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Drug delivery in catheterized arterial blood flow with atherosclerosis

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\textbf{A B S T R A C T}

We study the problem of drug delivery in a catheterized artery in the presence of atherosclerosis. The problem is modeled in the context of a two-phase flow system which consists of red blood cells and blood plasma. The coupled differential equations for fluid (plasma) and particles (red cells) are solved for the relevant quantities in the reasonable limits. The drug delivery problem is modeled with a partial differential equation that is developed in terms of the drug concentration, blood plasma velocity, hematocrit value and the diffusion coefficient of the drug/fluid. A conservative-implicit finite difference scheme is developed in order to numerically solve the drug concentration model with an atherosclerosis region. We find that the evolution of the drug concentration varies in magnitude depending on the roles played by the convection and diffusion effects. For the cases where the diffusion coefficient is not too small, then convection effect is not strong enough and drug was delivered mostly in the central part of the blood flow region and could not reach effectively the atherosclerosis zone. However, for sufficiently small values of the diffusion coefficient, the convective effect dominates over the diffusion effect and the drug was delivered effectively over the blood flow region and on the atherosclerosis zone.

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1. Introduction

Diseases in the blood arteries and in the heart can be major causes of death worldwide. A main cause for such diseases is the formation of atherosclerosis that sometimes is referred to as stenosis, which can be the result of fatty materials in the artery. Such accumulation of fatty elements in the artery can reduce the area of the artery’s cross-section making it hard for the blood to pass through the artery resulting insufficient blood supply to the heart [1]. There have been relevant studies of catheterized arterial blood flow [2–4]. The use of catheter is important in modern medicine for diagnosis and treatment aspects of some illnesses. In particular, to reduce the effect of atherosclerosis, a catheter with a tiny balloon attached at the end is placed in the artery and the balloon is inflated to fracture the accumulated fatty section and to widen the narrow part in the artery.

As we explained in the previous paragraph, the problem of damaged and block arteries is a real life and serious illness that affects great number of people worldwide. We consider the problem due to its importance and impact in society and because more work needs to be done to increase the understanding of such problem. We are interested in the problem of

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drug delivery in the catheterized arterial blood flow, and we use experimentally generated data that was provided by [2] for the cross-sectional area of the artery section that contained mild atherosclerosis. The same authors in [2] also observed that the perimeter of such cross sectional area of the artery is approximated well by a circle. We made use of such data to determine the radial distance of the corresponding inside surface of the artery at each axial location along the artery direction in the section that contained the atherosclerosis zone. Fig. 1 shows the representation of radial distance of the inside surface of the artery in a section in the artery that contained a damaged region (atherosclerosis). We should also state explicitly that such experimental data was actually collected when these authors in [2] examined a cadaver (death body).

Some previous work included those by [5–9] considered two-phase flow model which is based on the continuum approach [10], where plasma and particles (red cells) are considered as two coexisting phases that span the flow domain in the artery. In [5] it was observed that for arterial blood flow, if inside artery’s diameter is less than 2.4 mm, then the presence of red cells becomes significant, and the blood flow in such arteries should be represented by a macroscopic two-phase flow model [9]. Riahi’s work [9] was related to the understanding of the arterial blood flow represented by a two-phase flow model for the problem of a catheterized artery. In his work several flow quantities were understood and computed in terms of the damaged arterial region. For the purposes of this paper, we rely on the previous formulation in [9]. Both the pressure gradient $\frac{dP}{dz}$, and blood plasma velocity $U_f$ are quantities that we use to set up and study the problem of drug delivery in a damaged artery in the presence of a catheter. For more details on these quantities we refer the reader to [9].

The present problem considers drug delivery in a catheterized arterial blood flow, where the two-phase blood flow model is taken into account since, in fact, the inside diameter of artery based on our consideration of the experimental data is less than 2.4 mm [2]. The problem of drug transport to a patient whose artery is damaged due to the presence of atherosclerosis is important for understanding how such drug can be distributed and how its amount varies along the artery and, in particular, how the presence of atherosclerosis can affect the amount of drug that needs to reach its target for the patient’s particular illness. We find number of interesting results. In particular, we find that the drug transport depends notably on the drug diffusivity, and smaller values of the diffusivity coefficient lead to faster drug delivery, provided initial injected drug value is not too small.

