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MODELING DRUG ELUTING STENTS FOR CORONARY ARTERY BIFURCATION CONSIDERING NON-NEWTONIAN EFFECTS

Marjan Molavi Zarandi*
Department of Mechanical Engineering
McGill University
Montreal, Quebec H3A 2K6, Canada
Email: marjan.molavizarandi@mail.mcgill.ca

Rosaire Mongrain
Department of Mechanical Engineering and
McGill University
Montreal, Quebec H3A 2K6, Canada
Email: rosaire.mongrain@mcgill.ca

Olivier F. Bertrand
Faculty of Medicine
Laval University
Quebec City, G1V 4G5, Canada
Email: olivier.bertrand@criucpq.ulaval.ca

ABSTRACT

Drug Eluting Stents (DES) are commonly used for the treatment of stenotic arteries. Restenosis can be treated by delivering anti-thrombotic and anti-proliferative drugs to the arterial wall. The main mechanism of the drug eluting stent is to allow diffusion of the drug from the coating on the stent, into the arterial wall over a prolonged period of time. Investigation of blood flow hemodynamics and shear stress are of great importance in understanding the transport of drugs through the circulatory systems and predicting the performance of drug eluting stents.

While drug eluting stent effectively reduces restenosis rate, the conventional drug eluting stent should be optimized to be used in the bifurcation stenting. Various flow patterns due to specific designs of drug eluting stent influence drug delivery. Numerical simulation techniques are appropriate approaches to study such phenomena which can be used to optimize the design of drug eluting stents for bifurcations. In this paper, the complexity of drug eluting stent function in the bifurcation is presented by employing computational fluid dynamics analysis for various stent strut designs. Drug transportation through the lumen and determination of local drug concentrations in arterial wall is carried out for both Newtonian and non-Newtonian flow conditions. It is, to the author's best knowledge, the first investigation of drug dispersion in arterial bifurcation considering the effects of both the blood rheological properties and stent strut design.

NOMENCLATURE

ρ	density of the fluid
u	velocity vector
p	pressure
τ	stress tensor
μ_∞	viscosity at infinite shear rate
μ_0	viscosities at zero shear rates
η	apparent blood viscosity
λ	time constant
n	power law index
$\dot{\gamma}$	shear rate
D_L	diffusion coefficients of drug in the lumen
D_p	diffusion coefficients of drug in the coating
D_w	diffusion coefficients of drug in the arterial wall
C	local normalized drug concentration

* Corresponding author

INTRODUCTION

Arterial diseases like atherosclerosis are the leading causes of death in the industrial world. Atherosclerosis reduces arterial lumen size through plaque formation. Atherosclerosis reduces arterial lumen size through plaque formation and growth. Intravascular stents, which are small thin-walled slotted tube structures, can be expanded into the stenotic artery to restore the normal blood flow in the artery. Nowadays, stent implantation is a common procedure in treatment of stenotic arteries with a high rate of success when compared with angioplasty treatment [1].

