SENRA Academic Publishers, Burnaby, British Columbia
Vol. 3, No. 1, pp. 725-730, 2009
ISSN: 1715-9997

Canadian Journal of pure&applied sciences

MATHEMATICAL MODEL AND NUMERICAL SIMULATION OF THE DRUG ELUTING STENTS IN THE CAROTID ARTERY

*Ruchi Agarwal[1], VK Katiyar[2] and Prabhakar Pradhan[1]
Department of Mathematics
[1]Gurukul Kangari University, Haridwar, India, [2]Indian Institute of Technology, Roorkee, India

ABSTRACT

The release of substances in living tissues for therapeutic purposes is becoming quite important in medicine. Therefore the development of appropriate pharmacokinetic models for the numerical simulation of these release processes is important to increase the understanding. One of the main problems of the release processes from stents arises due to the different geometric changes caused by stenting in carotid arteries. To describe the drug release of stents to the wall of artery, a model is presented in this paper using appropriate transient flux boundary condition at the interface of arterial wall and fluid dynamical approach for the blood flow and arterial wall. This numerical simulation can provide a convenient way to study the effects of geometrical changes on the drug release of stents. The results are explained with appropriate plots presented at the end of the paper in order to illustrate the applicability of the present model under study.

Keywords: Drug delivery, stent, FEM, carotid artery, mass release.

INTRODUCTION

Every year, 800,000 angioplasty procedures are performed to treat plaque-clogged carotid arteries. This procedure consists of inserting a meshed metal-wire stent surrounding a balloon catheter into the carotid artery (Fig. 1). The balloon is inflated to expand and insert the stent into the arterial wall. The balloon-catheter is promptly removed while the expanded stent provides structural support in the artery wall to relieve constriction. However, in 15-30% of patients who undergo angioplasty, the artery becomes clogged again in a condition called restenosis in which endothelial cell growth proliferates around the device as part of the body's natural wound-healing response. To address this problem, many leading biomedical companies, such as Johnson & Johnson, Boston Scientific, and Medtronic, have developed drug-eluting stents, which have proven to significantly reduce the rate of restenosis.

The main mechanism of the drug-eluting stent is to allow diffusion of the drug from the polymer coating on the stent, into the arterial wall over a prolonged period of time. There are two layers of the arterial wall: the intima which is closest to the lumen or blood cavity and the adventitia which is the outer layer. Drugs currently on the market act solely in the intima layer by inhibiting microtubule formation and preventing smooth muscle growth in the artery. Any excess drug not taken up in the intima layer will continue to diffuse through the adventitia layer. The positioning of the stent can also be adjusted at the time of placement to allow for the maximal surface area of contact between the stent surface and the arterial wall.

A number of recent studies has been devoted to the mass transfer process in the arterial wall, modeled as a multi-layered medium, coupled with the transport in the lumen (Kargol *et al*., 1996; Lally *et al*., 2005; Hwang *et al*., 2001; Song *et al*., 1997; Nicoud *et. al*., 2005; Chen and Lu, 2006; Li and Kleinstreuer, 2006). Some work has been done to correlate the number and the location of the metallic net structure of a stent with the extension of the perfused area (Morris *et al*., 2004; Zunino, 2004). Other mathematical models have been developed to predict the release of a substance in a tissue and the influence of the physical properties of the drug. However, computational difficulties in coupling different geometrical scales are reported Nicoud (2002), Chan *et al*. (2007), Alicea *et al*. (2004) and Natarajan and Dehghan (2000). The effect of drug release after stenting has also been studied previously using different vessels like carotid artery, aorta etc. These studied also explained the behavior of the wall shear stress due to stenting (Tortoriello and Pedrizzetti, 2004; Balakrishnan *et al*., 2005; Pontrelli and de Monte, 2007; Safian *et al*., 2006; Ackerstaff *et al*., 2005; Wu *et al*., 2007. In our study a mathematical model has been presented to include the stent coating by means of an appropriate transient flux boundary condition at the interface to the arterial wall. Though limited to an idealized configuration, the present model is shown to catch most of the relevant and combined aspects of the drug and fluid dynamics using a numerical approach (FEM). Results of numerical simulations are obtained for the drug mass, concentration of drug at the arterial wall and wall shear stress due to stenting is discussed and compared.

