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● *Original Contribution*

MONODISPERSE VERSUS POLYDISPERSE ULTRASOUND CONTRAST AGENTS: NON-LINEAR RESPONSE, SENSITIVITY, AND DEEP TISSUE IMAGING POTENTIAL

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Abstract—It has been proposed that monodisperse microbubble ultrasound contrast agents further increase the signal-to-noise ratio of contrast-enhanced ultrasound imaging. Here, the sensitivity of a polydisperse pre-clinical agent was compared experimentally with that of its size- and acoustically sorted derivatives by using narrow-band pressure- and frequency-dependent scattering and attenuation measurements. The sorted monodisperse agents had up to a two-orders-of-magnitude increase in sensitivity, that is, in the average scattering cross section per bubble. Moreover, we found, for the first time, that the highly non-linear response of acoustically sorted microbubbles can be exploited to confine scattering and attenuation to the focal region of ultrasound fields used in clinical imaging. This property is a result of minimal pre-focal scattering and attenuation and can be used to minimize shadowing effects in deep tissue imaging. Moreover, it potentially allows for more localized therapy using microbubbles through the spatial control of resonant microbubble oscillations. (E-mail: t.j.segers@utwente.nl) **© 2018 World Federation for Ultrasound in Medicine & Biology. All rights reserved.**

Key Words: **Monodisperse bubbles, Ultrasound contrast agents, Non-linear echo.**

INTRODUCTION

Ultrasound contrast agents (UCAs) consist of a suspension of microbubbles that are stabilized against dissolution and coalescence by a surfactant shell, typically composed of biocompatible phospholipids. The compressibility of the microbubbles gas core allows for ultrasound-driven radial bubble oscillations. The resulting non-linear echo can be used to visualize and quantify organ perfusion (Lindner 2004). Even though the scattering cross section of UCA microbubbles is typically nine orders of magnitude higher than that of particles of the same size (de Jong et al. 1991), the scattering efficiency is quite low. The larger part of the incident acoustic energy is lost because of viscous damping. The intermolecular viscous dissipation within the lipid shell accounts for approximately 80% of the energy loss; the remainder is dissipated by the viscosity of the surrounding fluid and, in addition, through thermal diffusion (Khismatullin and Nadim 2002; van der Meer et al. 2007). The energy loss results in the attenuation of an ultrasound wave propagating through a microbubble suspension (de Jong et al. 1992; Leighton 1994).

The radial microbubble oscillation amplitude in response to a driving ultrasound field is strongly dependent on the coupling between the frequency of the ultrasound field and the resonance frequency of the microbubble. The microbubble resonance frequency is inversely proportional to its size through the Minneart eigenfrequency (Minnaert 1933). In addition, it is highly affected by the physical properties of the microbubble shell that can be modeled as a viscoelastic membrane with a shell viscosity, resulting in increased damping, and with a shell elasticity, which increases the resonance frequency (van der Meer et al. 2007). Commercial UCAs are available as a suspension of microbubbles with a relatively wide size distribution with radii typically ranging from 0.5 to 8 μm. Clinical ultrasound scanners operate over a relatively narrow frequency bandwidth with respect to that of the resonance frequencies of the microbubbles present in a typical UCA. Thus, it is expected that only a small fraction of the UCA population contributes to the overall echo. Therefore, the

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sensitivity of contrast-enhanced ultrasound imaging, and in particular that of single-bubble molecular imaging (Klibanov 2006), can be substantially increased through the use of monodisperse bubbles that are resonant to the driving ultrasound pulse.

The sensitivity increase that may result from the use of a monodisperse UCA has been suggested before (Gong et al. 2014; Hettiarachchi et al. 2007; Kaya et al. 2010; Parrales et al. 2014; Segers et al. 2016a; Shih et al. 2013; Stride and Edirisinghe 2009; Talu et al. 2007). *In vitro* experiments have revealed that the echoes of monodisperse bubbles are more correlated than those of a polydisperse population (Talu et al. 2007). *In vivo* experiments in rats indicate a higher video intensity for monodisperse bubbles as compared with a polydisperse agent (Streeter et al. 2010).

