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ENHANCED NANOPARTICLE DEPOSITION IN PC3 TUMORS BY MILD WHOLE BODY HYPERTHERMIA – A THEORETICAL SIMULATION

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INTRODUCTION

Recent advancement in cancer treatment suggests targeting tumor pathophysiological micro-environment with nanoparticles. However, heterogeneous perfusion, increased vascular tortuosity, and high interstitial fluid pressure (IFP) impair their accumulation, and penetration inside tumors. Previous studies observed reductions in IFP and increases in blood perfusion rates in various tumors implanted in mice after the mice were subjected to whole body hyperthermia.[1-2] This would greatly enhance delivery of drug-carrying nanoparticles.

Nanoparticles-mediated delivery involves nanoparticle extravasation into the tumor tissue, its migration via interstitial transport, and cellular uptake. An integrated computational predictive model based on *in vivo* animal experiments on tumors would be useful to understand the interplay among different nanoparticles mediated heat and mass transport mechanisms. Theoretical simulations are powerful tools to evaluate contributions of individual factors such as perfusion, permeability, porosity, interstitial fluid pressure, and diffusion coefficient to the nanoparticle depositions in tumors.

In this study, we develop a comprehensive theoretical model to simulate nanoparticle extravasation from tumor capillary and nanoparticle diffusion and deposition in PC3 tumors after i.v. injections of a nanofluid. Experimental results of reduction of local IFPs are used to extract hydraulic conductivity of the porous PC3 tumor, and our previously developed nanoparticle trajectory model is used to quantify nanoparticle accumulation in tumors. The effects of tumor IFP and blood perfusion are evaluated to quantify how whole body hyperthermia facilitates nanoparticle delivery to PC3 tumors.

METHODS

The tumor is modeled as a porous medium (porosity ε=0.2) in a sphere of 10 mm in diameter. All the variables are considered as a 1-D in the radial direction in a spherical coordinate system. The fluid extravasation from the capillary is considered as a fluid source term expressed as the amount of fluid to the interstitial space per unit time per unit volume of the interstitial space, calculated by the Starling's law:

$$\boldsymbol{\phi_b}(\boldsymbol{r}) = \left(\frac{L_p S}{V}\right)[\boldsymbol{p_{blood}} - \boldsymbol{p} - \boldsymbol{\sigma_s}(\boldsymbol{\pi_{blood}} - \boldsymbol{\pi_i})] \quad (1)$$

This fluid source term is determined by the pressure difference $\boldsymbol{p_{blood}}$, IFP $\boldsymbol{p}$, the effective osmotic pressure difference (-460 Pa), the hydraulic permeability of the capillary wall in the tumor $\boldsymbol{L_p}$ ($2*10^{-11}$ m/Pa s), and the vasculature surface area per unit tissue volume $\boldsymbol{S/V}$ (20000 1/m). This source term is used in the mass conservation equation determining the interstitial velocity from the tumor center to tumor periphery, governed by the Darcy's law.

$$\nabla \cdot \left(\varepsilon \overrightarrow{V_f}\right) = \boldsymbol{\phi_b} \textbf{ and } \varepsilon \overrightarrow{V_f} = -\boldsymbol{K}\nabla \boldsymbol{p} \quad (2)$$

The general equation for molecular transport in tumor tissues is based on the transient conservation laws for chemical species in porous media, which is expressed as:

$$\frac{\partial \boldsymbol{C}}{\partial \boldsymbol{t}} = \boldsymbol{D_{eff}}\nabla^2 \boldsymbol{C} - \nabla \cdot \left(\overrightarrow{\boldsymbol{V_f}}\boldsymbol{C}\right) + \boldsymbol{\Phi_b} - \boldsymbol{k_f}\boldsymbol{C} \quad (3)$$

where $\boldsymbol{C}$ is the nanoparticle concentration based on tissue volume, $\boldsymbol{D_{eff}}$ ($9.57*10^{-12}$ m^2/s) is the effective diffusion coefficient, and $\boldsymbol{\Phi_b}$ is the nanoparticle source term representing the rate of nanoparticle transport across a capillary wall modeled by the Patlak equation, assuming that the diffusion is much smaller than advection:

$$\boldsymbol{\Phi_b} = \boldsymbol{\phi_b}(1 - \boldsymbol{\sigma_f})\boldsymbol{C_p} \quad (4)$$

where $\boldsymbol{\sigma_f}$ is the filtration reflection coefficient ($\boldsymbol{\sigma_f}$ =0), and $\boldsymbol{C_p}$ is the nanoparticle concentration in the plasma. In Eq. 3, $\boldsymbol{k_f}$ is the deposition rate coefficient of the particles on tumor cells. This term represents a nanoparticle sink to reduce the nanoparticle concentration in the interstitial fluid, therefore limiting the diffusion depth of the nanoparticles in tissue. $\boldsymbol{k_f}$ was determined via a particle trajectory model[3], and for the nanoparticles used in this study, it was derived as

$$\boldsymbol{k_f} = \boldsymbol{0.042}\ (\boldsymbol{s^{-1}}) \quad (5)$$

The accumulation rate of nanoparticles $M_{accumulation}(t)$ is the integration of the last term on the right side of Eq. 3 over the entire tumor as

$$M_{accumulation}(t) = \iiint_{tumor} k_f(r,t) * C(r,t)dV \qquad (6)$$

In a previous animal experimental study by our group,[1,4] we observed that the IFPs in PC3 tumors after 1-hour whole body hyperthermia were approximately half of that in the tumors without heating.[1] The observed IFP reductions were maintained for at least 24 hours. Three cases are simulated in this study: case A (the control) for a tumor without heating when p_{blood} = 2400 Pa, and the other two cases are simulated in for a tumor with whole body heating where p_{blood} is equal to either 2400 Pa (case B, assuming no blood perfusion rate increase) or 3000 Pa (case C, assuming an average 25% increase in the blood perfusion rate in the tumor during heating[4]). The hydraulic conductivity K will be adjusted so that the predicted tumoral IFP at the center agrees with our experimental measurement (control: 1600 Pa vs. heating: 800 P). All the properties are from literature.[5] The accumulation rates in the entire tumor will be compared to evaluate how the whole body hyperthermia affects nanoparticle delivery to PC3 tumors.