*Corresponding author email: ruchiiitr83@gmail.com

MATHEMATICAL MODEL

In this study we reduce our observations on the calculations of the drug distribution in the arterial wall of the internal carotid artery and, if needed, the stent coating. The arterial lumen is not considered. We will call the model that considers the transport in the wall and the drug coating the "two domain approach". The model that considers only the wall will be called "one domain approach". The fluid dynamical equations and the geometry of carotid artery is also been considered for the success of the presented strategy. They constitute a link between mass release and CFD and are possible indicators of an optimal delivery.

The two domain approach

In this model the solute transport of the drug is modeled in the stent coating and the arterial wall by using the macroscopic convection-diffusion equation Pontrelli and de Monte (2007). At the initial time, the drug is contained only in the coating Ω_c and it is uniformly distributed at a maximum concentration C_c and subsequently released into the wall.

Thus, the dynamics of the drug in the coating is described by the following 1D diffusion equation,

$$\begin{aligned} &\frac{\partial c_c}{\partial t} - D_c \nabla^2 c_c = 0 && \text{in } \Omega_c \\ &\nabla c_c \cdot n_c = 0 \ \text{(symmetry)} && \text{on } \Gamma_w \\ &\nabla c_c \cdot n_c = 0 \ \text{(impermeability)} && \text{on } \Gamma_a \\ &c_c = C_c && \text{at } t = 0 \end{aligned} \qquad (1)$$

In this work, D denotes the drug diffusivity and n the normal external to the considered medium, c_c denotes the concentration of the coated drug.

Let us now consider the drug dynamics in the wall. Here mass transfer is not governed by diffusion only, but convection due to the filtration velocity of the plasma results equally important and a transport term is added. Furthermore we account for a metabolic process (due to drug binding or chemical reaction) and a linear mass consumption is assumed. Similarly, $c_w = 0$ at Γ_b (the interface between wall and lumen) because of the wash out of the blood stream. Therefore, a fraction of drug is lost in the tissues adjacent to the adventitia and a fraction dispersed in the lumen. Thus, we have the following convection-diffusion-reaction problem

$$\begin{aligned} &\frac{\partial c_w}{\partial t} + \nabla \cdot \left(\frac{\alpha_w}{\varepsilon_w} U_w \cdot c_w - D_w \nabla c_w \right) + \beta c_w = 0 \\ &\text{in } \Omega_w \\ &c_w = 0 \quad \text{(washout or large distance)} \qquad \text{on } \Gamma_b \\ &\nabla c_w \cdot n_w = 0 \ \text{(symmetry)} \\ &\text{on } \Gamma_w \\ &c_w = 0 \\ &\text{at } t = 0 \end{aligned} \qquad (2)$$

where U_w is a wall volume-averaged plasma filtration velocity, assumed assigned and constant, ε_w the wall porosity, β>0 a consumption rate coefficient. The coefficient α_w is the so-called tortuosity in the axial direction (i.e., the hindrance to drug diffusion imposed by local boundaries).

To close the previous system of equations (1)-(2), the conditions at the coating-wall interface have to be assigned. The two transport domains are coupled by appropriate conditions at the interface Γ. One of them is obtained by imposing continuity of the mass flux

$$D_c \nabla c_c \cdot n_c = D_w \nabla c_w \cdot n_w \quad \text{on } \Gamma \qquad (3)$$

