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Investigation of the Effects of Pulsatile Blood Flow on Arterial Drug Uptake for Drug-eluting Coronary Stents

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Abstract

Blood flow characteristics have a considerable impact on drug uptake from drug-eluting stents. Therefore, this study investigated the effect of pulsatile blood flow induced by heartbeats on hemodynamics and drug transfer from drug-eluting stents using computational fluid dynamics. Previous studies have investigated the impact of this feature on renal vessels; However, this issue has not been investigated in the case of coronary arteries. For this purpose, the blood flow and drug transport in the lumen and tissue of a stented right coronary artery have been simulated unsteady and non-Newtonian. To analyze the impact of pulsatile flow waveform, three different pulsatile flows including a physiological waveform in the human right coronary artery, a general physiological waveform in the arteries of the human body, and a simple sinusoidal waveform were imposed. Furthermore, the results were compared for three Womersley and two Reynolds numbers. The results indicate that the flow waveforms and their frequency (Womersley number) have a negligible effect on hemodynamics and drug transfer. However, the impact of Reynolds number is significant. The results also show that the impact of blood viscosity on hemodynamics and drug transfer is negligible. Therefore, assuming blood as a Newtonian fluid in these simulations could be accurate.

Keywords: Pulsatile Blood Flow, Drug-eluting Stent, Drug Delivery, Hemodynamics, Computational Fluid Dynamics.

1. Introduction

The advent of drug-eluting stents (DES) has revolutionized the treatment of coronary artery disease, significantly reducing the rates of restenosis following percutaneous coronary interventions (PCI). DES functions by providing mechanical support to the artery while simultaneously delivering pharmacological agents that inhibit neointimal hyperplasia, thereby preventing the re-narrowing of the vessel lumen [1]. Despite their widespread use and clinical success, the intricate interplay between hemodynamic forces and drug delivery mechanisms within these devices remains an area of active research [2].

Blood flow characteristics are critical in determining the efficacy of drug transfer from stents to surrounding tissues [3]. Hemodynamics, influenced by factors such as blood flow pulsatility [4] and rheology [5] can affect both the distribution and absorption of therapeutic agents. Previous investigations have primarily focused on renal vasculature, leaving a gap in our understanding of how these dynamics operate within coronary arteries. The unique pulsatile nature of blood flow in the cardiac cycle introduces complexities that warrant detailed exploration, particularly in relation to the performance of DES.

This study aims to fill this knowledge gap by employing computational fluid dynamics (CFD) to simulate blood flow and drug transport in a stented right coronary artery under various pulsatile flow conditions. By analyzing three distinct pulsatile waveforms—representative of physiological conditions in both coronary and systemic arteries—as well as varying Reynolds and Womersley numbers, we seek to elucidate the effects of these parameters on hemodynamics and drug transfer efficiency. Our findings will contribute to a deeper understanding of how blood flow characteristics influence DES performance, potentially guiding future design improvements and therapeutic strategies.

2. Methodology

The geometry under investigation comprises an axisymmetric two-dimensional model of a drug-eluting stent strut positioned against the wall of the right coronary artery. This study assumes that the blood flow within the lumen is characterized as laminar, incompressible, and non-Newtonian, adhering to the principles outlined in the continuity and momentum conservation equations:

$$\nabla . v_l = 0 \quad (1)$$

$$\rho\left[\frac{\partial v_l}{\partial t} + v_l.\nabla v_l\right] = -\nabla P + \nabla.\tau \quad (2)$$

The shear-thinning behavior of blood is modeled using Carreau's non-Newtonian model. The tissue of the arterial wall is considered a homogeneous porous material in which the interstitial transfer of blood fluid adheres to the principles of continuity and momentum conservation, incorporating the Darcy permeability correction factor:

$$\nabla.v_t = 0 \quad (3)$$

$$\rho\left[\frac{\partial v_t}{\partial t} + v_t.\nabla v_t\right] = -\nabla P + \nabla.\tau - \frac{\mu}{K}v_t \quad (4)$$

Unsteady mass transfer within the lumen is governed by the advection-diffusion equation, whereas mass transfer in the tissue is described by the diffusion equation:

$$\frac{\partial C}{\partial t} + v_l\,.\nabla \mathrm{C} = D_l\,\nabla^2 C \quad (5)$$

$$\frac{\partial C}{\partial t} = D_t\,\nabla^2 C \quad (6)$$

The finite volume solver ANSYS Fluent 2021 R2 (ANSYS Inc.) was used to solve mass and momentum transport equations. A semi-implicit (SIMPLEC) method coupled the pressure and velocity using a second-order central differencing scheme to discretize the pressure and momentum variables spatially. The number of elements and the time step size, after assessing mesh and time step independence, were determined to be 65,925 and 0.02 seconds, respectively. The total solution time is considered to be 60 seconds, equivalent to 75 heart cycles.

