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Inverse effects of flowing phase-shift nanodroplets and lipid-shelled microbubbles on subsequent cavitation during focused ultrasound exposures

Siyuan Zhang [a], Zhiwei Cui [a], Tianqi Xu [a], Pan Liu [a], Dapeng Li [a], Shaoqiang Shang [a], Ranxiang Xu [a], Yujin Zong [a], Gang Niu [b], Supin Wang [a], Xijing He [c], Mingxi Wan [a,*]

[a] The Key Laboratory of Biomedical Information Engineering of the Ministry of Education, Department of Biomedical Engineering, School of Life Science and Technology, Xi'an Jiaotong University, Xi'an 710049, People's Republic of China
[b] Department of Radiology, The First Affiliated Hospital of Xi'an Jiaotong University, Xi'an 710061, People's Republic of China
[c] Department of Orthopedics, The Second Affiliated Hospital of Xi'an Jiaotong University, Xi'an 710004, People's Republic of China

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ABSTRACT

This paper compared the effects of flowing phase-shift nanodroplets (NDs) and lipid-shelled microbubbles (MBs) on subsequent cavitation during focused ultrasound (FUS) exposures. The cavitation activity was monitored using a passive cavitation detection method as solutions of either phase-shift NDs or lipid-shelled MBs flowed at varying velocities through a 5-mm diameter wall-less vessel in a transparent tissue-mimicking phantom when exposed to FUS. The intensity of cavitation for the phase-shift NDs showed an upward trend with time and cavitation for the lipid-shelled MBs grew to a maximum at the outset of the FUS exposure followed by a trend of decreases when they were static in the vessel. Meanwhile, the increase of cavitation for the phase-shift NDs and decrease of cavitation for the lipid-shelled MBs had slowed down when they flowed through the vessel. During two discrete identical FUS exposures, while the normalized inertial cavitation dose (ICD) value for the lipid-shelled MB solution was higher than that for the saline in the first exposure (p-value <0.05), it decreased to almost the same level in the second exposure. For the phase-shift NDs, the normalized ICD was 0.71 in the first exposure and increased to 0.97 in the second exposure. At a low acoustic power, the normalized ICD values for the lipid-shelled MBs tended to increase with increasing velocities from 5 to 30 cm/s ($r > 0.95$). Meanwhile, the normalized ICD value for the phase-shift NDs was 0.182 at a flow velocity of 5 cm/s and increased to 0.188 at a flow velocity of 15 cm/s. As the flow velocity increased to 20 cm/s, the normalized ICD was 0.185 and decreased to 0.178 at a flow velocity of 30 cm/s. At high acoustic power, the normalized ICD values for both the lipid-shelled MBs and the phase-shift NDs increased with increasing flow velocities from 5 to 30 cm/s ($r > 0.95$). The effects of the flowing phase-shift NDs vaporized into gas bubbles as cavitation nuclei on the subsequent cavitation were inverse to those of the flowing lipid-shelled MBs destroyed after focused ultrasound exposures.

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1. Introduction

Focused ultrasound (FUS) is an emerging precise and non-invasive technique to selectively and locally produce different bioeffects deeply into the interior of the body via viscous heating, acoustic cavitation, or their combination [1–3]. FUS is now being widely investigated for localized drug delivery [4], gene transfer [5], sonothrombolysis [6], histotripsy [7], hemostasis [8], neurosurgery [9], and the thermal ablation of tumors located in various tissues, including uterine fibroids [10], bone [11], liver [12], prostate [13], kidney [14], brain [15], and breast [16]. Focused ultrasound therapy is a continuously expanding field due to the progresses in the medical imaging techniques used for targeting and monitoring recent years, such as magnetic resonance imaging (MRI) [17] and ultrasound (US) imaging [18,19]. However, some remaining problems need to be addressed and the improvement of therapeutic efficiency will be of benefit in the application of FUS before ultrasonic therapy becomes a practical possibility as a clinical intervention.

One way to enhance the efficiency of therapeutic ultrasound may be found in the interaction between ultrasound and cavitation

* Corresponding author.
E-mail address: mxwan@mail.xjtu.edu.cn (M. Wan).

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microbubbles. Cavitation is one of the primary mechanisms by which numerous therapeutic applications of FUS function and refers to the nucleation, growth, oscillations and rapid inertial collapse of bubbles [20–23]. When cavitation bubbles oscillate and collapse, several physical and chemical effects are generated such as the formation of hot spots, shock waves, microjets, turbulence, shear forces, microstreaming, highly reactive free radicals, toxic chemicals and so on [20–23]. The concentration of energy during the collapse is enormous and bubble implosion can generate local conditions of thousands of Kelvin degrees and hundreds of atmospheres accompanied by shock waves of extremely short duration [20–23]. Ultrasound-driven cavitation has been shown to improve the efficiency of localized drug delivery [4], gene transfer [5], sonothrombolysis [6], lithotripsy [24], histotripsy [7], and the thermal ablation of tumors located in various tissues [2,3,10,12,13]. Recently, various encapsulated gas-filled microbubbles (MBs) and phase-shift nanodroplets (NDs) have been used to enhance local cavitation and create interests in developing ultrasound therapy methods using these MBs and NDs [4,5,25–31].