The one domain approach

In this model the transport of the solute is modeled by the macroscopic convection-diffusion equation only in the arterial wall with appropriate boundary conditions. Also, to slow down the drug release rate, a thin film (called *topcoat*) of permeability P (*cm/s*) is located at the interface. A continuous mass flux passes through it orthogonally to the coating film with a possible concentration jump. In the present case, the mass transfer through the topcoat can be described using the second Kedem-Katchalsky equation Kargol *et al*. (1996). Thus, the continuous flux of mass passing across the membrane orthogonally to the coating is expressed by

$$-D_c \nabla c_c \cdot n_c = P(c'_c - c'_w) \quad \text{on } \Gamma \qquad (4)$$

or, alternatively,

$$-D_w \nabla c_w \cdot n_w = P(c'_c - c'_w) \quad \text{on } \Gamma \qquad (5)$$

In equations (4)-(5) the fluid-phase concentration *c'* is used. This is related to the volume-averaged concentration *c* through the formula $c' = c/k\varepsilon$, where ε is the porosity and k is the partition coefficient. As one of the last three equations is redundant, we can choose any two of them, for example equations (4) and (5).

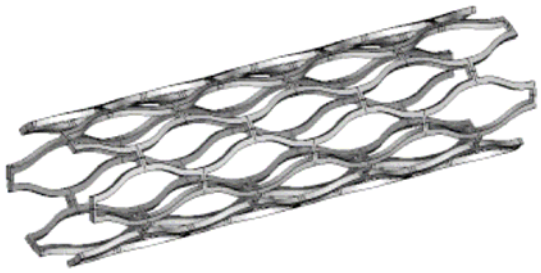

Fig.1. Typical structure of stent.

Fluid dynamical approach

Since the blood flow affects the lumen radius, the knowledge of the shear stress and the pressure drop are of paramount importance. In particular, once the shear stress τ is known, it is possible to experimentally individuate the correct formulation (polymer concentration, amount of crosslinker used, crosslinking time and so on yielding to a solute able to resist, at least sufficiently long time, to the erosive action played by the blood stream. Accordingly, a fluid dynamical analysis is needed. To this aim, we consider an artery of circular cross section *R* having a rigid wall (that is a reasonable assumption for a stented carotid artery). Let us assume the blood as a viscous fluid with rheological properties governed by a simple power-law viscosity Chen and Lu (2006)

$$\eta(\dot{\gamma}) = K\dot{\gamma}^{n-1} \tag{6}$$

where $\dot{\gamma}$ is the shear rate,

$$\dot{\gamma} = \left(\frac{1}{2}tr\left(A_1^2\right)\right)^{\frac{1}{2}} \quad \text{where } A_1 = \nabla v + (\nabla v)^T$$

with *v* the fluid velocity. In the case of steady and laminar flow, denoting by ρ and *p* the fluid density and the pressure, the mass and momentum conservation laws are

$$\nabla \cdot v = 0$$

$$\rho\left(\frac{\partial v}{\partial t} + v \cdot \nabla v\right) = \nabla \cdot T - \nabla p \tag{7}$$

where *T* is the stress tensor and linearly dependent on the rate of deformation tensor A_1 with a relation of $T = \eta(\dot{\gamma})A_1$, η represents the viscosity of the blood.

The equations (7) are solved in the present configuration in a tube of length *L*, letting as inlet condition a velocity profile obtained by integration of equations (7) in the case of an unstented artery

$$v(y,t) = \left(\frac{\Delta p}{2KL}\right)^{\frac{1}{n}} \frac{n}{n+1} R_A^{\frac{n+1}{n}} \left[1 - \left(\frac{y+R}{R_A}\right)^{\frac{n+1}{n}}\right]$$

$$-R \le y \le -d \tag{8}$$

with $R_A(x,t) = R - d$, d is the thickness of the drug layer.