However, some limitations are still present and the major ones are those associated with the 'in-stent restenosis'. When it happens, the stented vessel may become stenotic and therefore blocked again. The reported in-stent restenosis rates from various clinical trials with DES vary between 0% and 16.7%, which compare favorably to bare metal stent restenosis rates varying between 11% and 35% [2]. The biology of restenosis in stents includes plaque redistribution, thrombosis and neointimal hyperplasia (NIH) [3]. Restenosis is a combined result of a biological response and mechanical reaction to Percutaneous Coronary Interventions. The biological response to the procedure can be grouped into four steps. Platelet aggregation is the early reaction to Percutaneous Transluminal Coronary Angioplasty. The injury created after stent placement causes platelets activation. Thrombosis can occur on a timescale of days, and begin with the adhesion of blood-borne platelets. The attachment of these cells to the wall depends heavily on local blood flow patterns, which in turn depend on the stent geometry. The next step, the inflammatory phase, can spread over a few days or weeks. In this phase, a variety of white cells will gather at the injury site and exert their influence on the healing tissue. The proliferation phase is the third step which stimulates smooth muscle cells (SMCs) migration and proliferation. It is an attempt to repair the wound. The SMCs migrate to the thrombus that acts as a scaffold, providing the substrate for neointimal formation [4, 5]. This part of the arterial wall response, is largely due to the chronic injury caused by the high stress associated with the stent. The final phase of restenosis response is the late remodelling of the vessel [1]. Restenosis can be treated by delivering anti-thrombotic and anti-proliferative drugs to the arterial wall. To address this problem drug-eluting stents are being developed. Drug eluting stent is a regular metal stent which is coated with a drug that is known to interfere with the process of restenosis. The main mechanism of the DES is to allow diffusion of the drug from the coating on the stent, into the arterial wall over a prolonged period of time. However, the design of such devices is a very complex task because their performance in preventing restenosis is influenced by many factors such as the geometrical design of the stent, the mechanical properties of the materials and the chemical properties of the drug that is released.

Arterial mass transport also is believed to be influenced by luminal flow patterns and biomechanical forces, especially shear stress [6].

Stent implantation changes the arterial blood flow patterns. Various flow patterns due to specific designs of DES influence magnitude and distribution of shear stress and subsequently drug transportation. The purpose of this study is to investigate the effects of strut profile on the flow patterns and drug distribution in a stented coronary artery bifurcation. The impact of disturbed Newtonian and non-Newtonian flow conditions on arterial drug distribution and comparison of different stent strut designs in terms of hemodynamic performances and mass transports are of particular interests in this study.

MATERIAL AND METHODS

A two-dimensional model of the stented bifurcation was developed to determine the corresponding velocity field and drug concentration in the arterial wall. A Computational Fluid dynamic (CFD) analysis was carried out using COMSOL, which is dedicated for various physics and engineering applications. The study of the impact of luminal flow variability on the arterial drug distribution was done within the framework of a coupled computational fluid dynamics and mass transfer model. The geometrical model of the bifurcation consisted of the left main coronary artery and a 45° bifurcation of two daughter vessels. This model is similar to the bifurcation between the left anterior descending artery and coronary artery. The parent vessel diameter was 3 *mm* and daughter vessels diameters were 2.5 *mm* and 1.7 *mm* respectively [7]. The dimensions which were adopted for this model are 10 struts, 0.15 *mm* in diameter, and located 0.7 *mm* center to center apart; polymer coating thickness=0.05 *mm*; diameter of the artery=3 *mm*; arterial wall thickness=0.5 *mm* (Fig. 1). These stent dimensions are typical of common coronary stents [8], and the wall thickness corresponds to a moderately thickened wall since a normal intima thickness is about 200 μm [9]. Using this model, two strut profiles were investigated: circular and square cross-sectional profiles. The dimensions for square stent struts are 10 struts, 0.15 *mm*, and located 0.7 *mm* center to center apart [10].

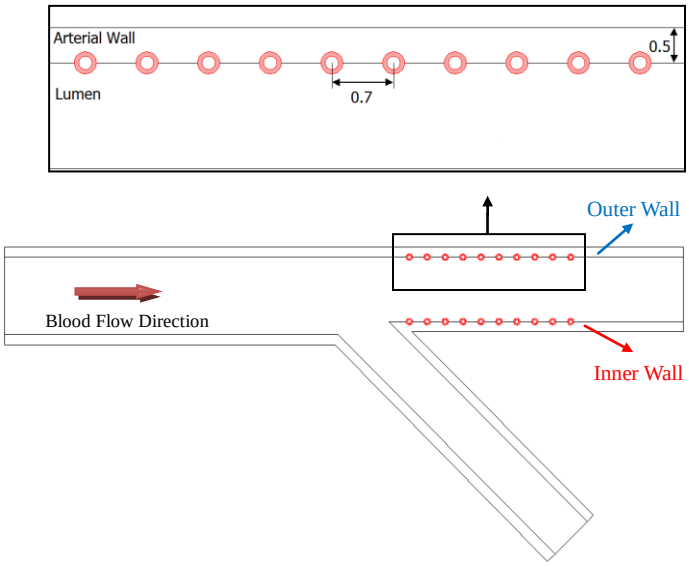


Figure1. Stented coronary artery bifurcation.

