Ultrasound in Med. & Biol., Vol. 43, No. 11, pp. 2725–2732, 2017

0301-5629/$ - see front matter

http://dx.doi.org/10.1016/j.ultrasmedbio.2017.07.012

● *Technical Note*

COMBINING SUBHARMONIC AND ULTRAHARMONIC MODES FOR INTRAVASCULAR ULTRASOUND IMAGING: A PRELIMINARY EVALUATION

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(*Received* 13 *May* 2017; *revised* 13 *July* 2017; *in final form* 15 *July* 2017)

Abstract—Contrast-enhanced intra-vascular ultrasound (CE-IVUS) imaging could provide clinicians a valuable tool to assess cardiovascular risk and guide the choice of therapeutic strategies. In this technical note, we evaluated the feasibility of combining subharmonic and ultraharmonic imaging to improve the performance of CE-IVUS. Vessel phantoms perfused with phospholipid-shelled ultrasound contrast agents were visualized using subharmonic, ultraharmonic and combined CE-IVUS modes with commercial peripheral and coronary imaging catheters. Flow channels as small as 0.8 mm and 0.5 mm were imaged at 12-MHz and 30-MHz transmit frequencies, respectively. Subharmonic and ultraharmonic imaging modes achieved a contrast-to-tissue ratio (CTR) up to 18.1 ± 1.8 dB and 19.6 ± 1.9 dB at 12-MHz, and 8.8 ± 1.8 and 12.5 ± 1.1 dB at 30-MHz transmit frequencies, respectively. Combining these modes improved the CTR to 32.5 ± 3.0 dB and 25.0 ± 1.6 dB at 12-MHz and 30-MHz transmit frequencies. These results underscore the potential of combined-mode CE-IVUS imaging. Furthermore, the demonstration of this approach with commercial catheters may serve as a first step toward the clinical translation of CE-IVUS. (E-mail: himanshu.shekhar@uc.edu) © 2017 World Federation for Ultrasound in Medicine & Biology.

Key Words: **Vasa vasorum, Intravascular ultrasound, Subharmonic imaging, Ultraharmonic imaging, Ultrasound contrast agents, Non-linear imaging.**

INTRODUCTION

Neovascularization has been related to the progression and disruption of atherosclerotic plaques (Barger et al. 1984; Gössl et al. 2007). Plaque *vasa vasorum* serve as a pathway for inflammatory cells (Rademakers et al. 2013; Ritman and Lerman 2007), leading to intraplaque hemorrhages and subsequent plaque rupture (Falk et al. 1995; ten Kate et al. 2010). Contrast-enhanced ultrasound imaging techniques that exploit the linear and non-linear response of ultrasound contrast agents (UCA) have been reported for imaging the *vasa vasorum* (Feinstein 2006; Granada and Feinstein 2008; Magnoni et al. 2009). It is envisaged that contrast-enhanced ultrasound could be used clinically to assess cardiovascular risk (ten Kate et al. 2010) and to guide therapeutic interventions (Hellings et al. 2008, 2010). In particular, contrast-enhanced intravascular ultrasound imaging (CE-IVUS) is under development for imaging the *vasa vasorum* in the coronary and peripheral arteries (Goertz et al. 2006b, 2007). This approach relies on the administration of microbubble UCA along with minimally invasive imaging to visualize vascular organs and the microcirculation. In addition to *vasa vasorum* imaging, CE-IVUS could also be useful for plaque delineation (Sridharan et al. 2013), parametric imaging (Eisenbrey et al. 2012), endo-leak assessment (Partovi et al. 2015) and molecular imaging (Hamilton et al. 2004). Linear CE-IVUS imaging (Cachard et al. 1997) typically offers limited sensitivity and specificity, and may be confounded by motion artifacts. Recently, linear imaging based on radial modulation was reported to improve contrast-to-tissue ratio (CTR) by 7–15 dB relative to standard B-mode IVUS imaging (Yu et al. 2014). However, non-linear imaging modes may be well suited for CE-IVUS, as they produce up to 30-dB improvement in CTR better than linear imaging (Goertz et al. 2006b, 2007).

Several non-linear CE-IVUS techniques have been reported using *in vitro* (Goertz et al. 2006a; Ma et al. 2015) and *in vivo* flow models (Goertz et al. 2006b, 2007). Nonlinear CE-IVUS imaging is typically performed with the aid of multi-pulse techniques such as pulse inversion imaging (Frijlink et al. 2011).

