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An optical and acoustic investigation of microbubble cavitation in small channels under conditions relevant to vascular disruption therapy

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Background, Motivation and Objective

Therapeutic ultrasound (US) using microbubbles (MBs) is widely investigated for local drug delivery by enhancing vascular permeability. At higher pressures, MBs can induce microvascular damage and shut down blood flow. This method has been called vascular disruption therapy (VDT) or mechanical ablation. These effects can inhibit tumor growth and we have shown they can profoundly enhance the effects of anticancer agents. These experiments have been conducted under similar conditions (1 MHz, 0.1 ms pulses, nonlinear with ~1.5 MPa negative, 3 MPa positive) with both conventional (e.g. Definity) and submicron formulations. There is little known about the specific mechanisms of this approach. In this study we employ a combination of high speed microscopy and cavitation monitoring to assess MB behavior in small vessel phantoms with relevant VDT exposure schemes.

Statement of Contribution/Methods

Vessel phantoms were cast in agarose with diameters of 15, 50, 100 and 200 microns. High speed microscopy (Photron, 10kframes/s; shutter 1us) was employed to examine the evolution of MB behavior over millisecond timescales. Broadband Tx and Rx transducers were centered at 2.25 MHz. Pulsing schemes were 100 bursts of 0.1ms (1kHz) or 5ms (1 Hz). The majority of data were 1.4 MHz sine pulses, with a subset of asymmetric waveforms (1.4 + 2.8 MHz). Pressures were 0.25, 0.5, 1, 1.5, 2 and 3 MPa. Both native Definity and a 0.45 micron filtered version were assessed. ImageJ software was used to count and size bubbles. The cavitation signals were analyzed for frequency content within and between pulses.

Results/Discussion

A variety of behaviors were observed (Fig. 1). For all pulse types, pressures > ~1-2 MPa resulted in MBs far greater than the initial radii, accompanied by inertial cavitation (IC). Volume matched filtered Definity had a higher threshold but increased number density of MBs. Larger vessels had lower pressure thresholds (IC and optical), but reduced MB persistence (e.g. 100 vs <5 bursts for 15 vs 200 um) and were prone to radiation forces accumulating and clustering MBs at the distal side. For 0.1ms (1kHz) pulses, cycles of formation and dissipation of clusters were observed, whereas for 5ms (1 Hz), persistence of clusters for the duration of sonications was observed. Collectively these data indicate a complex relationship between cavitation, pulsing schemes, pressure and vessel sizes.

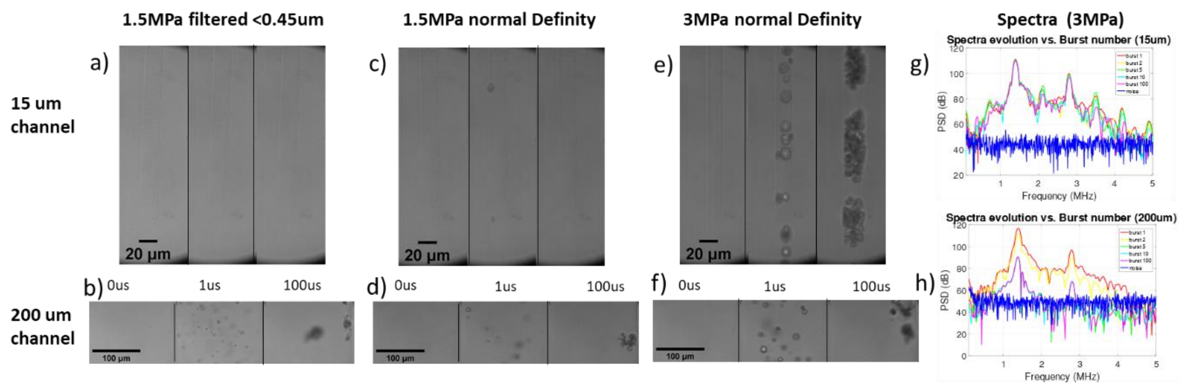

Fig.1. Example optical data for the 15 (a,c,e) and 200 (d,e,f) micron channels. Each figure is comprised of 3 selected frames: pre-exposure, 1 microsecond after burst arrived and 100 microseconds into the pulses. All data are for 0.1ms pulses at 1.4 MHz. Smaller channels require higher pressure threshold to initiate initial cavitation, at 1.5MPa a) no observable growing bubbles in 15um tubing whereas in b) 200um tubing the filtered <0.45um bubbles grow to large bubbles, c) Native Definity requires lower pressure threshold to initiate inertial cavitation compared to a) filtered. d) native Definity has fewer but larger cavitating bubbles compared to filtered. The expanded bubble size and numbers increased with pressure. With high pressure (3 MPa), bubbles will form clusters at the end of 100us. For the 200 um channel radiation forces direct MBs to the distal side. Broadband cavitation persists longer (100 bursts) in the smaller channel (g) than the larger (h) – < 5 bursts.