2. Mathematical formulation

We consider axisymmetric flow of blood in a catheterized artery in the form of a circular cylindrical annulus tube in the presence of an atherosclerosis in part of the tube that we described before in Section 1. The simplified non-dimensional form of the two-phase flow modeling system that is an extension of the governing system for two-phase flow [11–13] includes equation and the boundary condition for the drug concentration within such flow system. Other studies related to the study of blood flow in the presence of a catheter are given in [14–19]. For the details of the two-phase flow system and its derivation, the reader is referred to [9]. We consider a Taylor-series expansion in powers of small ratio $\gamma = \delta/R_0 \ll 1$ for the dependent variables and keep only leading terms in the resulting two-phase flow system. Here $R_0$ is the dimensional radius of the artery outside the stenosis zone and $\delta$ is the maximum height of the stenosis, which is considered to be mild [2], into the lumen. This is in agreement with the experimentally generated data [2] that indicates that the value of $\delta$ is small ($\delta \ll 1$).
Fig. 2. Pressure gradient for given catheter size $r_1 = 0.2$ and different Hematocrit values.

The simplified modeling system for the present study is, thus, given by

$$(1 - C) \frac{dP}{dz} = \left[ \frac{1}{1 - mC} \right] \left[ \frac{1}{r} \frac{\partial}{\partial r} \left( r \frac{\partial U_f}{\partial r} \right) \right] + CS \beta^2 (U_p - U_f),$$  \hspace{1cm} \text{(1)}

$$\frac{dP}{dz} = S \beta^2 (U_f - U_p), \quad S := \frac{4 + 3(8C - 3C^2)^{1/2} + 3C}{(2 - 3C)^2},$$  \hspace{1cm} \text{(2)}

$$Q = 2\pi \int r \left[ (1 - C)U_f + CU_p \right] dr,$$  \hspace{1cm} \text{(3)}

$$U_f \frac{\partial G}{\partial z} = D \left[ \frac{1}{r} \frac{\partial}{\partial r} \left( r \frac{\partial G}{\partial r} \right) \right],$$  \hspace{1cm} \text{(4)}

$$U_f = U_p = 0 \text{ on } r = r_1 \text{ and on } r = R(z), \quad G = G_0 \text{ at } z = 0.$$  \hspace{1cm} \text{(5)}

The above system is supplemented with suitable boundary conditions. In this paper we explore the case of Dirichlet boundary conditions (zero boundary conditions) to model a situation in which the drug loses effectiveness far downstream. Here $r_1$ is radius of the catheter, $r$ is the radial variable of the cylindrical coordinate system with origin at $z = 0$ that the investigated artery section begins, $z$ is the axial variable on $z$-axis along the catheter, $P$ is the blood pressure, $U_f$ is the axial velocity of the fluid (plasma), $U_p$ is the axial velocity of the particles (red cells), $G$ is the drug delivered by the blood flow, $G_0$ is the value of the drug at $z = 0$, $C$ is the volume fraction density of the red cells in the blood, which is red cells percentage in the blood and is referred to as hematocrit, $\beta = \delta/0.004$, $m$ is a given function of $C$ [9] and $Q$ is a prescribed volume flow rate of the blood flow in the annulus. The first two equations (1)–(2) are basically the force balances in the axial momentum equations between the pressure gradient force and viscous force taking into account the drag force that act by one phase flow on another phase flow and a unidirectional flow assumption [20], where the axial flow velocity component dominates over the radial velocity component. In addition, Eqs. (3) were already described and Eq. (4) is basically a balance between convection and conduction.

