Published in final edited form as:

Ultrasound Med Biol. 2013 April ; 39(4): 706–713. doi:10.1016/j.ultrasmedbio.2012.10.020.

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

David Maresca^{*}, Guillaume Renaud^{*}, Gijs van Soest^{*}, Xiang Li[†], Qifa Zhou[†], K. Kirk Shung[†],
Nico de Jong^{*,‡,§}, and Antonius F. W. van der Steen^{*,‡}

^{*}Biomedical Engineering, Thorax Centre, Erasmus University Medical Centre, Rotterdam, the Netherlands [†]Biomedical Engineering, University of Southern California, Los Angeles, California, USA [‡]Interuniversity Cardiology Institute of the Netherlands, Utrecht, the Netherlands [§]Imaging Science and Technology, Delft University of Technology, Delft, the Netherlands

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 μ m 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.

Keywords

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, intra-plaque 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 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 up-sweep and down-sweep 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, $0.5 \times 0.5 \text{ mm}^2$, 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 $270 \mu\text{m}$ 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, Geneva, Switzerland), digitally filtered and scan converted. No power amplifier or filters were used in the circuit in order to minimize waveform distortion.

Contrast agent handling for IVUS

We used the commercial UCA Definity (Lantheus Medical Imaging, North Billerica, MA, USA). It essentially contains microbubbles with a diameter between 1.1 and $3.3 \mu\text{m}$ with 98% of the bubble population $<10 \mu\text{m}$ according to the manufacturer's specifications. Micrometer-sized bubbles that resonate at IVUS frequency (20–50 MHz) were selected by means of decantation as described by Goertz et al. (2007). A vial of the commercial UCA Definity was decanted for 1 h. 0.2 mL of UCA was extracted, diluted in 200 mL of degassed water (dilution ratio 1:1000, of the order of dilution ratios administered for human use; Giannoni et al. (2009)) and stirred with a magnetic stirrer for 30 seconds. This protocol ensured an average resonance frequency of the prepared UCA close to 20 MHz and therefore suited for IVUS imaging. A tank containing the tissue mimicking phantom was filled with the UCA solution, ensuring that a uniform concentration of UCA was expected in the lumen and in the side channels. The UCA suspension remained static (no flow) during image acquisition.

IVUS pulse-inversion ultraharmonic sequence

The transmission of pairs of phase-inverted excitations, referred to as pulse inversion (Simpson et al. 1999), is a powerful technique to selectively detect the nonlinear response of UCAs (Frinking et al. 2000). To test ultraharmonic IVUS imaging, we transmitted sequences of inverted Gaussian modulated sine bursts with a center frequency of 22 MHz, fractional bandwidth of 50%, duration of $0.2 \mu\text{s}$ and peak negative pressure of 500 kPa (Fig. 3a, 3b). The pressure level was chosen to limit tissue harmonics generation (Goertz et al. 2006b) and ensure a minimal destruction of the UCA. The harmonic content of received radiofrequency lines was extracted by summing consecutive inverted pulses and digital filtering from 30–50 MHz to extract the ultraharmonic and second harmonic components.

IVUS chirp reversal sequence

Chirp reversal (Sun et al. 2007; Novell et al. 2009; Maresca et al. 2012) is a specific contrast detection method relying on the resonant behavior of microbubbles. The transient resonant response of a bubble close to resonance to up and down frequency sweeps differs, whereas the response conserves the waveform of the excitation in a non-resonant medium, such as tissue at low acoustic pressures. Novell et al. (2009) reported that chirp reversal was most efficient for a transmitting frequency above the resonance frequency of the interrogated bubble. The IVUS chirp reversal imaging sequence was made of chirp-coded excitations centered at 35 MHz (20–50 MHz linear frequency sweep, duration of $0.42 \mu\text{s}$, peak negative pressure of 300 kPa, Tukey windowed with a 90% taper ratio) as shown in Figure 4. The peak negative pressure was chosen to minimize artifacts generated by nonlinear propagation,

visible at higher pressures (Maresca et al. 2012). Pairs of upsweep and downsweep chirps were subsequently transmitted at 1 degree angular position steps. The received ultrasound data were digitally filtered (20–50 MHz) and compressed by cross correlation with the chirp excitation signal (matched filtering) as reported by Maresca et al. (2012).