To analyze the impact of pulsatile flow waveform, three different pulsatile flows including a physiological waveform in the human right coronary artery [6], a general physiological waveform in the arteries of the human body [7], and a simple sinusoidal waveform [8] were imposed. Then the results of these three time-dependent profiles have been compared with the results of a parabolic flow profile ($Q=Q_{mean}$). Furthermore, the results were compared for three Womersley numbers and two Reynolds numbers.

3. Results and Discussion

To assess the accuracy of the current simulation, a comparative simulation was conducted based on the methodology established by O'Brien et al. [4] for the renal artery. The outputs from this simulation were evaluated against the results presented in this article. The findings obtained are consistent with those reported in this article. Consequently, it can be concluded that the simulation performed is both accurate and reliable.

The contour of streamlines and the distribution of drug concentration for the first pulsatile profile at the end of the simulation are depicted in Figure 1. This figure illustrates that separation occurs in both the proximal (upstream) and distal (downstream) regions of the strut, resulting in the formation of two circulation zones. These zones create drug pools with the highest concentrations of drug within the lumen, which aligns with findings from previous studies on drug-eluting stents [3–5].

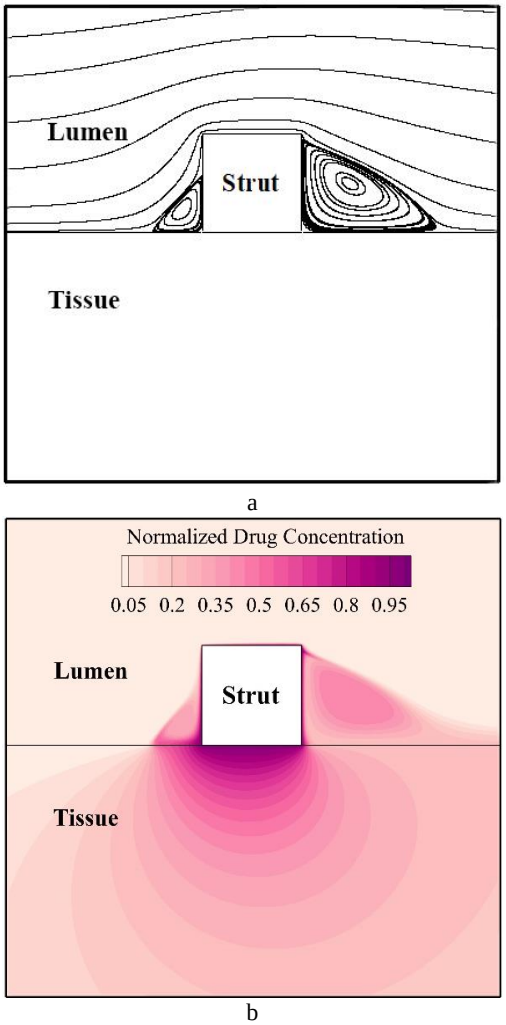

Figure 1. Contours of (a) Streamlines and (b) normalized drug concentration for the first pulsatile profile at the end of the simulation time. The direction of blood flow is from left to right.

Drug uptake in arterial tissue occurs through two primary mechanisms: diffusion and convection. The diffusion mechanism takes place at the interface where the strut contacts the arterial tissue. Due to the concentration gradient of the drug on the strut body and its interaction with the vessel wall, an imbalance in drug concentration facilitates the transfer of drug mass via diffusion. Conversely, the convection mechanism facilitates drug transfer through blood flow from the three non-contact sides of the strut. Research by Kolachalama et al. [3] indicates that approximately 40% of drug absorption from drug-eluting stents occurs via convection. Consequently, it is anticipated that hemodynamic characteristics, such as pulsatility,

significantly influence drug delivery simulations for stents. Additionally, previous studies have demonstrated that a drug pool formed in the proximal circulation area substantially enhances drug absorption into arterial tissue. In contrast, in distal areas, blood flow tends to wash away the drug [5]. This phenomenon is illustrated in Figure 1-b. Therefore, it can be concluded that an increase in the length of the proximal circulation area correlates with enhanced drug absorption in arterial tissue; however, an increase in the length of the distal area results in reduced absorption.

To investigate the impact of flow waveform profiles on drug uptake, the area-weighted average concentration (AWAC) of the drug over time for three pulsatile profiles, as well as a parabolic profile, is presented in Figure 2.

