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NUMERICAL SIMULATION OF MAGNETIC NANOPARTICLES TARGETED AT AN ATHEROSCLEROTIC LESION IN THE LEFT CORONARY ARTERY OF PATIENT

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ABSTRACT

A numerical investigation simulating feasibility of magnetic drug targeting (MDT) at an atherosclerotic lesion of the left coronary artery of a patient using iron nano-particles coated with a therapeutic agent is reported. Progression of a plaque in the left coronary artery over a six month period was previously determined by intravascular ultrasound (IVUS). The site where the progression is active is located on the leeward side of the plaque. The proximal segment of the left coronary artery including the lesion was reconstructed by our 3D IVUS technique, and a Doppler measurement provided velocity waveforms in the lumen. These data are used to simulate blood flow employing computational fluid dynamics (CFD). Wall shear stress (WSS) and flow pathlines show that few nanoparticles would reach the active lesion region of the plaque. Therefore, MDT is considered as a possible effective therapy. Numerical investigations are performed to examine the feasibility for treatment by modeling hypothetical magnet fields, iron nano-particles, and coronary artery flow conditions. The magnetic field in the lesion segment produced by a permanent magnet located outside the lumen is calculated. The motion of the nano-particles in the segment is a combined result of the velocities produced by hemodynamic and magnetic forces. Various particles and magnets are investigated in the simulations. Two kinds of results are presented: the distribution of the magnetic force produced by the magnets, and the quantity of captured particles at the lesion during various time intervals (number of heart beats).

INTRODUCTION

MDT has been proposed as a potential efficient treatment of vascular diseases for decades [1]. Its principle is based on the fact that iron particles in fluids may be magnetized by an external magnetic field and will move along the field gradient. This movement may then be influenced and controlled by the magnetic field. In practice, an external magnetic field is produced in a particular region of interest to attract iron particles that, conveyed by the blood stream, carry chemotherapeutic agents bound to them to desired targets (e.g., cancer) for specific targeted delivery. Through this controlled congregating action, it may be possible to use such magnetized particles as cargo vehicles for a variety of anticancer agents (e.g., radionuclides, cancer-specific antibodies and stem cells).

On the other hand, coronary atherosclerosis and plaques are caused by an accumulation of lipids and subsequent inflammatory responses [2] such as expression of adhesion molecules (e.g., VCAM-1 and ICAM-1) that participate in monocyte adhesion. These pro-atherogenic processes are known to be enhanced in low WSS regions. The low WSS zones can be relatively isolated from the mainstream, and any therapeutic agents injected in the blood stream may find it difficult to enter the region of interest.

MDT has been postulated to be an effective method that can force iron nanoparticles to enter and reside in low WSS regions through use of an external magnetic field. In this study, we investigated the possibility and conditions of MDT in an active atherosclerotic region in the proximal left anterior descending (LAD) of a patient.

METHODS

Nano-particles γ -Fe_2O_3 coated with polyethylene glycol-phospholipid (PEG-phospholipid) were simulated in this investigation. The diameters of the iron core are 15nm, 50nm and 100nm. The coating is a thin layer to prevent agglomeration in the transporting fluid (blood). After coating, the total diameters of the particles

increase 20 nm. The simulated magnetic field is produced by a permanent magnet (NdFeB, Grade N52, Residual Flux Density: 14800 Gauss, K&J Mahnetics, Inc.). The 3D IVUS reconstruction of the lumen of left coronary artery and blood flow conditions in the lumen have been reported previously [3].

RESULTS AND DISCUSSION

In order to estimate the effect of magnetically influencing the paths of nano-particles, the flow field in the lesion region is computed with and without magnets. Because of the small size of the nano-particles, their motion will follow that of the fluid itself. As this is a pulsatile flow, 313 nano-particles uniformly distributed over the inlet plane are released and repeated this releasing 48 times during each cardiac cycle. This provides particle trajectories for a total of 313×48 nano-particles with each heartbeat. When nano-particles approach the artery wall within a defined neighborhood of the active region of the lesion, it is assumed that they attach. From these data it is possible to estimate the relative number of particles that would deliver a drug to the desired site as a function of particle size and number of heartbeats.

Figure 1 illustrates simulated nano-particle motion during one cardiac when a specified permanent magnet is located close to the region to create field gradients. It can be seen that the effect is to attract more nano-particles to the region of interest than would occur in the absence of the magnet field.

The effect of nano-particle size is illustrated in Figure 2, where the number of particles entering a defined region of interest is presented as a function of the number of heartbeats. The strong effect of particle size is clearly seen. Because the force arising from the magnetic field gradient is a function of particle volume whereas the viscous drag force is a function of particle size, it is desirable to use particles that are larger. There is additionally a nonlinear effect due to interactions with the fluid velocity field.

Targeting atherosclerotic plaques with intra-arterial administration of MDT nano-particles presents different challenges than targeting cancer tumors which are often susceptible to delivery via the microcirculation. Arterial pulsatile flow present strong convective effects that must be overcome with very strong magnetic field gradients. The present study illustrates some of these challenges and emphasizes the need for hemodynamic modeling if MDT is to be effective.

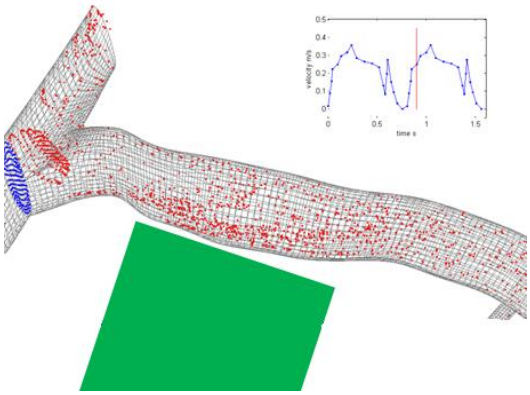

Figure 1. The movements of nano-particles during one cardiac cycle that are released from the left main coronary artery (LM) when a permanent magnet (green) is close to the lesion region.

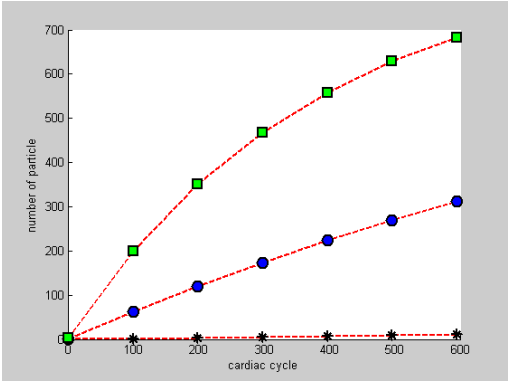

Figure 2. The relationship between the number of particles that enter and reside in the lesion region and cardiac cycles. Three kind particles with 15, 50 and 100nm diameters are shown from bottom to top.

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