Transmitted excitations do not have the same temporal length in both pulse sequences. Chirp excitations were designed (duration, bandwidth and envelope) to obtain, after compression, an axial resolution equal to that of the pulse inversion excitations.

RESULTS

Hydrophone characterization of axial resolution and tissue cancellation

To characterize the imaging performance of both IVUS contrast imaging pulse sequences, the transmitted waveforms were recorded in water at the transducer focus using a calibrated hydrophone (75 μm polyvinylidene fluoride needle hydrophone; Precision Acoustics Ltd., Dorchester, Dorset, UK) and corrected for frequency dependent hydrophone sensitivity (Figs. 3a, 3b, 4a, 4b). The axial resolution (full width at half maximum) of the pulse inversion waveforms (ultraharmonic imaging) was 122 μm for the input excitation and 171 μm experimentally (Fig. 3c), computed with the average speed of sound in tissue (1540 m/s). The axial resolution of the compressed chirp signals (chirp reversal imaging) was 122 μm theoretically and 144 μm experimentally (Fig. 4c). The experimental waveforms of the ultraharmonic pulse inversion sequence overlapped accurately in the frequency domain (Fig. 3d). In the time domain, their summation gave a residual signal of relatively small amplitude (20% of the experimental waveform amplitude at focus) that corresponds to the second harmonic component generated by nonlinear propagation in water (Fig. 3e). The experimental chirp reversal waveforms (Fig. 4a, 4b) were not fully symmetrical in terms of envelope, and their frequency spectra did not overlap perfectly in the 40–50-MHz range (Fig. 4d) because of the transducer response. However, the compressed chirp signals overlapped in the time domain with a limited mismatch, and their subtraction gave a residual signal of small amplitude (16% of the compressed chirp amplitude; Fig. 4e). In practice, the residual signals in contrast modes are expected to be smaller in tissue than in water. Nonlinear propagation creates part of the residual signal because it distorts the waveform. The higher attenuation in tissue reduces nonlinearity compared to water.

Detection of tissue-mimicking phantom side channels

IVUS contrast imaging results are presented in Figure 5. B-mode images are displayed with a 40 dB dynamic range. For both B-mode and contrast mode images, the 0 dB level is defined by the maximum amplitude in the B-mode. For both contrast-imaging sequences, the three largest phantom side channels were resolved in the absence of UCA, whereas the smallest VV mimicking channel was not visible (Fig. 5a, 5d). After UCA injection, all channels had tissue level echogenicity, and were therefore undetectable with conventional B-mode imaging (Fig. 5b, 5e). In both contrast modes (Fig. 5c, 5f), the central channel and the four side channels were detected above residual tissue signal level. The smallest VV mimicking channel was at the edge of detection with the chirp reversal sequence, but well resolved with the ultraharmonic pulse inversion sequence.

Contrast images (Fig. 5c, 5f) were further characterized in terms of contrast-to-noise ratio (CNR), measured as the ratio of the maximum intensity in a contrast-filled region of interest over the maximum noise intensity, and contrast-to-tissue ratio (CTR), defined as the ratio of the maximum contrast intensity over adjacent maximum residual tissue intensity at equal depth. Results per phantom channel were computed for three datasets and are presented in Figure 6. As expected from chirp processing, the CNR of chirp reversal imaging proved to

