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Streaming flow from ultrasound contrast agents by acoustic waves in a blood vessel model

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ABSTRACT

To elucidate the effects of streaming flow on ultrasound contrast agent (UCA)-assisted drug delivery, streaming velocity fields from sonicated UCA microbubbles were measured using particle image velocimetry (PIV) in a blood vessel model. At the beginning of ultrasound sonication, the UCA bubbles formed clusters and translated in the direction of the ultrasound field. Bubble cluster formation and translation were faster with 2.25 MHz sonication, a frequency close to the resonance frequency of the UCA. Translation of bubble clusters induced streaming jet flow that impinged on the vessel wall, forming symmetric vortices. The maximum streaming velocity was about 60 mm/s at 2.25 MHz and decreased to 15 mm/s at 1.0 MHz for the same acoustic pressure amplitude. The effect of the ultrasound frequency on wall shear stress was more noticeable. Maximum wall shear stress decreased from 0.84 to 0.1 Pa as the ultrasound frequency decreased from 2.25 to 1.0 MHz. The maximum spatial gradient of the wall shear stress also decreased from 1.0 to 0.1 Pa/mm. This study showed that streaming flow was induced by bubble cluster formation and translation and was stronger upon sonication by an acoustic wave with a frequency near the UCA resonance frequency. Therefore, the secondary radiant force, which is much stronger at the resonance frequency, should play an important role in UCA-assisted drug delivery.

1. Introduction

An ultrasound contrast agent (UCA) consists of micrometer-size gas bubbles encapsulated by biodegradable shells such as albumin and lipids and is used in diagnostic imaging [1]. When a UCA is inserted into the blood stream, the bubbles oscillate and create ultrasound signals upon external ultrasound sonication and thus provide imaging signals. Ultrasound also plays an important role in the therapeutic arena, including shock wave lithotripsy, hypothermic treatment, and drug delivery. Ultrasound has been used in cancer and gene therapy to increase the specificity and efficiency of drug delivery [2] because of its noninvasive nature and local delivery characteristics. The use of ultrasound with UCAs further enhances the efficacy of drug delivery because it can induce a temporary increase in the permeability of tissue and cellular membrane via the pressure and stress fields caused by the cavitation of microbubbles [3–6]. Furthermore, microbubbles can be used as carrier particles by encapsulating plasmid DNA or other drugs and modifying their outer surface using receptor-specific ligands [3]. Streaming flow enhances the convective transport of blood-borne particles toward the vessel wall, and stress fields generated by cavitating bubbles physically induce a temporary increase in the porosity and permeability of the cell membrane [7–9]. In addition, radiant acoustic pressure transports the bubbles toward the vessel wall, where they promote the binding of therapeutic compounds attached to UCA shells to the vessel wall and the generation of a strong stress field near the wall. Therefore, the migration of bubbles and the streaming flow induced by the cavitating bubbles are important physical factors that determine the efficacy of ultrasound-assisted drug delivery.

Streaming flow induced by acoustic wave has been intensively studied since the pioneering work of Nyborg [10]. He analyzed the streaming velocity using successive approximations to the solutions of nonlinear hydrodynamics equations, and showed streaming speeds depend on the attenuation constant [11]. Wu and Du [12] derived an approximation solution to the Nyborg equation adapting relevant assumptions, and solved axial velocities for unfocused plane beams and focused Gaussian beams. Their solution was modified by directly deriving boundary conditions, and streaming velocity was estimated [13]. The theoretical estimation of streaming velocity was verified experimentally using a 32 MHz pulse Doppler unit [14]. Streaming flow by the focused ultrasound beams was also measured experimentally, and the effects of ultrasound parameters on streaming velocities were

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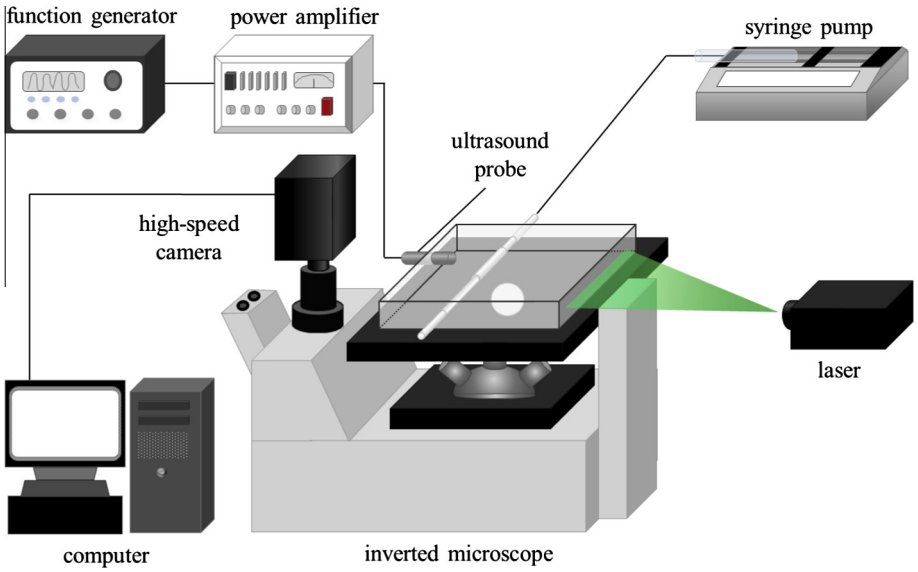

Fig. 1. Schematic diagram of the experimental setup.