Numerical Simulation

We are interested in studying the variation of the concentration field in the wall with the geometrical parameters such as the penetration depth *s* that measures the stent embedding degree, or the mesh length directly related to the void fraction. Our aim is to compare the mass release in the configurations of conventional DES Pontrelli and de Monte (2007). Comparison is difficult because much of the parameters and the materials are intrinsically related to the specific methodology. Let us consider a stent coated by a thin layer of a drug and embedded into the arterial wall, as illustrated in figure 2. The following physical values are fixed for computational experiments:

$L_y = 0.005cm$ (Length of the stent), $D_w = 7\times10^{-8} cm^2/s$

All the concentrations (considered as averaged mass per area) are non-dimensionalized with respect to their initial values ($c \to c/C_c$). For the conventional stent, the following constants are considered:

$P = 10^{-6} cm/s$, $D_c = 10^{-10} cm^2/s$, $k_c = 1$, $k_w = 1$, $\varepsilon_c = 0.1$, $\varepsilon_w = 0.61$

They have been chosen according to a physical basis and in agreement with the typical scales in DES and data literature for the carotid arterial wall and heparin drug in the coating layer (Pontrelli and de Monte, 2007; Ackerstaff *et al*., 2005; Wu *et al*., 2007).

In case of preliminary fluid dynamics numerical simulations were independently carried out, based on the following set of parameters:

$n = 0.6$, $K = 0.02423 Pa.s^{0.6}$, $\rho = 1.064 g/cm^3$, $L = 6.5cm$, $Q = 240 ml/\min$

The radius of the carotid artery is taken based on the literature Safian et al., (2006), Ackerstaff *et al*. (2005) and Wu *et al*. (2007). These values imply a pressure gradient $\Delta p/L = 3296 Pa/m$ in equation (8) and a blood pressure p_b upstream the stented region equal to $21331.2 Pa(160 mmHg)$ (such flow rate and pressure values correspond to stressed physiological conditions). The fluid dynamics problem was solved in transient state with a finite element method using unstructured triangular mesh and an implicit second order Euler scheme as time integrator. The numerical problem has been solved by finite element method using MATLAB 7. The spatial domain has been discretized by a not uniform triangular mesh (having a number of elements ≈ 3200) with second order Lagrangian polynomial as shape functions and a Runge-Kutta integration scheme in time, using an

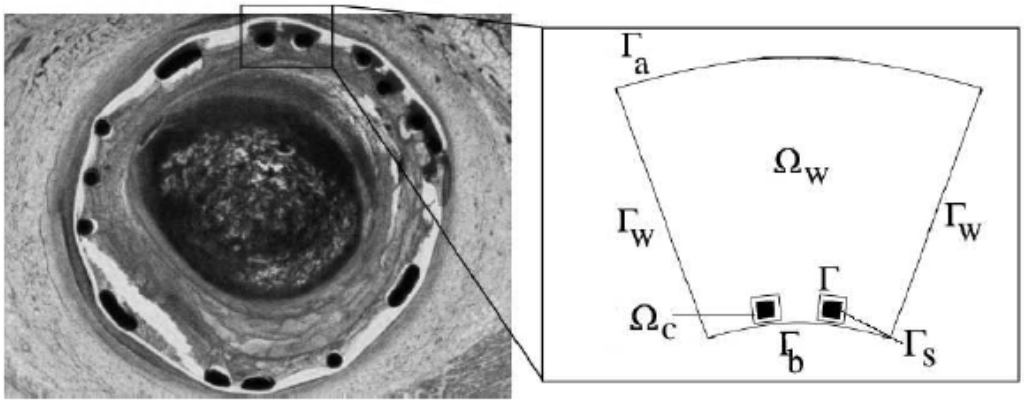

Fig. 2. Schematic representation of the considered transport domains consisting the arterial wall Ω_w and the stent coating Ω_c (Zunino, 2004).

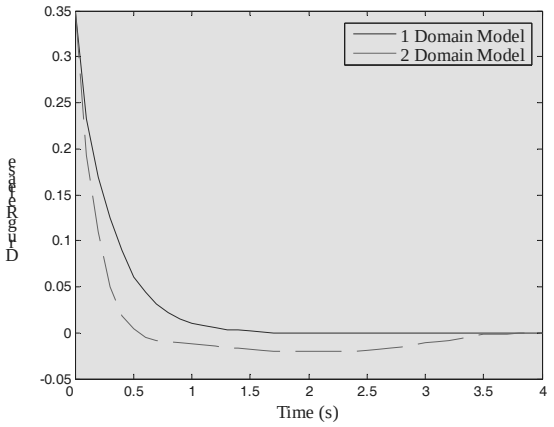

Fig. 3. Comparison of the amount of drug stored in the coating between the 2 domain (lower curve) and the 1 domain model (higher curve).

