Lowering of the Interstitial Fluid Pressure As a Result of Tissue Compliance Changes During High Intensity Focused Ultrasound Exposure: Insights From a Numerical Model

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Abstract

Interstitial fluid pressure (IFP) is elevated in tumors and decays sharply in the tumor margin (Figure 1) [1]. Owing to this elevated IFP, the interstitial fluid velocity (IFV) is negligible throughout the tumor but significant near the tumor margin (Figure 2). Any therapeutic strategy that can lower the IFP and the rate of fluid seepage from the tumor margin will likely improve drug convection within the tumor and decrease convection of drugs, growth factors, or metastatic cancer cells from the tumor margin. High intensity focused ultrasound (HIFU) operated in thermal mode has been shown to reduce IFP and improve the penetration of therapeutics in tumors [2]. In this study, a mathematical model able to predict the lowering of the IFP by HIFU in a tumor model has been developed. Use of COMSOL Multiphysics: The model describes the overall average profiles of the IFP and IFV, as well as the dilatation and displacement of the solid tissue matrix. Briefly, HIFU exposure induces a sudden increase of the tissue compliance that reduces IFP and increases the transport of fluid and macromolecules within the tumor. The model has been implemented using the Heat Transfer Module because of identical PDEs and the Equation-based interface. Some representative results are illustrated in the figures. Figure 1 shows the IFP relative to the vascular pressure for a spherical tumor of radius one in dimensionless units surrounded by normal tissue which has an IFP close to zero. The tumor IFV normalized with respect to the velocity at the outer edge of the tumor has been plotted in figure 2 for the same conditions as in figure 1. Figure 3 depicts the lowering of the IFP after a time t (typically of several minutes) for the same tumor model in the region exposed to HIFU. Typically, HIFU induces thermal lesions of approximately ellipsoid shape. The lowering of the IFV in the focal region by the same HIFU exposure is shown in figure 4. Efficient delivery of drugs in tumors still remains a big challenge in medicine. HIFU has been shown to improve drug delivery in tumors. The interstitium, which is the space between the tissue cells and blood capillaries composed primarily by a gel of polysaccharides within a framework of collagen fibers and containing connective tissue cells named fibroblasts, has a natural tendency to swell. At equilibrium, the swelling pressure of the gel is counteracted by the fibroblasts which exert a contractive force on the collagen-fiber network via collagen-binding integrins [3]. HIFU exposure may release or reduce the tension from the fibroblasts on to the collagen fibers thus reducing the IFP and facilitate drug delivery. As fluid accumulates in the interstitium, the IFP will rise again.

Reference

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2. Watson KD, Lai CY, Qin S, Kruse DE, Lin YC, Seo JW, Cardiff RD, Mahakian LM, Beegle J, Ingham ES, Curry FR, Reed RK, Ferrara KW, Ultrasound increases nanoparticle delivery by reducing intratumoral pressure and increasing transport in epithelial and epithelial-mesenchymal transition tumors. Cancer Res. 2012 ;72:1485-93.
3. Aukland K and Reed RK. Interstitial-lymphatics mechanisms in control of extracellular fluid. Physiol. Rev. 1993;73:1-78.

Figures used in the abstract

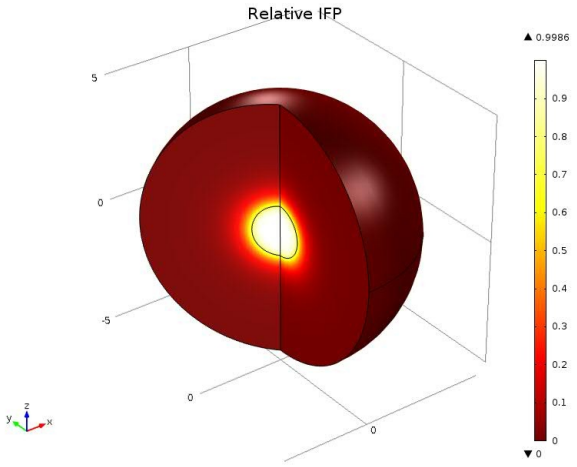

Figure 1

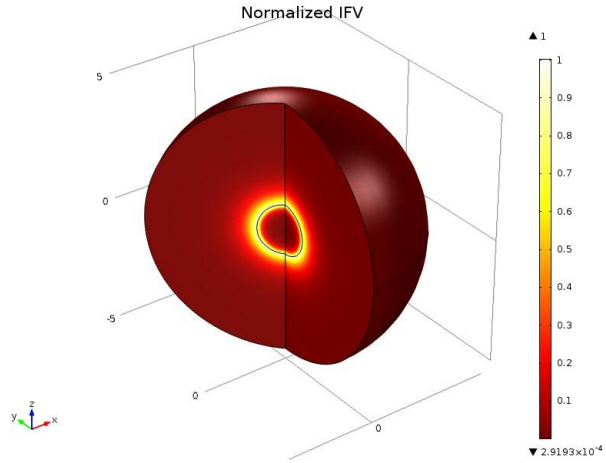

Figure 2

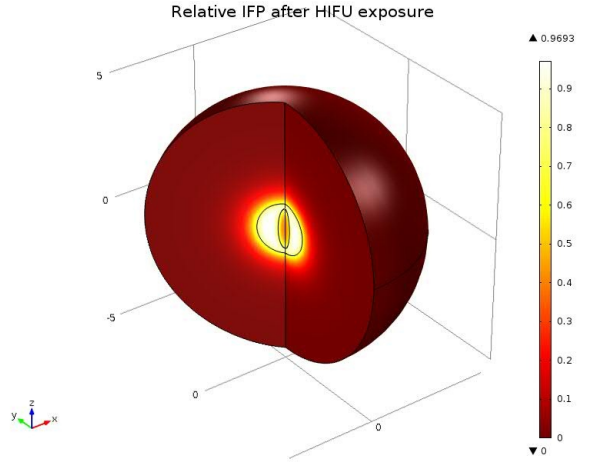

Figure 3

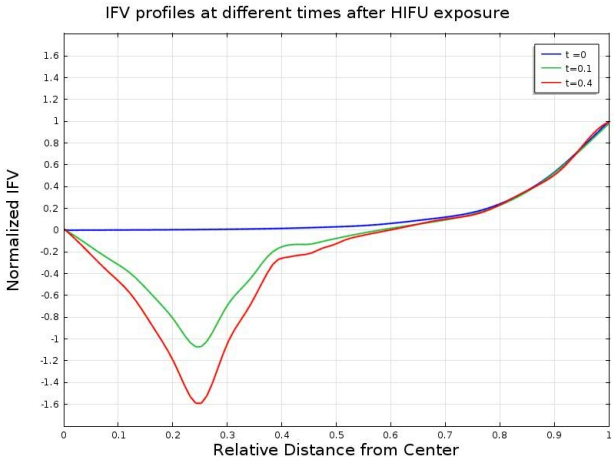
IFV profiles at different times after HIFU exposure
t =0
t=0.1
t=0.4
Normalized IFV
Relative Distance from Center
1.6
1.4
1.2
1
0.8
0.6
0.4
0.2
0
-0.2
-0.4
-0.6
-0.8
-1
-1.2
-1.4
-1.6
0
0.1
0.2
0.3
0.4
0.5
0.6
0.7
0.8
0.9
1

Figure 4