For the study of blood flow in the arteries, we assumed that blood can be represented by an incompressible fluid which is governed by the momentum equation:

$$\rho(u.\nabla u) = -\nabla p + \nabla.\tau \qquad (1)$$

and the continuity equation:

$$\nabla . u = 0 \tag{2}$$

where, ρ denotes the density of the fluid ($kg\ m^{-3}$), u the velocity vector ($m\ s^{-1}$), p the pressure (Pa) and τ the stress tensor which is dependent on the viscosity and shear rate. It is shown that in the most general situation, the arterial blood flow in the stented regions appears to have non-Newtonian properties [11]. To model the non-Newtonian properties of blood, a constitutive equation is necessary to define the relationship between apparent viscosity and shear rate.

From the various non-Newtonian blood models, the Carreau model approaches the constant Newtonian value at high shear rates and provides adequate information to model blood behaviour [12]. The non-Newtonian blood properties in this model are blood viscosity at infinite shear rate μ_∞ *=0.035 mPa.s*, blood viscosities at zero shear rates μ_0=0.56 *mPa.s*, λ=3.313 *s* and *n*=0.3568 [13]. Blood density is ρ =1060 [14].

In the Carreau model, the viscosity is modeled by the equation:

$$\eta = \mu_\infty + (\mu_0 - \mu_\infty)[1 + (\lambda \dot{\gamma})^2]^{\frac{(n-1)}{2}} \tag{3}$$

Here η is the effective apparent blood viscosity, μ_∞ and μ_0 are the blood viscosities at infinite and zero shear rates (*Pa. s*) respectively, $\dot{\gamma}$ is the shear rate (s^{-1}); λ is a time constant, and *n* is power law index which is a dimensionless parameter determined with experimental fit [14]. In the Carreau model, the viscosity is dependent on the shear rate ($\dot{\gamma}$) , which for two dimensions is defined according to equation:

$$\dot{\gamma} = \sqrt{\frac{1}{2}\left((2\frac{\partial u}{\partial x})^2 + 2(\frac{\partial u}{\partial y} + \frac{\partial v}{\partial x})^2 + (2\frac{\partial v}{\partial y})^2\right)} \tag{4}$$

where *u*, *v* are the velocity vectors, respectively [15].

To solve the governing equations, a set of boundary conditions is required. In this analysis, the mean velocity of 28 *cm/s* was considered for a coronary artery of 3 *mm* in diameter [10]. The flow was considered laminar and fully developed throughout the study section. At the walls, the velocity obeyed the no-slip condition. At the outlet of the daughter vessels, a stress-free condition was assumed as the boundary conditions.

For modeling the mass transport processes, a convection-diffusion equation was used. The coating and the arterial wall were considered nonporous media, and the physiological mass transport processes were modeled by a pure diffusion equation. These assumptions are summarized by the following system of equations:

$$u.\nabla C = D_L \nabla^2 C \tag{5}$$

$$D_P \nabla^2 C = 0 \tag{6}$$

$$D_W \nabla^2 C = 0 \tag{7}$$

Equation (5) is the convection-diffusion equation to model the dispersion of the substance in the blood; Equations (6) and (7) are the diffusion equations to model the substance diffusion in the coating and wall, respectively. In these equations, *u* is the blood velocity (*m/s*), *C* is the local normalized drug concentration ($kmol/m^3$) and D_L, D_p, and D_w are the diffusion coefficients of the drug molecule in the lumen, the coating, and the arterial wall, respectively (m^2/s) [10].