Encapsulated MBs have been recently shown to enhance local cavitation and heating caused by the ultrasound exposure. Increased therapeutic effects have been shown both theoretically [32] and experimentally [33,34] when stabilized, gas-filled MBs are introduced prior to or during ultrasound procedures, creating interests in the potential use of MBs in the therapeutic applications of FUS. The encapsulated gas-filled MBs are initially used as ultrasonic contrast agents (UCA) when injected intravenously into the body and have been successfully employed in contrast-enhanced ultrasound medical imaging, molecular-targeted imaging, and quantitative perfusion assessment [35]. Recently, many more studies have investigated the use of polymer-shelled and lipid-shelled MBs loaded with targeting ligands and drugs and have explored how they concentrate selectively and disrupt the ultrasound focal regions [4,5]. The presence of MBs during FUS exposure has been associated with a dramatic increase in measured heating rate and peak temperature [36]. The introduction of encapsulated MBs during FUS ablation treatment of tumors can effectively increase the volume of tissue coagulated with shorter exposures or the required ultrasound intensity, thus increasing the efficiency of FUS cancer therapy [33,34]. Polymer-shelled and lipid-shelled MBs loaded with targeting ligands and drugs are selectively concentrated and disrupted at the ultrasound focal regions for localized drug delivery, gene transfer, and non-invasive thrombolysis [4,5]. Encapsulated MBs as cavitation nuclei have been found to reduce the pressure threshold of inertial cavitation and increase cavitation activity [37]. Naturally, during a violent collapse, large mechanical forces and high temperatures develop in a cavitation bubble's vicinity, causing thermal and sonochemical damage to the surrounding tissue [20]. The selective deposition of cavitation bubbles tends to increase locally the attenuation coefficient and enhance local heating related to absorption of sound [38]. The linear or non-linear oscillations of cavitation bubbles enhance local heating related to the diffusion of heat from the hot compressed gas of the bubble interior and higher harmonics scattered or emitted by cavitation bubbles are more readily absorbed and converted to heat in the tissue [36]. Oscillation and cavitation activity of MBs have been investigated under various FUS parameters, including peak negative acoustic pressure, pulse-repetition frequency and pulse length [39,40]. In addition, different concentration and diameter of the MBs, composition of the shells and the vessel diameter may also influenced the cavitation characteristics of encapsulated MBs [41–44]. Spatiotemporally resolve cavitation events were investigated under physiologically relevant flow conditions during ultrasonic exposure in a flow environment [45].

The phase-shift droplet emulsions contain micron- or nanometer-sized liquid droplets containing low-boiling-point perfluorocarbon (PFC) compounds encapsulated in shells made of lipids, albumin, or PLGA [30]. When in the body, phase-shift NDs become superheated at body temperature and can be vaporized into gas bubbles at a desired location once ultrasound pulses are applied; this process is known as acoustic droplet vaporization (ADV) [30,31,46,47]. When used as cavitation nuclei, phase-shift NDs have a number of therapeutic applications, such as the targeted delivery of therapeutic agents [29], enhanced high-intensity focused ultrasound (HIFU) therapy for cancer treatment [31], and gas embolotherapy, in which gas MBs selectively formed from liquid droplets are used to prevent blood flow to tumors [30]. Additional applications for phase-shift NDs potentially lie in ultrasound molecular imaging [48], phase aberration correction [49], and intraoperative assessment of cancer ablation margins produced by thermal techniques [50]. A large body of work has investigated the cavitation characteristics of the phase-shift NDs under various sonication parameters, surrounding fluid properties, and droplet parameters [46,47,51,52]. Ultrasound-mediated cavitation thresholds of phase-shift NDs were measured as a function of its content and FUS properties such as frequency, amplitude, pulse repetition frequency and pulse width [46,47]. The relationship between ADV and cavitation thresholds was also investigated by studying various parameters that are known to influence the cavitation threshold, including bulk fluid properties such as gas saturation, temperature, viscosity and surface tension, droplet parameters such as degree of superheat, surfactant type and size [46,47,51,52].

Our previous work have demonstrated the potential use of flowing lipid-shelled MBs to minimize thermal losses from perfusion during focused ultrasound exposures [53] and compared ultrasound-induced cavitation from flowing polymer-shelled and lipid-shelled MBs [54]. The variation in components of a MB shell and the different types of gases inside a bubble may mean that different MBs exhibit different efficiencies in cavitation [34,54]. Thus, comparing the efficiencies in cavitation between different MBs is important when using them for treatments that involve cavitation effects. In the published literature, little work has appeared on the comparison of phase-shift NDs and encapsulated gas-filled MBs and their potential for effects on cavitation during focused ultrasound exposures. Such information would provide a reference for the various investigations and applications of cavitation-enhanced FUS. Meanwhile, in potential clinical applications, the encapsulated gas-filled MBs and phase-shift NDs are introduced into the body by means of an intravenous bolus injection. Few researches concerned about the cavitation characteristics of flowing encapsulated gas-filled MBs and phase-shift NDs through the blood vessels when exposed to focused ultrasound. The objective of the present work is to compare how flowing phase-shift NDs and lipid-shelled MBs affect cavitation during focused ultrasound exposures. The cavitation activity was monitored using a passive cavitation detection method as solutions of either phase-shift NDs or lipid-shelled MBs flowed at varying velocities through a 5-mm diameter wall-less vessel in a transparent tissue-mimicking phantom and were exposed to FUS at a range of acoustic power levels. Pure controls (saline) were also monitored with the same exposure parameters and flow velocities.

2. Materials and methods

2.1. Phase-shift nanodroplets and lipid-shelled microbubbles

In this work, the phase-shift NDs and lipid-shelled MBs are studied. The phase-shift NDs were prepared with liquefied dodecafluoropentane (DDFP) gas and bovine serum albumin (BSA). The preparation procedure of DDFP was described elsewhere

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