34 MHz, −6 dB frequency bandwidth of 56% ranging 24–44 MHz) was mounted in a catheter assembly with an outer diameter of 0.9 mm (Zhou et al. 2007). The flat transducer had a natural focus distance of 2 mm and a lateral resolution of 270 μm at focus (Maresca et al. 2012). A schematic of the circuit is depicted in Figure 2. Interleaved sequences of excitations were transmitted using an arbitrary waveform generator (model WW2571A; Tabor Electronics, Tel Hanan, Israel) with angular steps of 1 degree. The received ultrasound radiofrequency data were amplified by 43 dB (Miteq AU1263), digitized at a sampling frequency of 350 MHz with a 12 bit dynamic range (DP310; Acqiris,

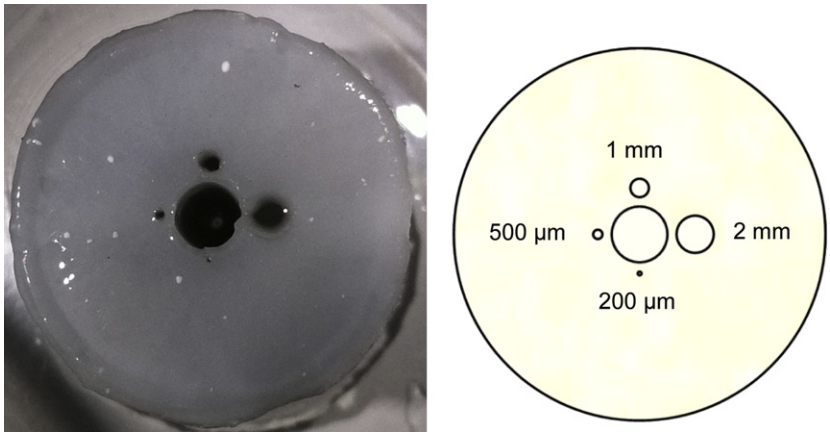

Fig. 1. Channel phantom mimicking arterial wall vasculature. The 200 μm diameter vasa vasorum mimicking channel is visible below the central lumen. The phantom diameter is 2 cm.