3. Results

The analytical solutions for $P$, $U_f$ and $U_p$ are obtained easily [9] by first finding $U_f$ and $U_p$ from Eqs. (1)–(2) in terms of $\frac{dP}{dz}$, and then using these in (3) for a prescribed value of $Q$ such as $Q = 1$ and integrating with respect to the radial variable. This leads to the expression for $\frac{dP}{dz}$. Using this expression in (1)–(2) and carrying out integration in $r$ and using the boundary conditions (5), the expressions for plasma velocity and red cell velocity are found. Based on [9] but in contrast to their computation of pressure gradient, here we compute the pressure gradient force, which is the force that drives the blood flow from smaller values of the axial variable $z$ to larger values of $z$ as seen in Fig. 2. Fig. 2 results consider different hematocrit C values accounting for patients with low ($C = 0.1$), nearly normal ($C = 0.5$) and somewhat high blood pressure ($C = 0.6$). Fig. 3 represents the blood pressure of patients for different levels of hematocrit values. Here magnitude $|P|$ of the pressure is the fluid pressure due to a zero reference pressure taken after performing numerical integration for $\frac{dP}{dz}$.
The velocity of plasma quantity $U_f$ was computed as described above. Fig. 4 represents the blood plasma velocity for different cases of catheter radius and given radial value vs z-axial variable. It can be seen that when a catheter of bigger size is used then the blood plasma velocity increases near the damaged region in the artery. This is consistent with the modeling focus of the present study (blood as an incompressible fluid) and with the usual understanding of fluid motion as flow goes from a large to a narrow pipe.

The drug delivery problem is formulated in terms of the partial differential equation (4) that accounts for the drug concentration $G$, blood plasma velocity $U_f$, hematocrit value $C$ and diffusion coefficient $D$. Using (4) with inlet and outlet boundary conditions corresponding to the amount of drug given or administered to a patient, the problem of how a drug concentration travels through a damaged artery is obtained. To overcome the challenges imposed by numerical instability, a finite difference formulation that is conservative in $r$-radial variable and implicit in $z$-axial variable is developed. This gives an unconditionally stable scheme (6) with no restrictions in the values for $\Delta r$ and $\Delta z$.

$$U_f(z_i, r_j) \frac{G_{i+1,j} - G_{i,j}}{\Delta z} = \frac{D}{r_j} \left[ \frac{r_{j+\frac{1}{2}} - r_{j-\frac{1}{2}}}{\Delta r} G_{i+1,j+1} - G_{i+1,j} - \frac{G_{i+1,j} - G_{i+1,j-1}}{\Delta r} \right] \frac{1}{\Delta r}.$$

The range of the variables is given by $r_1 \leq r_j \leq R(z)$ and $0 \leq z_i \leq 2$. Here $\Delta z = 2/N_z$ and $\Delta r = \max(R(z))/N_r$ where $N_z = 200$ and $N_r = 100$ are the number of subintervals in the z-axial $(z_0, z_1, \ldots, z_{N_z})$ and r-radial $(r_0, r_1, \ldots, r_{N_r})$. 

Fig. 3. Blood pressure for given catheter size $r_1 = 0.2$ and different Hematocrit values.

Fig. 4. Velocity of blood plasma vs z-axial variable for different catheter sizes and given radial value.
direction respectively. Boundary conditions at the catheter and damaged zone are given by $G(z, r = R(z)) = G(z, r = r_1) = 0$. Inlet boundary condition $G(z = 0, r) = G_0$.

We solve the for the drug concentration problem (6) under several cases. First we explore the impact of the diffusion coefficient. Then we determine other interesting cases including high and low blood pressure patients. We find the diffusion coefficient plays a role in the way that the drug is absorbed around the damaged region. For higher values of diffusion parameter, the drug seems to reach out or spread out better past the atherosclerosis region on the other hand lower values of $D$ do not allow for drug concentration to spread out that well past damaged region but concentration is carried at higher values.

4. Discussion

The results for the pressure gradient force versus axial variable and for different values of the hematocrit (Fig. 2) indicates that such force increases with increasing the hematocrit, which indicates that such blood pressure force intensifies with increasing the red cells that facilitate higher rate of change of blood pressure. The results shown in Fig. 2 also indicate that the blood pressure gradient force intensifies notably in the atherosclerosis zone, which is the result of the fact that the artery narrows down in the damaged zone and, thus, higher pressure driven force is required to drive the blood flow.

The results for the pressure versus axial variable and for different values of the hematocrit are given in Fig. 3, which shows magnitude of pressure, which is referred here as blood pressure, increases with the hematocrit, which is also confirmed medically since higher hematocrit corresponds to higher number of red cells in the patient, which usually indicates higher blood pressure in medicine. It is also seen from this figure that $P < 0$, so that $P$ decreases with increasing the axial variable, and it agrees with our earlier explanation that $\left(- \frac{dP}{dz}\right)$ is the force that drives the blood flow from smaller value of axial location to larger value of axial location.