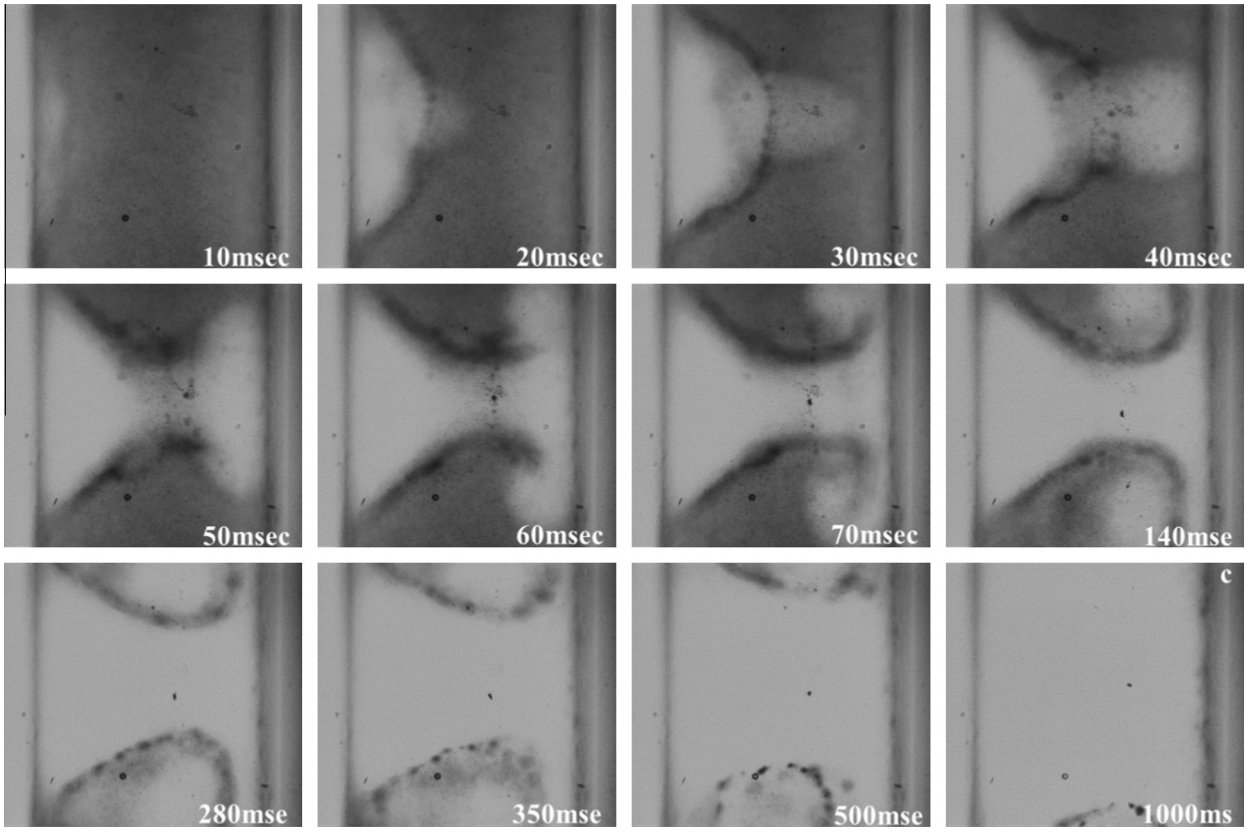

Fig. 2. UCA bubble cluster translation during sonication using a 2.25 MHz continuous wave with a pressure amplitude of 600 kPa.

investigated [15]. Though intensive studies on acoustic streaming have been performed theoretically and experimentally, streaming flow from acoustically activated microbubbles has not been studied extensively.

There have been studies on microbubble cluster formation and migration as well as on streaming flow from bubbles by acoustic waves. Translation of a 1.5-μm-radius contrast agent by acoustic radiant force has been measured using high-speed photography [16]. Cavitation bubble streaming in an ultrasound standing-wave field has been measured by laser Doppler velocimetry, and the structures of the cavitating bubbles were observed [17]. In addition, bubble cluster formation and movement have been observed by high-speed microscopy [18,19]. These studies focused on the coalescence and translation of microbubbles caused by primary and secondary radiant forces from ultrasound, but streaming velocity fields from cavitating microbubbles and clusters have not been studied. The streaming flow from a single bubble attached to the wall has been studied theoretically [20,21] and

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