The potentially higher sensitivity of a monodisperse contrast agent was reported to be of great interest for molecular imaging (Klibanov 2006) and drug delivery applications (Carson et al. 2012; Deelman et al. 2010; Dewitte et al. 2015; Hernot and Klibanov 2008; Tsutsui et al. 2004), for which typically only a small amount of bubbles are retained at the target site (Talu et al. 2007). For blood pool imaging in humans, large amounts of microbubbles can be injected (on the order of 1 billion bubbles) to compensate for the lower sensitivity of a polydisperse agent. Therefore, monodispersity was thought to be of less importance here (Kaya et al. 2010; Talu et al. 2007). However, it has been reported that the resonance behavior of narrow-size-distribution bubble populations is more narrowband, and more non-linear, than that of a polydisperse agent (Emmer et al. 2009). The strong driving pressure-dependent resonance behavior in particular (Overvelde et al. 2010; Segers et al. 2016a; Xia et al. 2015) may result in very different scattering behavior of a monodisperse agent as compared with that of a polydisperse agent in a typical ultrasound field employed for clinical contrast-enhanced ultrasound imaging. The clinically used ultrasound beams are focused, with pressure amplitudes increasing toward the acoustic focal region and deceasing thereafter (Segers et al. 2016a; Sojahrood et al. 2015), resulting in the insonation of the UCA at a broad range of acoustic pressures. A systematic experimental comparison between a polydisperse agent and a monodisperse agent with the same microbubble coating properties has never been conducted, neither to study sensitivity nor to study the pressure-dependent scattering in a clinically relevant focused ultrasound field.

A monodisperse microbubble suspension can be synthesized in a microfluidic flow-focusing device (Anna et al. 2003; Gañán-Calvo and Gordillo 2001; Garstecki et al. 2005; Segers et al. 2016b). Recently, the full parameter space for stable lipid-coated microbubble synthesis was characterized (Segers et al. 2017). Alternatively, a narrow-size-distribution bubble population can be obtained by sorting a polydisperse UCA, for example, by means of filtration (Emmer et al. 2009), decantation (Goertz et al. 2007) and centrifugation (Feshitan et al. 2009) methods. Microbubbles can be sorted with a higher degree of control in microfluidic devices; for example, they can be sorted to size in a pinched microchannel (Kok et al. 2015) and they can be sorted to their resonance behavior using the primary radiation force induced by a traveling acoustic wave (Segers and Versluis 2014). An advantage of sorting methods over the flow-focusing method is that sorting methods may allow for a direct comparison of the effects of the bubble size distribution on the acoustic properties of the polydisperse agent and its monodisperse derivatives, because the different populations originate from the very same native bubble population.

The aim of this work was to characterize and to compare the non-linear behavior and the sensitivity of a native agent with that of its microfluidically sorted derivatives using pressure- and frequency-dependent scattering and attenuation measurements. The systematic characterization was used to understand the pulse-echo response of the different bubble populations in a clinically relevant focused ultrasound field for which the focal position and the focal pressure were varied.

METHODS

Agent handling and bubble sorting procedures

We used a polydisperse pre-clinical perfluorobutane-based ultrasound contrast agent (Bracco BR-14, Bracco Research, Geneva, Switzerland) containing bubbles coated with DSPC and DPPG lipids (Sijl et al. 2010). The UCA was reconstituted with 5 mL of Milli-Q water (Millipore Corp., Billerica, MA, USA) and left to rest for at least 10 min to allow the bubbles to stabilize. The optically measured size distribution is illustrated in Figure 1A with a total bubble concentration of 2.5×10^8 bubbles/mL.

The native BR-14 agent was sorted to its acoustic property by using the acoustic bubble sorting method outlined by Segers et al. (Segers and Versluis 2014; Segers et al. 2016a). In total, two acoustically sorted bubble populations were produced: sample 1 and sample 2. The sorting chip, illustrated in Figure 1B, had an overall channel height of 14 μm. It comprised two outlet channels to separate the resonant from the non-resonant bubbles through the primary radiation force induced by a 2-MHz traveling acoustic wave. The cross section of the sorting channel was 14×200 μm^2 with a total length of 5 mm. The width of the resonant-bubble outlet was 50 μm (Fig. 1B). The traveling wave was generated by a 6-mm-diameter piezo driven by a continuous-wave sinusoid with a 1.8-V amplitude (Tabor Electronics, WW1072, Tel Hanan, Israel). The maximum acoustic pressure amplitude within the sorting channel was measured as described by Segers and Versluis (2014) to

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