The results for the velocity of the blood plasma versus axial variable and for different values of the catheter radius are given in Fig. 4 for given values of $r$ and $C$. As can be seen from this figure, the plasma velocity in the axial direction is positive since blood flow is driven from left to right by the pressure gradient force. The plasma velocity is constant outside the damaged zone, but it is variable with significant higher values inside the atherosclerosis regime, which is reasonable due to significant increase in the pressure driven force there. The velocity of the blood plasma also increases with the catheter radius since higher value of such radius reduces the cross-sectional area of the blood flow in the annulus region make the velocity higher due to the volume flow rate that is maintained at a constant value. We also calculated the plasma velocity for different values of the hematocrit and found that the plasma velocity increases very slightly with increasing the hematocrit. We also calculated the red cells velocity and found qualitatively similar results as those explained for the plasma velocity.

Figs. 5a and 5b present drug transport in the blood flow region for diffusion coefficient $D = 0.01$ and for given values of the other parameters. It can be seen from these figures that drug is delivered mostly in the central part of the blood flow region after a short distance that it is initiated. The regions close to the catheter surface and close to the artery surface and especially near the stenosis zone have very little amount of drug delivered. This is due mostly to the fact that diffusion is more significant than the flow velocity, and this results in a less significant role by the flow velocity to transport the drug.

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Fig. 5. Numerical solution to (1) with the parameters $G_0 = 0.5, r_1 = 0.1, C = .5$ and $D = .01$. Left: (a) vertical axis is for the variable $r$ and lateral axis is for $z$-axis values. Red color represents 0.5 of drug concentration and blue represents 0 remain of drug concentration; Right: (b) 3-dimensional plot for the evolution of the drug concentration. Vertical axis represents the amount of drug and the evolution is captured as drug flows along the on $z$-axial direction. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)
Figs. 6a and 6b present drug transport in the blood flow region for smaller value of the diffusion coefficient \(D = 0.001\), and the values of the other parameters are same as those for Figs. 5a and 5b. It can be seen from Figs. 6a and 6b that drug now is delivered in more places in the blood flow region, and so flow velocity has more active role to deliver drug to more parts of the blood flow region mostly in the central part of blood flow region.

Figs. 7a and 7b present drug transport in the blood flow region for much smaller value of the diffusion coefficient \(D = 0.0001\), and the values of the other parameters are the same as those for Figs. 5a and 5b. It can be seen from Figs. 7a and 7b that the region before the stenosis and as well as the stenosis zone are fully covered by drug, which is delivered more fully from the catheter surface to about 70 percent of the blood flow region including good part of the stenosis zone. These results indicate that convection now dominates over diffusion and have more significant role to deliver drug.

However, it can be seen from all the three cases that were shown in Figs. 5–7 that the region beyond the stenosis and close to the artery surface drug is not delivered, which indicate possible improvement in the present modeling system may be needed such as, for example, take into account convective terms due to the radial velocity in the drug concentration equation, take into account the elastic aspects of the artery, etc., which will be left for future investigations by the present authors.

5. Conclusions

We conducted an investigation for the drug concentration evolution in the catheterized arterial blood flow system and on an atherosclerosis damaged region part of such system. We first calculated the blood flow velocity, pressure and pressure gradient force for different values of the parameters. We then computed numerically the solution to the drug
concentration and its delivery in the investigated blood flow system. We found that for the cases where the diffusion coefficient for the drug concentration equation is not too small, then convection effect is not strong and the drug was delivered mostly in the central part of the blood flow region and could not reach effectively the atherosclerosis zone. However, for sufficiently small diffusion coefficient, the convective effect dominated over the diffusion effect, and the drug was delivered effectively over region before and on the stenosis zone.

The results of the present investigation point at usefulness of drugs that have adequate diffusion properties for the treatment of the patients with atherosclerosis illness and or complication. This may indicate ways that could be used by the pharmaceutical industries and drug production companies (bio-technology industries) to make diffusivity of an effective drug as small as possible.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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