The initial concentration in the polymer coating is set to unity C_0=1 representing a normalized initial concentration. This allows us to obtain the values of subsequent local concentrations in the wall directly as percentages of the initial concentration. The following combinations of the diffusion constants are used: D_w=3.65 10^{-12} m^2/s, D_p=10^{-12} m^2/s, D_L=3.89 10^{-11} m^2 / *s* [10, 14].

RESULTS

The computed velocity fields and wall shear stress distributions in a stented bifurcation are presented for two different strut profiles. The problem was solved based upon the steady laminar flow of a homogeneous, incompressible, non-Newtonian fluid through a bifurcated channel with rigid walls.

The placement of a stent in an artery affects the flow condition adjacent to the artery wall, as well as the overall flow patterns in the artery. Figure 2 shows the velocity profiles in a stented bifurcation as well as the velocity vector plot and recirculation zones between two adjacent stent struts for two different strut profiles.

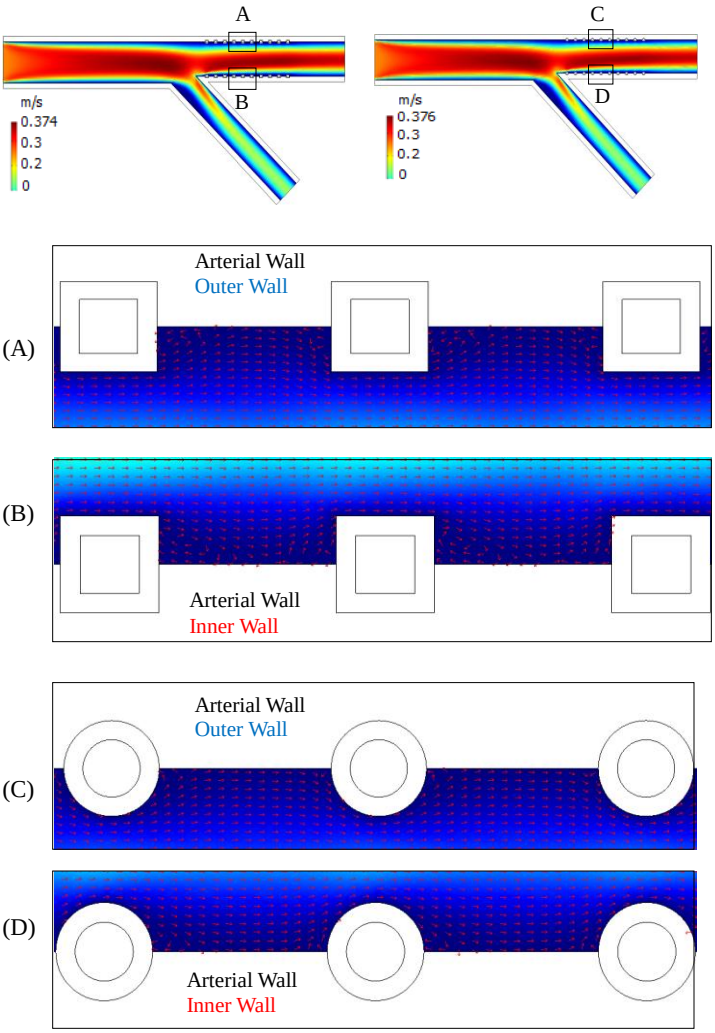
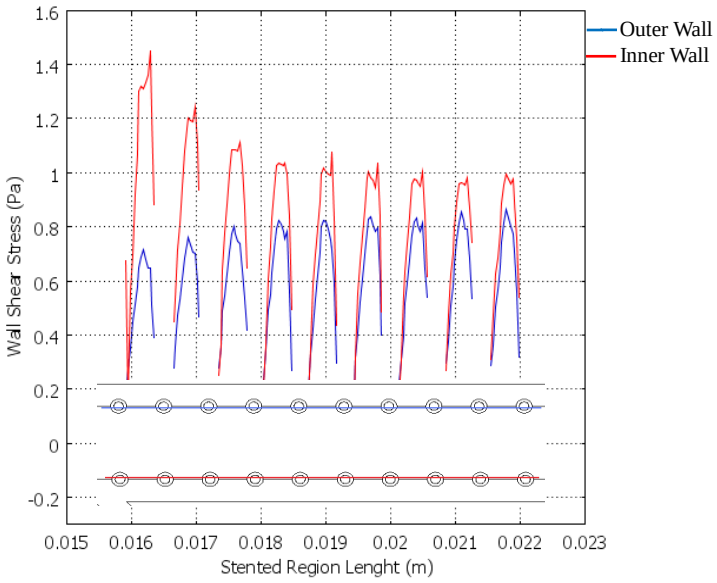
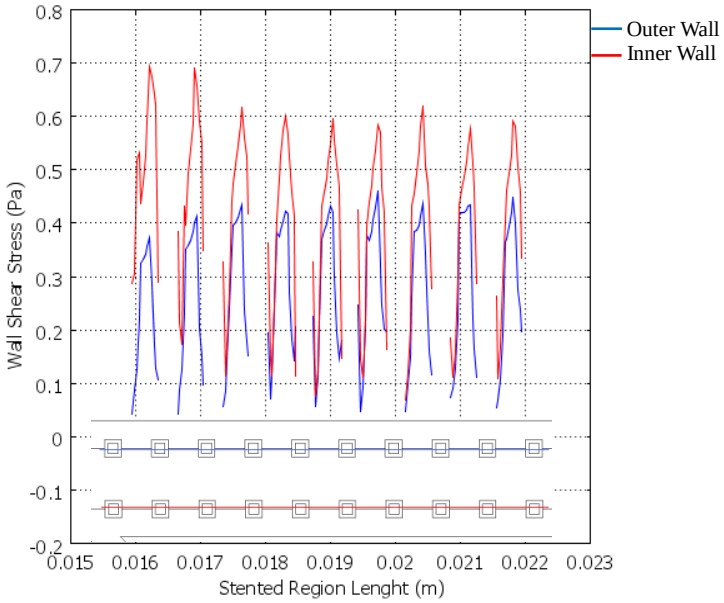


