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● *Original Contribution*

AMBIENT PRESSURE EVALUATION THROUGH SUB-HARMONIC RESPONSE OF CHIRP-SONICATED MICROBUBBLES

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Abstract—The sub-harmonic response generated by oscillating ultrasound contrast microbubbles has been proven to be a potentially efficient and effective measure for non-invasive blood pressure evaluation. In this work, an improved approach to ambient pressure measurement is proposed, and the general principle underlying this approach is the combination of sub-harmonic responses of microbubbles with a chirp excitation technique. Agreement between theoretical and experimental studies indicates that compared with sinusoidal excitation, the chirp technique is beneficial in that it produces bubble sub-harmonics with higher amplitudes and lower generation thresholds and thus offers better sensitivity for ambient pressure evaluations. Studies that took the chirp parameters (*e.g.*, central frequency, bandwidth and pulse length) into account were also carried out to determine an optimized routine for the proposed method. (E-mail: guoxs@nju.edu.cn or dzhang@nju.edu.cn and di_hsu@126.com) © 2016 World Federation for Ultrasound in Medicine & Biology.

Key Words: **Chirp signal, Sub-harmonic response, Microbubble, Ambient blood pressure measurement.**

INTRODUCTION

The local blood pressure in human heart cavities and large blood vessels, such as the aorta, is closely related to heart rate, respiration rate, oxygen saturation status and body temperature. Because it can provide valuable information on the circulatory system, the local blood pressure can be used as a vital sign to evaluate the physical condition of patients and diagnose diseases in their cardiocerebral vascular systems. The sensitivity of the blood pressure measurement process thus affects both the accuracy of clinical diagnosis and the related treatment strategy. Catheterization, which is commonly used to measure blood pressure, requires the insertion of a microcatheter with pressure sensors into either the heart chamber or large blood vessels (Benisty 2002). Because of the invasiveness of such a procedure, patients may suffer increased pain and/or risk of complications. In contrast, the Doppler echocardiography-based pressure measurement technique, which is also currently available and is considered non-invasive, has been reported to provide non-reproducible results (Reddy et al. 2003; Strauss et al. 1993).

Ultrasound contrast agents (UCAs) are regarded as a promising tool for the development of non-invasive diagnostic and therapeutic approaches. UCAs usually comprise a suspension of gas-filled microbubbles (1–10 μm in diameter in most cases) that are encapsulated by thin stabilization shells. Given their advantages of great echogenicity and high compressibility, UCAs were initially used to improve the quality of ultrasound imaging. Fairbank and Scully (1977) applied UCAs to pressure estimation for the first time. Their results indicated that the resonance frequencies of individual microbubbles shifted with variations in ambient pressure. However, accurate pressure estimation based on such resonance frequency shifts required stable microbubbles of uniform size. Hök (1981) subsequently suggested that the echo amplitude from a single bubble could also be of use in blood pressure evaluation. Unfortunately, the errors in the reported experimental results exceeded 30%. Bouakaz et al. (1999) then proposed a new solution based on detection of the disappearance time of free bubbles that were generated from destroyed UCAs, but their

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measurement sensitivity was severely limited by the uncontrolled size and rapid disappearance of the generated free bubbles (Brayman et al. 1996). It is also widely accepted that microbubbles exhibit strong non-linear vibrations in response to ultrasound excitation, thus leading to the generation of second- and higher-order harmonics, sub-harmonics and ultra-harmonics. Shi et al. (1999) found in their experiments that sub-harmonic components are better able to reflect the ambient pressure than their fundamental and second harmonic counterparts. In experiments conducted by Frinking et al. (2010), the sub-harmonic component radiated by the microbubbles either decreased by 9.6 dB at an incident pressure of 400 kPa or increased by 28.9 dB at a lower ultrasound pressure of 50 kPa when ambient pressure increased by 180 mm Hg. In contrast, Katiyar et al. (2011) calculated numerically that the ambient pressure dependence of sub-harmonic waves should be dominated by the ratio of the excitation frequency to the bubble's resonant frequency, and could exhibit rather diverse behavior (including monotonic increasing, monotonic decreasing and non-monotonic behavior) depending on the value of this ratio.

