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● *Original Contribution*

SECOND HARMONIC AND SUBHARMONIC FOR NON-LINEAR WIDEBAND CONTRAST IMAGING USING A CAPACITIVE MICROMACHINED ULTRASONIC TRANSDUCER ARRAY

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Abstract—When insonified with suitable ultrasound excitation, contrast microbubbles generate various non-linear scattered components, such as the second harmonic (2H) and the subharmonic (SH). In this study, we exploit the wide frequency bandwidth of capacitive micromachined ultrasonic transducers (CMUTs) to enhance the response from ultrasound contrast agents by selective imaging of both the 2H and SH components simultaneously. To this end, contrast images using the pulse inversion method were recorded with a 64-element CMUT linear array connected to an open scanner. In comparison to imaging at 2H alone, the wideband imaging including both the 2H and SH contributions provided up to 130% and 180% increases in the signal-to-noise and contrast-to-tissue ratios, respectively. The wide-frequency band of CMUTs offers new opportunities for improved ultrasound contrast agent imaging. (E-mail: ayache.bouakaz@univ-tours.fr) © 2013 World Federation for Ultrasound in Medicine & Biology.

Key Words: **Contrast agent imaging, Capacitive micromachined ultrasonic transducer, Wideband imaging, Subharmonic, Harmonic, Pulse inversion, Signal-to-noise ratio, Contrast-to-tissue ratio.**

INTRODUCTION

Ultrasound contrast agents (UCAs) consist of gas–filled microbubbles that are injected intravenously to enhance the echo from the bloodstream (Bouakaz and de Jong 2007). Currently, UCAs play a significant role in clinical decision making in, among other fields, echocardiography for myocardial perfusion assessment (Davidson and Lindner 2012; Miller and Nanda 2004) and in radiology for tumor detection and characterization (Wilson and Burns 2010). The persistent challenge in contrast agent imaging is to improve the contrast between blood and surrounding tissue. In recent years, new methods based on the specific scattering properties of the microbubbles have been introduced to recover UCA responses while eliminating or reducing the echoes from surrounding tissues (de Jong et al. 2002). These specific microbubble properties are based mainly on their non-linear behavior. Indeed, numerous studies have shown that non-linear microbubble oscillations occur when the driving pressure exceeds an acoustic threshold, causing asymmetric variation of the bubble radius during the compression and expansion phases of the driving pressure. As a consequence, on suitable excitation, microbubbles generate various non-linear components, such as second harmonic (2H), subharmonic (SH), ultraharmonics and superharmonics (de Jong et al. 2009).

Multi-pulse excitation sequences, such as pulse inversion (Simpson et al. 1999), power modulation (Brock-Fisher et al. 1996) and cadence contrast pulse sequence (CPS) (Phillips 2001), have been introduced and are currently clinically used to improve contrast detection and imaging performances. Pulse inversion consists of transmitting two successive pulses (called pulse 0° and pulse 180°) in which the second pulse is a 180° delayed replica of the first signal. Then, backscattered echoes from the two pulses are added together, resulting in enhancement of the second harmonic component, whereas the fundamental component is suppressed or reduced. However, even if second harmonic imaging considerably improved the contrast between microbubbles and surrounding tissue compared with fundamental imaging, the contrast-to-tissue ratio (CTR) is still degraded by tissue non-linear propagation (Humphrey 2000). Power modulation is used to detect odd and even non-linear orders generated by microbubbles. This

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technique consists of the transmission of two consecutive pulses with different amplitudes, because the amplitude modulation modifies the degree of non-linearity in microbubble response. After processing, the resulting signal is composed of a component at f_0 (*i.e.,* non-linear fundamental component) and harmonic components (*i.e.,* $2f_0$, $3f_0$, …) (Eckersley et al. 2005). CPS is based on a combination of pulse inversion and power modulation techniques. A sequence of several successive pulses is transmitted with phase and amplitude modulation. CPS removes the linear fundamental signal and allows better conservation of odd and even non-linear orders, inducing, thus, a stronger response from contrast agents.