RESULTS

In our previous experiment, 0.2 ml of a gold nanofluid was injected into the tail vein of a mouse of 25 g.[1,4] The initial nanoparticle concentration can be calculated as 6.9 mol/m^3. In this study, we assume that C_p does not decay due to a very long half time of the clearance of the nanoparticles in the blood stream (~ hours).[6]

Figure 1 gives the pressure distribution in the radial direction in the interstitial fluid space. It clearly demonstrates higher IFPs at the tumor center than that at the periphery. For the tumor without heating (case A), the hydraulic conductivity K is adjusted to 1.74*10^{-12} (m^2/Pa s) so that the tumor center IFP is 1600 Pa. The hydraulic conductivity has to be 2.74 folds (case B) or 3.46 folds (case C) of the control (case A) to match the IFP reduction to 800 Pa at the tumor center with whole body hyperthermia. Note that the pressure profiles of case B and case C are almost the same. The resulted velocity profiles in the radial direction are given in Figure 2, with higher radial velocities in the tumor with heating.

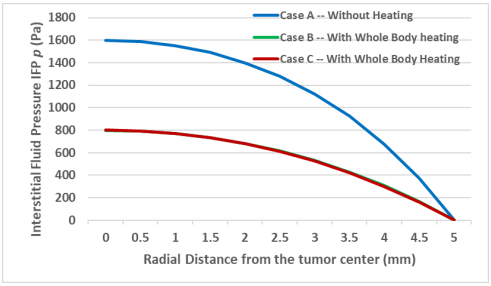

Figure 1: IFP distribution in the radial direction.

Initially, the nanoparticle concentration is zero in the tumor. It gradually increases due to nanoparticle extravasation from the capillaries. However, nanoparticle deposition on tumor cell surfaces and fluid advection result in a steady state concentration profile in the radial direction after approximately 300 seconds. The steady state nanoparticle concentration profiles in the radial direction are illustrated in Figure 3, with higher nanoparticle concentrations in the tumor periphery than that in the center. Figure 3 demonstrates the marked increase in the nanoparticle concentration in the tumor with whole body hyperthermia when IFP is smaller in case B. Contribution of local blood perfusion rate in the tumor to nanoparticle delivery can be seen from the concentration profile in case C, illustrating the highest nanoparticle concentrations in the tumor among the three cases.

Nanoparticle deposition in the tumor is directly proportional to the local nanoparticle concentration (Eq. 3) and the deposition rate coefficient k_f. Figure 4 illustrates increases in $M_{accumulation}$ with time. In steady state, $M_{accumulation}$ in the tumor without heating is 8.94*10^{-9} mol/s, in case B with heating the accumulation rate increases by 17% from the control. When the blood perfusion rate increase is considered in case C, it enhances the total accumulation rate in the tumor by 44% from that without heating.

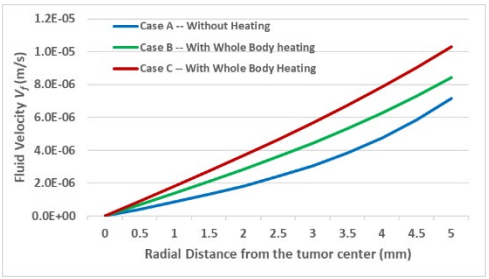

Figure 2: Fluid velocity V_f in the radial direction.

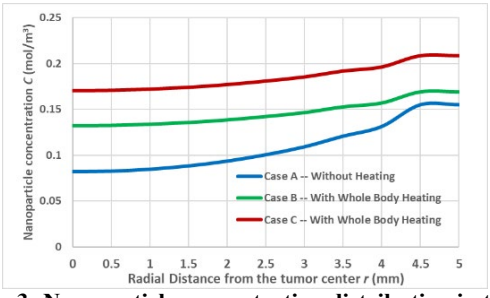

Figure 3: Nanoparticle concentration distribution in the tumor after steady state is established.

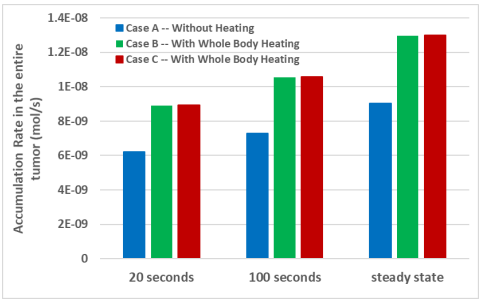

Figure 4: Rate of nanoparticle accumulation in the entire tumor at various time instants.

DISCUSSION

The current study evaluates the role of increased hydraulic conductivity in porous tumors on IFP reduction in tumors after whole body hyperthermia. The hydraulic conductivity K was adjusted to match experimentally measured IFPs in PC3 tumors. In the tumor with heating, it is evident with higher nanoparticle extravasation due to lower IFPs and/or higher p_{blood} induced by whole body hyperthermia, nanoparticle concentrations are elevated in the tumor, resulting in larger overall nanoparticle accumulation rates in the tumor than that without heating.

ACKNOWLEDGEMENTS

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