Figure 2. Velocity field, velocity vectors and recirculation zones in the stented coronary artery bifurcation.

The results show that wall shear stress distribution between stent struts is sensitive to stent strut profile. This results show that depending on the profile of strut the WSS value changed markedly. Figure 3 illustrates the effects of different half-embedded strut profiles on WSS along the outer and inner walls of bifurcation.



(a)



(b)

Figure 3. Distributions of WSS for the daughter vessel for non-Newtonian flow for half-embedded (a) circular and (b) square cross sectional profiles of struts.

These results make it is possible to compare the WSS distributions for each strut profile. The square and circular profiles have the highest WSS on the inner wall in comparison with the outer wall, while this value is significantly higher for the circular profile compare to square profile. Furthermore, the WSS on the outer wall is higher for circular profiles, while the square profile shows the lowest levels of WSS.

Several conventional drug eluting stent designs have been used for bifurcation stenting. The impact of strut cross-sectional profile on the drug transportation in the vascular wall of a stented coronary artery bifurcation is investigated and the results are presented in this section. The total drug concentrations along the outer and inner walls for two different struts cross-sectional profiles (square, circular) are computed. Figures 4 illustrate the concentration of drug for the outer and inner walls of stented bifurcation for both square and circular cross-sectional strut profiles.

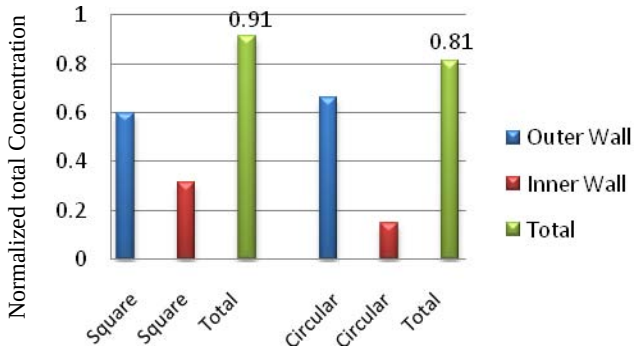


Figure 4: Concentration of drug for half-embedded square and circular cross-sectional strut profiles in the outer and inner wall.

Our results suggest that although most of the drug is being convected in the blood stream, the total accumulation of drug in the vascular wall for stent with the square cross-sectional profile is higher. There is a remarkable difference between the total accumulation of drug for in the inner wall of bifurcation compare to the outer wall for both strut profiles in the two dimensional simulation.

To examine the possible effect of the non-Newtonian behavior of blood on the total drug concentration in the arterial wall, the complexity of DES function in the bifurcation was studied considering both Newtonian and non-Newtonian flow conditions. The analysis was performed for both circular and square strut profiles which are half embedded in the bifurcation. Figure 5 shows the total drug concentration in arterial wall considering Newtonian and non-Newtonian blood viscosity models.

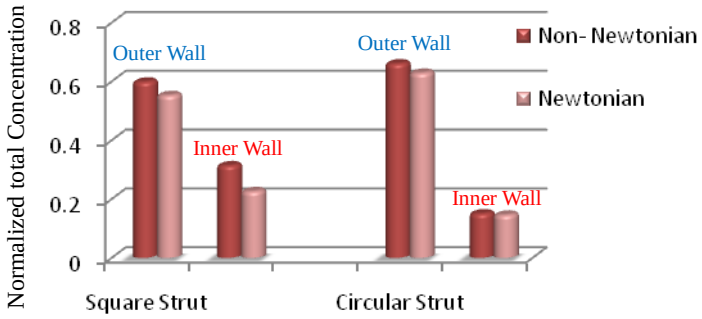


Figure 5. Total drug concentration in arterial wall for Newtonian and non-Newtonian blood viscosity models.

Comparison Newtonian and non-Newtonian blood viscosity models (Fig. 5) shows that the total drug concentration in the square and circular profiles for the non-Newtonian flow condition is higher and consequently different compared to the usually assumed Newtonian flow conditions.

CONCLUSION

In this study, we have used computational fluid dynamic simulations to investigate the effect of rheological properties of blood and the design parameters of the strut profile on the flow patterns and drug distribution in a stented arterial bifurcation.

Our simulations showed that the presence of a different stent strut profiles within the bifurcation induces local disturbance in the flow field and consequently produces different shear stress in the outer and inner walls of bifurcation. It was shown that the higher wall shear stress was occurred on the surface of inner arterial wall. Wall shear stress was considerably higher in stented segment with circular strut profile compare to square strut profile.

It was observed from this study that the drug concentration is depended on both stent strut cross-sectional profile and rheological properties of blood.

The recirculation flow zone between struts was larger for inner wall when stent with square cross-sectional strut profile was implanted. Since the drug can reside in the recirculation zone, the drug concentration in this region was considerably higher. There was not a remarkable difference between recirculation flow zone and consequently drug concentration for both circular and square strut profiles in the outer wall of bifurcation. The total drug concentration in the arterial wall for stent with square strut profile is higher especially for the inner wall of bifurcation. It means that for the specific type of stented bifurcation presented in this study, for the better dispersion of drug from DES in to the arterial wall; struts with square cross-sectional profile are more appropriate compare to circular profile.

The non-Newtonian property of blood significantly affects the drug concentration in the arterial wall. Considering the Newtonian property of blood to determine the drug distribution in the arterial wall, results in an underestimation of the magnitude of drug concentration. Therefore, the rheological properties of blood should be taken in to the account for the future stent strut designs.

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