be-superior for all channels (up to 20 dB for the 2 mm channel), whereas the CTR proved to be superior for the three largest channels (up to 9.8 dB for the 2 mm channel) than in the pulse-inversion ultraharmonic sequence. The VV mimicking channel was detected more clearly in the ultraharmonic contrast image that featured a larger echogenic area corresponding to the 200 μm channel as well as a higher CTR (+0.6 dB) compared with the chirp reversal image. Despite the lower peak negative pressure, residual tissue-to-noise ratio was 20% higher for chirp reversal imaging (Fig. 5c) than for ultraharmonic imaging (Fig. 5f). CTR is critical for the detection of sub-resolution targets, such as VV, which can be easily misinterpreted from a tissue residual signal. Our results indicate that ultraharmonic IVUS is more robust for VV detection. Subharmonic contrast imaging was also evaluated by transmitting a 0.35 μs , Gaussian-modulated sine-burst with a center frequency of 45 MHz and with a peak negative pressure of 560 kPa (maximum pressure output of our system at 45 MHz). The subharmonic component was extracted using pulse inversion (Goertz et al. 2006b). A maximum CTR value of 7 dB was found for the 2 mm channel.

Ultraharmonic contrast IVUS

The analysis of the frequency content of the pulse inversion contrast image (Fig. 5f) revealed that most of the UCA signal came from the ultraharmonic frequency band rather than from the second harmonic band (Fig. 7b, 7c). This finding is understandable because the sensitivity of the transducer at the second harmonic frequency is low. The amplitude of the 200 μm channel was indeed 4.2 dB higher in the contrast image filtered in the ultraharmonic band (Fig. 7b) than in the image filtered in the second harmonic band (Fig. 7c). To illustrate the nonlinear components extracted by the pulse-inversion sequence, we simulated the pressure backscattered by a single Definity bubble (diameter = 1 μm ; viscosity $\kappa_s = 4.2 \times 10^{-10}$; shell elasticity $\chi = 0.75 \text{ N/m}$; low initial surface tension $\sigma[R_0] = 0.0015 \text{ N/m}$) in response to the experimental pair of phase-inverted IVUS excitations (Marmottant et al. 2005). Figure 7a presents the pulse inversion spectrum of the single bubble response. While the fundamental frequency peak is suppressed, the subharmonic, ultraharmonic and second harmonic components are observed. Knowing the transducer -6 dB frequency bandwidth (Fig. 7a), the transmitted pulse frequency was chosen to generate a UCA ultraharmonic response at the maximum transducer sensitivity (34 MHz). The simulation also indicated that at high frequency, the amplitude of the ultraharmonic response of a single UCA microbubble can be of the same order as the amplitude of the subharmonic response.

Although the second harmonic component showed the highest peak in the simulated pulse-inversion spectrum, its frequency lay outside the transducer bandwidth of -6 dB. The second harmonic component therefore had a lower amplitude (Fig. 7c).

DISCUSSION

Ability to detect a vasa vasorum sized channel

Ultraharmonic IVUS contrast imaging enabled the detection of a 200 μm diameter channel invisible in conventional IVUS images, allowing for functional imaging of sub-resolution microvascular structures such as VV. The capacity of ultraharmonic IVUS contrast imaging to detect the smallest phantom channel proved to be superior to that of chirp reversal IVUS contrast imaging. This may be due to the higher susceptibility of chirp reversal to nonlinear propagation artifacts, to the effects of frequency dependent attenuation on chirp waveforms and to the transducer response. For all these reasons, chirp reversal IVUS is likely to be less robust than a pulse inversion sequence when it comes to imaging microvascular networks.

We observed that the B-mode chirp image (Fig. 5a) provided a better spatial resolution than the B-mode image of the ultraharmonic pulse inversion sequence (Fig. 5d). Although the

input excitations had a similar axial resolution (Figs. 3c, 4c), hydrophone measurements showed a superior axial resolution in chirp IVUS (144 vs. 171 μm). As the 22 MHz input excitation was outside the transducer bandwidth of -6 dB, its transmission resulted in an elongated waveform because of longer transducer ringdown. In addition, the lateral resolution in the B-mode chirp image (34 MHz center frequency) is finer than in the pulse-inversion B-mode image (22 MHz center frequency). Nonetheless the 200 μm channel was undetected in both B-mode images because its diameter was below the lateral resolution of the transducer, equal to 270 μm at the center frequency (Maresca et al. 2012).

