Microbubble Induced Indentation of Saturated Poroelastic Media: Implications for Fluid Transport in Fibrin Clots

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Background, Motivation and Objective

Ultrasound (US) stimulated microbubbles (MBs) can affect the local uptake of drugs in a variety of ways, the most investigated being microvascular permeabilization. When present adjacent to a boundary, microstreaming around MBs has also been observed as well as radiation forces on particle-like drug carriers. These factors may contribute to uptake beyond vascular walls or in MB mediated thrombolysis using enzymes. In addition to these behaviors we have reported that substantial indentations of fibrin clot boundaries can be induced by MBs experiencing radiation forces. Successive US pulses create a periodic forcing function at the boundary. In other fields, the indentation of the boundary of a fluid filled porous elastic medium is established to be associated with fluid transport within the medium. Here we conduct an initial investigation of this phenomenon in fibrin clots.

Statement of Contribution/Methods

Individual Definity™ MBs (n=36) were positioned via optical tweezers and stimulated by pulsed US (1-MHz, 1-ms, 15% duty cycle) in order to indent upon fibrin clots (2.97 ± 1.02 µm pore size). Digital image correlation was applied to the resulting high-speed microscopy footage (10 kFps) to quantify the induced spatiotemporal distribution of strain within clots. A preliminary finite element (FE) model has been developed using SIMULIA Abaqus FEA to analyze the pore pressure distribution induced solely by shallow indentation via translational motion of a MB. Fully-saturated fibrin clots were modeled via a continuum approach using axisymmetric poroelastic elements (CAX4P) while MBs were treated as impermeable rigid spherical surfaces.

Results/Discussion

Significant deformation, on the scale of pore size, is observed away from the boundaries as a result of single MB indentation. Furthermore, there are indications of an asymmetry in fibrin network recovery post-indentation characterized by a rapid primary relaxation followed by a prolonged secondary relaxation. Large strain is observed at depth within the fibrin network. FE modeling of indentation indicates a similar strain distribution. Furthermore, pore pressure elevation is observed to extend well beyond the clot boundary. The pore pressure (up to 2.03 kPa near the contact surface; 0.2 kPa at 5 µm depth) distribution coupled with the nonlinear stress recovery response of fibrin indicates fluid flow is occurring.

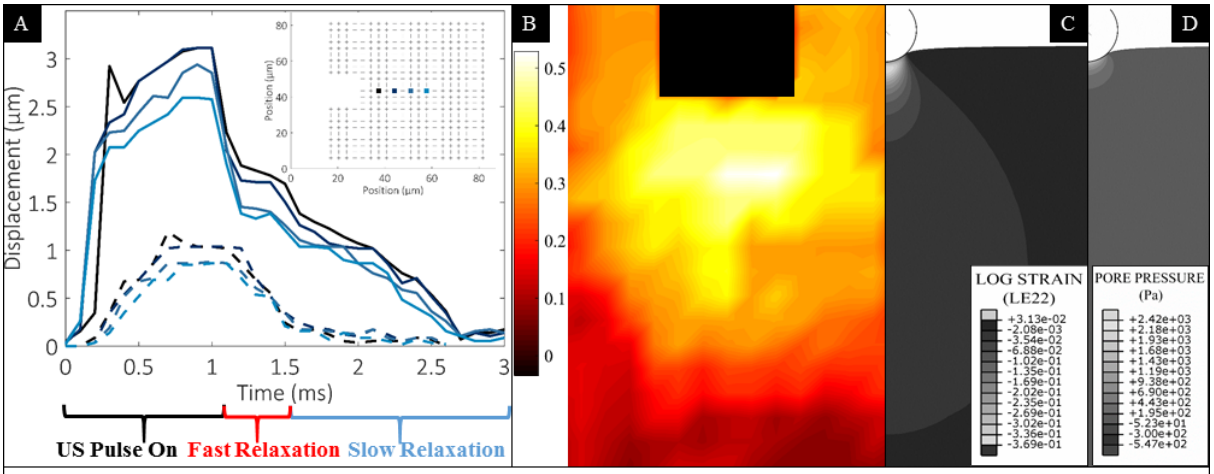

FIG. 1: (A) Displacement along axis of indentation for 3.92 µm MB (Dashed lines, 0.2 MPa sonication) and 3.09 µm diameter microbubble (Solid lines, 0.39 MPa). Colour indicates position. **(B)** Log strain along axis of indentation for 3.09 µm microbubble (0.2 MPa). **(C)** Log strain along axis of indentation and **(D)** pore pressure distribution for FE simulation of shallow (1 µm) indentation of 3.92 µm MB upon a poroelastic fibrin half-space.