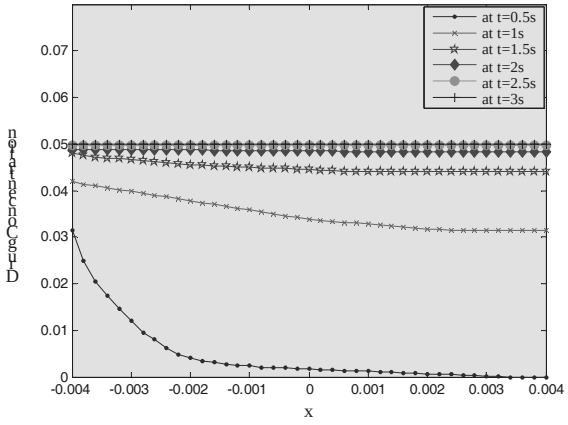

Fig. 4. Concentration profiles in the wall of the 2 domain problem at selected time points: t =0.5s (lowest curve), t=1s, t=1.5s, t=2s, t=2.5s, t=3s (higher curve).

adaptive time step with has been chosen (minimum $\Delta t \approx 10^{-2}$).

RESULTS AND DISCUSSION

Concentration of drug release

As figure 3 displays the comparison of the amount of mass in the coating between the 2 domain approach (lower curve) and the one domain approach (upper curve). It can be pointed out that the release in the simplified model is slower than in the two domain approach. This can be explained by the inner resistance that is taken into account in the computation of the flux (Pontrelli and de Monte, 2007). By taking an approximation of the release using an electrical analogy we linearize our problem. This model can't take into account the occurrence of a boundary layer resulting from the discontinuous initial condition ($c_0 = 1.0$ in the coating and $c_0 = 0.0$ in the wall). It can be seen that the largest error is made in the first time steps.

In figure 4 and 5 we show the concentration profile in the wall due to the drug coated stent. It can be noted that the error of the approximation of the flux at the beginning of the release significantly influences the concentration distribution in the arterial wall (Hwang *et al*., 2001; Pontrelli and de Monte, 2007; Wu *et al*., 2007). The concentration values of the first time step ($t = 0.5s$) is three times lower when using the one domain approach (Fig. 5). The figure 6 shows that drug mass in the coating layer is monotonically decreasing, while mass in the wall, first increasing to a maximum at time *t*, decreases to zero with the same rate as showed by the drug mass in the coating layer. Since drug is absorbed in the semi-permeable membrane, the total mass is not preserved and tends to zero at time large enough (Pontrelli and de Monte, 2007).

Wall shear stress due to stenting

After stenting there exist large hemodynamic changes due to the compliant and rigid surfaces of artery and stent. Figure 7 shows the wall shear stress in the non-stented

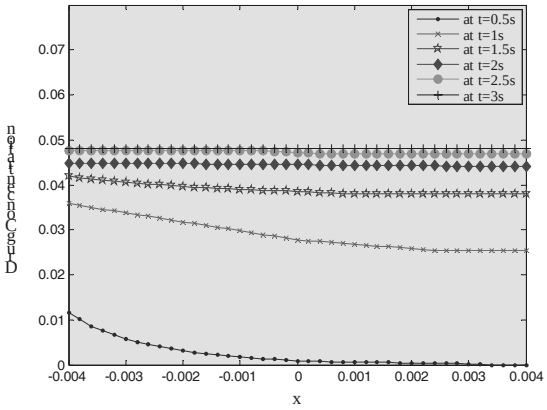

Fig. 5. Concentration profiles in the wall of the 1 domain problem at selected time points: t=0.5s (lowest curve), t=1s, t=1.5s, t=2s, t=2.5s, t=3s (highest curve).