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The specificity of second harmonic CE-IVUS imaging can be reduced by non-linear propagation (Goertz et al. 2006a). Subharmonic and ultraharmonic imaging modes are robust to artifacts produced from non-linear propagation, leading to substantial improvements in CTR relative to fundamental-mode imaging (Daeichin et al. 2015; Goertz et al. 2007; Maresca et al. 2013). Acoustic angiography IVUS is another promising technique that employs excitation at conventional diagnostic frequencies and displays the signal from UCA at high frequencies (>20 MHz) to reduce the impact of non-linear propagation (Ma et al. 2015; Martin et al. 2016). The excellent resolution of acoustic angiography is encouraging for visualizing the microcirculation. However, the main limitation of this approach is that it requires a specialized dual-frequency transducer that is not commercially available. Furthermore, this approach relies on bubble destruction and is therefore performed at lower frame rates to achieve adequate imaging sensitivity.

Goertz et al. (2006b, 2007) pioneered non-linear contrast-enhanced imaging using intravascular ultrasound. These investigators employed a dual-frequency IVUS catheter to image the *vasa vasorum* using subharmonic (Goertz et al. 2007) and second harmonic (Goertz et al. 2006b) modes, both *in vitro* and in an *in vivo* atherosclerotic rabbit model. More recently, extensive studies were reported by Maresca et al. (2013, 2014) *in vitro* and in an *in vivo* chicken embryo model. These studies demonstrated that when the transducer bandwidth is limited, ultraharmonic IVUS imaging can outperform other non-linear imaging techniques. These studies were performed using prototype transducers constructed with lead magnesium niobate-lead titanate (PMN-PT) crystals that offer enhanced bandwidth and sensitivity relative to currently available IVUS transducers (Zhou et al. 2007). Although the development of broadband and specialized IVUS transducers (Ma et al. 2014; Zhou et al. 2007) is necessary in the long-term, demonstrating CE-IVUS with *off-the-shelf* catheters could simplify the pathway to United States Food and Drug Administration approval and the Conformité Européene mark, and accelerate the clinical translation of this technique.

Our group has reported an approach based on subharmonic filtering with a commercially available catheter (Eisenbrey et al. 2012; Sridharan et al. 2013). However, the CTR of subharmonic images produced in these studies was comparable to fundamental imaging, likely due to the limited bandwidth of the transducer, and the lack of contrast agent-specific pulsing sequences. Recently, we demonstrated the feasibility of ultraharmonic IVUS imaging using commercially available catheters (Huntzicker et al. 2016; Shekhar et al. 2016) by implementing long duration chirp pulses to attain CTRs ranging 11–18 dB. Although these results are encouraging, combining non-linear imaging modes could improve the performance of CE-IVUS imaging substantially. In this technical note, we investigated the feasibility of performing combined subharmonic and ultraharmonic CE-IVUS imaging using a single transmission. Commercially available peripheral and coronary imaging catheters were used along with a prototype IVUS system (Shekhar et al. 2016), and vessel flow phantoms perfused with a phospholipid-encapsulated contrast agent were visualized. The performance of standalone subharmonic and ultraharmonic imaging was compared with combined-mode CE-IVUS imaging.

MATERIALS AND METHODS

We used a prototype imaging system (Fig. 1a) based on the iLab IVUS scanner (Boston Scientific/Scimed, Natick, MA, USA) and equipped with single-element imaging catheters—either Atlantis PV (8.5 F, 15-MHz center frequency, clinical use: peripheral imaging) or Atlantis SR Pro (3.2 F, 40-MHz center frequency, clinical use: coronary imaging). The −3-dB (full-width-half-maximum) fractional bandwidths of these transducers were 25% and 49% (Shekhar et al. 2016). The imaging catheter was connected to the motor drive *via* a breakout box (provided by Boston Scientific) to circumvent the transmit and receive circuitry of the iLab IVUS system (Yu et al. 2014). Two arbitrary function generators (models 33210 A and 81150 A, Agilent, Santa Clara, CA, USA) were used to (i) gate the amplifier and (ii) generate the excitation pulse, respectively. The excitation frequencies were chosen considering the trade-off between transducer sensitivity in the transmit and non-linear receive modes (both subharmonic and ultraharmonic). Accordingly, the transducers with 15-MHz and 40-MHz center frequencies were used to transmit pulses at 12 MHz and 30 MHz, respectively. Specifically, the excitation pulse for 12-MHz and 30-MHz transmit consisted of linear frequency modulated chirps (10% fractional bandwidth), with 1.67 μs and 0.67 μs pulse duration, respectively (Shekhar and Doyley 2012; Shekhar et al. 2016). Excitation pulses were tapered using a 70% Tukey window to reduce pulse distortion. A pulse repetition frequency of 10.8 kHz was used for imaging at both frequencies. The excitation pulses were boosted by 43 dB using a linear pulse amplifier (MR 5000 DA, ENI, Rochester, NY, USA) and relayed to the IVUS transducer through a diplexer (RDX-6, Ritec Inc., Warwick, RI, USA). For imaging at 30-MHz transmit frequency, a custom lowpass filter (E&I, Rochester, NY, USA) with −3-dB cut-off frequency of 34 MHz was used to filter the amplifier output to eliminate