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Stability of micron-sized cavitation nuclei within a therapeutic ultrasound field

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Abstract: Microbubbles are micron-sized cavitation nuclei (diameter: 1-10 μm), which are routinely used in imaging and therapeutic ultrasound applications. Non-invasive and localized blood-brain barrier (BBB) opening using focused ultrasound (FUS) is an emerging therapeutic technique, which requires intravenous injection of pre-formed microbubbles. Although microbubble behavior during exposure to imaging sequences has been studied extensively, our understanding of microbubble stability within a therapeutic field is still incomplete. Here, we studied the temporal stability of microbubble cavitation activity during therapeutic FUS exposure in two timescales: the short time scale (i.e., μs of low-frequency ultrasound exposure) and the long time scale (i.e., days post-activation). Microbubbles flowing through a 4-mm vessel within a tissue-mimicking phantom (5% gelatin) were exposed to therapeutic pulses (f_c: 0.5 MHz, peak-negative pressure: 300 kPa, pulse length: 1 ms, pulse repetition frequency: 1 Hz, n=10). We recorded and analyzed the microbubble acoustic emissions with concentration-matched samples (10^7 microbubbles/ml) on day 0, 7, 14, and 21 after activation. Microbubbles had a concentration decay constant of 0.02 d^{-1} but maintained a stable size distribution for up to 3 weeks (< 10% variation). Temporal stability decreased while inertial cavitation increased over time both in vitro and in vivo, possibly due to changes in the lipid shell. BBB opening volume in mice (n = 3) measured through T1-weighted contrast-enhanced MRI was equal to 19.1 ± 7.1 mm^3, 21.8 ± 14 mm^3, 29.3 ± 2.5 mm^3, and 38 ± 20.1 mm^3 on day 0, 7, 14, and 21, respectively, showing no significant difference over time (p-value: 0.49). In conclusion, micron-sized cavitation nuclei maintain their capacity to produce similar therapeutic effects over a period of 3 weeks after activation, as long as the natural concentration decay is accounted for.