An adequate comparison between the contrast imaging methods we propose in this study, and subharmonic imaging, would require higher transmitting pressure to attain sufficient subharmonic generation. This higher pressure can be generated only if a power amplifier were to be included in the transmit circuit. Because short transmission pulses and minimal dead time after transmission are key in these experiments, which use short ranging depths and small targets, fast gating of such an amplifier is essential. We had no access to a suitable instrument, and as a result were not able to perform this experiment. For this reason, we cannot truly rank chirp reversal, ultraharmonic and subharmonic imaging in terms of contrast detection capability. The scarcity, cost and bulk of suitable power amplifiers, which have sufficient harmonic suppression, places subharmonic imaging at a disadvantage for practical implementation.

Future developments in harmonic contrast IVUS imaging

To achieve a higher B-mode resolution, a short pulse at the transducer center frequency could be transmitted in addition to the two pulses dedicated to ultraharmonic imaging. If broadband IVUS transducers become available in the future, new possibilities would emerge for IVUS contrast imaging. With a transducer bandwidth of 70% (frequency bandwidth at half maximum), a pulse inversion sequence would be able to detect the ultraharmonic and the second harmonic responses of contrast microbubbles. However, such an approach would suffer from the generation of a second harmonic component by tissue and artifacts owing to the distortion of transmitted waveforms because of nonlinear propagation in contrast agent (Kate et al. 2012; Tang et al. 2010). With a 100% transducer bandwidth, a contrast mode combining the subharmonic and the ultraharmonic signals could be implemented. Contrary to the second harmonic component, these signals are only produced by UCA microbubbles. A gain in CTR of 6 dB can be expected compared with ultraharmonic imaging only, because the backscattered pressures at the subharmonic and ultraharmonic frequencies can have similar amplitudes (Fig. 7a).

CONCLUSION

Chirp reversal IVUS emerged from our experiments as a balanced two-pulse technique that performs well both in terms of B-mode imaging and contrast detection of targets within the system resolution, but could not detect the vasa vasorum sized channel. The ultraharmonic IVUS pulse sequence presented does not require any additional hardware implementation (contrary to chirp excitations) and could therefore be readily applied on existing commercial IVUS scanners in *in vivo* applications. Between the two methods investigated in this study, we recommend ultraharmonic imaging as the best method for IVUS imaging of vasa vasorum because it enabled the detection of a 200 μm channel.

Acknowledgments

Funding was provided by the Simon Stevin grant 2007 of the Dutch Technology Foundation (STW). The ultrasound contrast agent Definity was supplied by Lantheus Medical Imaging.

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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.

Fig. 2.
Overview of the intravascular ultrasound (IVUS) imaging system.

Fig. 3.

Needle hydrophone measurements. (a, b) Phase-inverted excitations of the ultraharmonic sequence. (c) Envelope of an excitation of the ultraharmonic sequence, (d) frequency spectra of the excitations of the ultraharmonic sequence and (e) residual signal after addition of the inverted excitations of the ultraharmonic sequence.

Fig. 4. Needle hydrophone measurements: (a, b) Upsweep and downswing chirps of the chirp reversal sequence. (c) Compressed chirp envelope, (d) frequency spectra of the chirp excitations and (e) compressed excitations and their residue after subtraction.

Fig. 5.

Images acquired in the tissue-mimicking phantom using the chirp reversal sequence and the pulse inversion sequence. (a) IVUS chirp image without contrast. (b) IVUS chirp image with contrast. (c) IVUS chirp reversal contrast image. (d) 22 MHz conventional IVUS image without contrast. (e) 22 MHz conventional IVUS image with contrast. (f) Ultraharmonic IVUS contrast image. Intensity scales in contrast modes are displayed relative to their respective B-mode intensity.

Fig. 6. Contrast to tissue ratio (CTR) and contrast to noise ratio (CNR) per phantom channel of the two IVUS contrast imaging modes presented.

Fig. 7. (a) Simulated pulse inversion backscattered pressure of a micrometer-sized Definity bubble. (b) Pulse-inversion contrast image filtered in the ultraharmonic band (31–44 MHz) and (c) filtered in the second harmonic band (44–52 MHz).