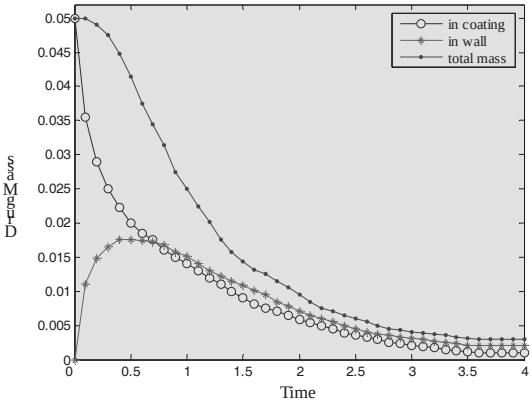

Fig. 6. Dimensionless drug mass in the coating, in the wall and total mass as function of time.

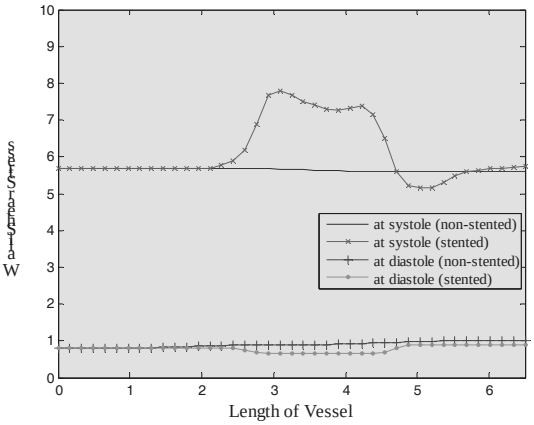

Fig. 7. Wall shear stress for systole and diastole assuming both non-stented and stented internal carotid artery.

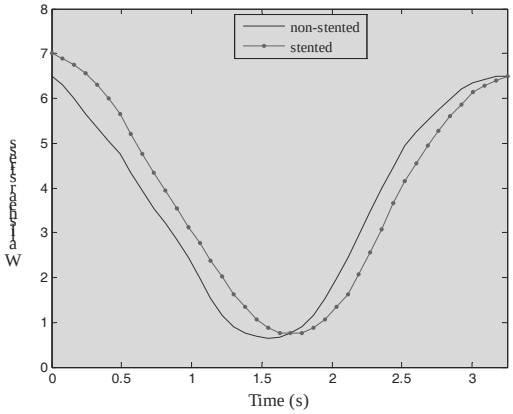

Fig. 8. Wall shear stress versus time for non-stented and stented internal carotid artery.

and stented internal carotid artery during systole and diastole. At systole, this quantity is larger in the medium part of the stented region than in the non-stented. This is consistent fact that the cross-sectional area at systole is smaller in that region. At diastole, the cross-sectional area within the stent is larger and the wall shear stress is smaller. In the transition zones between stent and artery, the stress experiences larger fluctuations, especially at systole (Tortoriello and Pedrizzetti, 2004; Nicoud, 2002). Extra stress is generated in the upstream transition zone, which acts as a convergence. Conversely, the downstream buffer region acts as a divergence at systole and tends to decrease the stress. Accordingly, the wall shear stress turns out to be locally smaller than its value in the non-stented artery. The transition zones have less effect at diastole, when the flow rate is smaller. Note that the numerical errors are much smaller than the physical effects related to the stent.

The figure 8 shows the time dependence of the stress in mid-region of the stent. The amplitude of this quantity over the cardiac cycle is larger for the stented vessel than for the non-stented (Nicoud *et al.*, 2005). It is worth noting that although the length of the stent is very small compared to the wavelength, the amplitude of the wall shear stress in case of stented behaves more like the non-stented one. If the increase in shear stress at systole is avoided the increase in stress amplitude limits drastically.