Chirp signals, namely, linear frequency-modulated signals, are often used in applications such as sonar, radar and seismic surveys. The chirp excitation technique has already been applied in combination with microbubbles to ultrasound imaging for medical diagnosis (Borsboom et al. 2003; Misaridis et al. 2000). Zhang et al. (2007) reported that sub-harmonic imaging based on chirp excitation could help to optimize image quality and, in particular, axial resolution, by enhancing the sub-harmonic signals and providing better signal-to-noise ratios. Given that UCA suspensions generally have a non-negligible microbubble size distribution, the effective resonance frequency of such a suspension should span a considerable bandwidth. It is therefore reasonable to speculate that the sub-harmonic responses of UCAs could be enhanced when using a wide-bandwidth excitation rather than sinusoidal ultrasound irradiation, and this should be helpful in optimization of blood pressure measurement sensitivity.

This work explores the feasibility of evaluating ambient pressure by combining microbubble sub-harmonics with chirp excitation. To illustrate the advantages of chirp excitation over the sinusoidal sonication technique, comparisons were made between the two cases by examining the ambient pressure dependence of sub-harmonics generated from microbubbles through both simulations and experiments. For further optimization of the sensitivity of the proposed technique, detailed simulations and experiments were also carried out to quantitatively investigate the effects of the chirp parameters.

METHODS

Single-bubble dynamics

Various modified Rayleigh–Plesset models have been proposed for the study of UCA microbubble dynamics in incompressible liquids (Church 1995; Dayton et al. 2002; de Jong 1994; Donikov and Bouakaz 2011; Faez et al. 2013; Khismatullin and Nadim 2002; Li et al. 2013; Yang and Church 2005). Among these models, the Marmottant model (Marmottant et al. 2005) specifically takes the non-linear modifications of surface tension induced by the buckling and rupture of the bubble shell into account. This model is used here to study the sub-harmonic response of microbubbles and its dependence on ambient pressure:

$$\rho R\ddot{R}+\frac{3}{2}\rho\dot{R}^2=\left[P_0+P_{\mathrm{ov}}+\frac{2\sigma(R_0)}{R_0}\right]\left(\frac{R_0}{R}\right)^{3k}\left(1-\frac{3\kappa}{c}\dot{R}\right)-(P_0+P_{\mathrm{ov}})-\frac{2\sigma(R)}{R}-\frac{4\mu\dot{R}}{R}-\frac{4\kappa_s\dot{R}}{R^2}-p_{\mathrm{ac}}(t) \quad (1)$$

R is the instantaneous radius of an individual microbubble; $\dot{R}$ and $\ddot{R}$ represent the first- and second-order time derivatives of R, respectively; R_0 is the equilibrium radius; κ_s is the surface dilatational viscosity of the bubble shell; κ is the polytropic exponent; ρ, c and μ are the density, sound velocity and viscosity of the surrounding liquid, respectively; p_{ac} (t) is the time-dependent acoustic pressure of excitation; P_0 is the hydrostatic pressure; and P_{ov} is the overpressure (which is used to describe the variation in ambient pressure). In the Marmottant model, the effective surface tension of the bubble shell has three successive stages that are defined by a specific set of parameters (*i.e.*, buckling radius R_{buckling}, elastic modulus χ, and breakup shell tension σ_{water}), and are described as

$$\sigma(R)=\begin{cases}0 & \text{if } R\le R_{\mathrm{buckling}}\\ \chi\left(\dfrac{R^2}{R_{\mathrm{buckling}}^2}-1\right) & \text{if } R_{\mathrm{buckling}}\le R\le R_{\mathrm{break\text{-}up}}\\ \sigma_{\mathrm{water}} & \text{if ruptured and } R\ge R_{\mathrm{ruptured}}\end{cases} \quad (2)$$

At a distance d from the bubble center, the scattered pressure $P_s(d,t)$ can be calculated as (Frinking et al. 2010)

$$P_s(d,t)=\rho\frac{R}{d}\left(2\dot{R}^2+R\ddot{R}\right) \quad (3)$$

Production of UCAs of strictly uniform size is difficult to achieve, and thus a weighting scheme based on a discretized size distribution is used to determine the cumulative scattered echoes (Zheng et al. 2006) in the form