For many years, many investigations on microbubble non-linear responses have been studied in the hope of improving contrast detection and contrast images. Superharmonic components, including higher harmonics (third to fiftth), have been explored for enhancing the resolution of echographic images (Bouakaz et al. 2002, 2003). Superharmonic imaging takes advantage of higher harmonics generated by microbubbles to discriminate tissue and UCA responses (Bouakaz et al. 2002). Nevertheless, because of the limited frequency bandwidth of lead zirconate titanate (PZT) transducers, superharmonic imaging still requires the design of a new ultrasound transducer that would be able to transmit at a frequency f_0 and to receive harmonic components at $3f_0$, $4f_0$, and $5f_0$ (Bouakaz et al. 2003; van Neer et al. 2010).

De Jong et al. (2007) have described a new non-linear bubble property called "compression-only" behavior. In their study, de Jong et al. observed an asymmetric response of coated bubbles, even at acoustic pressures as low as 50 kPa. This phenomenon is characterized by a strong compression of the microbubbles while their expansion was too weak. This asymmetric behavior is attributed to the shell buckling state as described by Marmottant et al. (2005). More recently, several studies have suggested a relationship between subharmonic generation and compression-only behavior of the microbubbles (Frinking et al. 2009; Sijl et al. 2008). The generation of subharmonics was first studied by Eller and Flynn (1969). Their study revealed the appearance of a frequency component at half the transmitted frequency in the bubble vibration. The subharmonic generation occurred when the driving pressure exceeded a threshold (Shi et al. 1999). Shankar et al. (1999) have shown that this threshold depends on bubble mechanical properties (such as shell elasticity and viscosity) and is minimal when the insonation frequency is close to twice the microbubble resonance frequency. For example, the pressure threshold for Levovist microbubbles was found to be 300 kPa (Shi et al. 1999), whereas that for isolated SonoVue microbubbles was found to be 30 kPa for (Biagi et al. 2007). Consequently, the detection of subharmonic components may be achieved at low driving pressures, thus avoiding destruction of the microbubbles and hence increasing their lifetime (Chomas et al. 2002). Moreover, subharmonic imaging (SHI) allows a significant increase in the CTR owing to the absence of subharmonic generation in tissue at diagnostic pressures and frequencies (Shankar et al. 1998). At high frequencies, Goertz et al. (2006) have studied the use of the subharmonic component for intravascular imaging (Tx: 40 MHz/Rx: 20 MHz) and compared imaging at subharmonics and standard harmonic imaging (Tx: 20 MHz/ Rx: 40 MHz) using the pulse inversion method. Their results indicate that for driving pressures higher than 0.8 MPa, SHI provides an enhancement of the CTR up to 17 dB compared with second harmonic imaging.

The amplitude, frequency and length of the driving pulse play a major role in subharmonic generation. Biagi et al. (2006) reported that pulse shape and microbubble concentration influence significantly the level of subharmonic emissions. Moreover, the subharmonic response is stronger when long pulses are transmitted. To overcome this limitation, Zhang et al. (2007) suggested using chirp excitation to enhance both sensitivity and axial resolution using compression filters. It has been found that a chirp signal produces subharmonics with amplitudes higher than those generated using a conventional pulse excitation with the same excitation frequency spectrum.

With the current contrast imaging methods, the restricted frequency bandwidth of standard PZT probes (approximately 80% at −6 dB) limits the ability to image several non-linear components. In pulse inversion or traditional harmonic imaging, only the 2H component generated at twice the transmitted frequency is chosen becaiuse it provides a stronger signal–to–noise ratio (SNR) than the other non-linear components. In practical terms, the excitation signal is transmitted at two-thirds of the center frequency of the PZT probe, whereas the 2H component is received at four-thirds. Moreover, other strategies such as CPS extract only the non-linear fundamental component in addition to the traditional second harmonic component.

Nevertheless, the recent appearance of capacitive micromachined ultrasonic transducers (CMUTs) has offered new possibilities for medical ultrasound imaging (Oralkan et al. 2002; Caliano et al. 2005). A CMUT element structure consists of a parallel plate capacitor composed of a rigid bottom electrode and a top electrode linked to a flexible membrane. On application of an alternating driving voltage, an electrostatic force is exerted between the top electrode and the bottom electrode leading to membrane vibrations and, thus, generating acoustic waves (Oralkan et al. 2002). Current studies report that CMUT arrays exhibit a frequency bandwidth