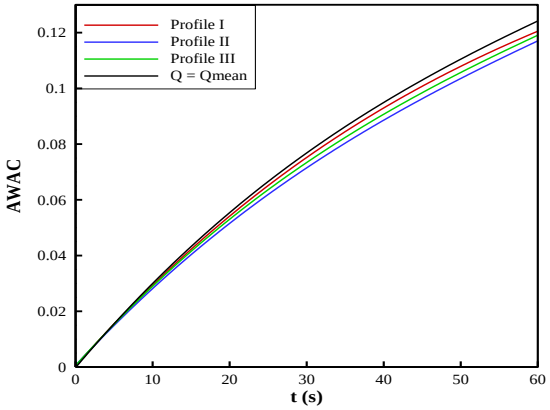

Figure 2. Drug AWAC during the simulation time for different inlet profiles.

It is evident that the AWAC of the drug is zero at the beginning and increases over time. Among the different simulated profiles, the third profile exhibits the highest AWAC value over time, followed by the first and second profiles. Additionally, the constant flow profile consistently results in the highest drug concentration absorption at all time points. Notably, these differences are approximately 4%. Therefore, it can be concluded that in simulating drug transfer from a drug-eluting stent, the pulsatility of blood flow can be disregarded with good accuracy, allowing for a consideration of parabolic flow with a constant flow rate.

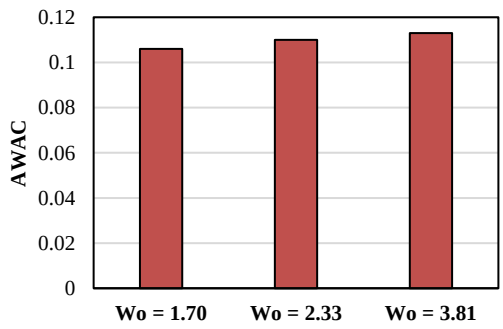

Figure 3. Drug AWAC for different Womersley numbers.

Regarding the impact of the Womersley number as a representative of flow frequency, the AWAC for three different Womersley numbers is presented in Figure 3. The results indicate that variations in the Womersley number have a negligible effect on drug uptake, with a difference of only 3%. In contrast, as the Reynolds number changes, drug uptake is significantly influenced. When the Reynolds number is reduced to one-third of its original value, the AWAC increases by 15% (see Table 1).

Table 1. AWAC and recirculation length for different Re numbers.

Re	AWAC	Recirculation Length (mm)	
		Proximal	Distal
318	0.11	0.200	0.042
106	0.13	0.116	0.061

On the other hand, the results indicated that modeling blood as a non-Newtonian fluid using the Carreau model resulted in a 3% increase in drug uptake. Therefore, consistent with previous studies on renal arteries, the effect of blood viscosity in unsteady simulations of drug-eluting stents is negligible. Thus, it is reasonable to assume Newtonian blood in such simulations with a high degree of accuracy.

4. Conclusions

In this study, the effects of pulsatile and non-Newtonian blood flow on hemodynamic parameters and drug delivery from drug-eluting stents were investigated using computational fluid dynamics simulations. To model blood flow in the stented coronary artery, a pulsatile flow boundary condition was applied at the inlet. Additionally, the impact of three different pulsatile flow profiles and variations in the dimensionless Womersley and Reynolds numbers were examined. Ultimately, the results were compared under two conditions: assuming blood as a Newtonian and non-Newtonian fluid.

The findings indicated that the shape of the pulsatile waveform had a negligible effect on hemodynamic parameters and drug delivery. Furthermore, it was observed that at a constant frequency, profiles with moderate amplitude resulted in lower drug uptake in arterial tissue. The steady parabolic inlet profile produced the highest average drug concentration in the arterial tissue compared to all pulsatile profiles; however, this difference was minimal. Therefore, in simulations of drug transfer from drug-eluting stents, it is reasonable to neglect the pulsatile nature of blood flow.

Regarding the impact of blood pulse frequency, the results demonstrated that variations in the Womersley number significantly influenced hemodynamic parameters, including flow patterns and streamlines; however, its effect on drug delivery was negligible. Evaluating the influence of varying amplitudes of pulsatile profiles through Reynolds number analysis revealed that this characteristic produced the most significant changes in outcomes.

The examination of blood viscosity types under both

Newtonian and non-Newtonian conditions showed that viscosity has a relatively minor effect on hemodynamics and drug delivery. Consequently, for the unsteady simulation of drug-eluting stents, blood can be accurately modeled as a Newtonian fluid.

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