Background-Free Ultrasound Pulse-Inversion Imaging for High Sensitivity and Specificity Detection of Optically Activated Perfluorohexane Nanodroplets

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Background, Motivation and Objective

An emerging theranostic ultrasound (US) and photoacoustic (PA) agent, perfluorohexane nanodroplets (PFHnDs), has been actively investigated to overcome the size restriction of microbubbles and the one-time activation limitation of traditional perfluorocarbon droplets. Optically triggered PFHnDs can vaporize, providing US contrast, and then stochastically condense to liquid droplets. Their repeatable activation and random recondensation enable super-resolution imaging and contrast-enhanced ultrasound (CEUS). However, imaging sensitivity and specificity are critical for the detection of these small-sized contrast agents. To address this issue, we introduced the method of ultrafast planar pulse-inversion (PI) US imaging together with PFHnD echogenicity dynamics to improve the detection of optically activated PFHnDs.

Statement of Contribution/Methods

The PFHnDs consisted of a PFH core (56°C boiling point), a stabilizing lipid shell (DSPE-PEG2k and DSPC), and a dye (1064 nm peak absorption) to enable optical triggering. The PFHnDs were injected intravenously in healthy BALB/c mice and were allowed to circulate for 30 minutes prior to sacrifice and resection of the spleen for *ex vivo* imaging. The spleen was placed in a water bath, irradiated with 5 ns laser pulses (10 Hz PRF, 1064 nm), and imaged by a CL15-7 transducer. Ultrafast 0° planar PI imaging containing both fundamental and harmonic signals was used to acquire 40 frames at 8 kHz (Vantage 256) per laser pulse.

Results/Discussion

Conventional US imaging identified the anatomy of the spleen (Fig. 1A). Immediately after optical activation, PI imaging (Fig. 1B) showed PFHnD contrast enhancement compared to conventional US. Furthermore, PI imaging (Fig. 1C) and differential imaging using PI data (Fig. 1D) both revealed the exponential echogenicity decay of PFHnDs. By fitting such decay, a corresponding PFHnD map (Fig. 1E) was created to highlight particular pixels containing PFHnDs. We have demonstrated a new method leveraging PI imaging of PFHnD to increase sensitivity and taking advantage of PFHnD echogenicity dynamics for specificity improvement. This result has direct implications for background-free CEUS imaging of PFHnDs and can be further developed for molecular imaging with PFHnDs. Furthermore, PA signals generated upon laser activation may be incorporated to increase detection specificity.

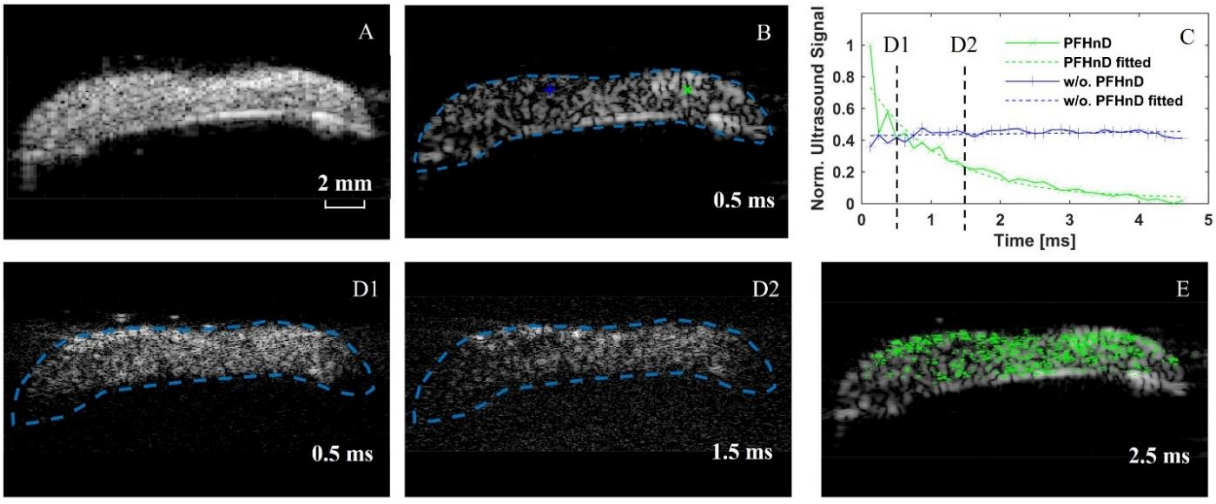

Fig. 1. A. Conventional ultrasound image for *ex vivo* mouse spleen; B. Pulse-inversion (PI) imaging after optical activation; C. PI signal dynamics for representative pixels with PFHnDs (exponential decay) vs. without PFHnDs (flat) in B; D. Differential imaging of PI imaging highlighting PFHnD echogenicity dynamics with corresponding time points in C; E. Background-free PFHnD imaging by filtering pixel-by-pixel signal dynamics as from C.