CONCLUSION

The release of a substance in a living tissue for therapeutic purposes is becoming quite common in medicine nowadays, through drug delivery devices. Drug-eluting stents are revealed a promising technique for healing the vascular wall and for the treatment of atherosclerosis and restenosis. However, the mechanism of release is quite complex and depends on many concurrent biochemical, physical and individual factors. The model presented here, although some simplifying assumptions, is able to simulate and predict the dynamics of a drug release from a stent. The model can be easily extended to a multi-layered structure, including both a more realistic wall configuration and a novel design for multi-coating DES. In addition, the mathematical formulation is able to incorporate the drug consumption

effect due to the tissue cell binding. The application of the dimensional analysis to the governing equations has indicated that the dynamics of a drug through an eluting stent is fully controlled by only four dimensionless operational parameters. Numerical experiments have been extensively carried out over several typical configurations. Results have shown the influence of the solution on each single parameter, in particular drug mass, concentration in the arterial wall and the wall shear stress due to the stenting. Also, some biomechanical indicators, such as the emptying time of the coating, geometry of the carotid artery, are suggested to obtain an optimal drug elution and a desired tissue concentration.

REFERENCES

Ackerstaff, RGA., Suttorp, MJ., Van den Berg, JC., Overtoom, TTh. C., Vos, JA., Bal, ET. and Zanen, P. 2005. Prediction of early cerebral outcome by transcranial Doppler monitoring in carotid artery bifurcation angioplasty and stenting. Journal of Vascular Surgery. 41 (4):618-624.

Alicea, LA., Alvarado, JJT. and Martinez, AV. 2004. Biofluid Dynamics of the Angioplasty: Ballooning and stenting. Congress on Biofluid Dynamics of Human Body Systems. 1-25.

Balakrishnan, B., Tzafriri, AR., Seifert, P., Groothius, A., Rogers, C. and Edelman, ER. 2005. Strut Position, Blood Flow and Drug Deposition Implications for Single and Overlapping Drug-Eluting Stents. Circulation. 111:2958-2965.

Chan, K. H., Armstrong, J., Withers, S., Malik, N., Cumberland, D. C., Gunn, J. and Holt, CM. 2007. Vascular delivery of c-myc antisense from cationically modified phosphorylcholine coated stents. Biomaterials. 28:1218-1224.

Chen, J. and Lu, XY. 2006. Numerical investigation of the non-Newtonian pulsatile blood flow in a bifurcation model with a non-planar branch. Journal of Biomechanics. 39:818-832.

Hwang, CW., Wu, D. and Edelman, ER. 2001. Physiological Transport Forces Govern Drug Distribution for Stent-Based Delivery. Circulation. 104:600-605.

Kargol, A., Kargol, M. and Przestalski, S. 1996. The Kedem-Katchalsky equations as applied for describing substance transport across biological membranes. Cellular and Molecular Biology Letters. 2:117-124.

Lally, C., Dolan, F. and Prendergast, PJ. 2005. Cardiovascular stent design and vessel stresses: a finite element analysis. Journal of Biomechanics. 38:1574-1581.

Li, Z. and Kleinstreuer, C. 2006. Computational analysis of type II endoleaks in a stented abdominal aortic aneurysm model. Journal of Biomechanics. 39:2573-2582.

Morris, L., Delassus, P., Walsh, M. and McGloughlin, T. 2004. A mathematical model to predict the in vivo pulsatile drag forces acting on bifurcated stent grafts used in endovascular treatment of abdominal aortic aneurysms (AAA). Journal of Biomechanics. 37:1087-1095.

Natarajan, S. and Dehghan, MRM. 2000. A numerical and experimental study of periodic flow in a model of a corrugated vessel with application to stented arteries. Medical Engineering and Physics. 22:555-566.

Nicoud, F. 2002. Hemodynamic changes induced by stenting in elastic arteries. Center for Turbulence Research, CTR Annual Research Briefs. 335-347.

Nicoud, F., Vernhet, H. and Dauzat, M. 2005. A numerical assessment of wall shear stress changes after endovascular stenting. Journal of Biomechanics. 38: 2019-2027.

Pontrelli, G. and de Monte, F. 2007. Mass diffusion through two-layer porous media: an application to the drug-eluting stent. International Journal of Heat and Mass Transfer. 50:3658-3669.

Safian, RD., Bresnahan, JF., Jaff, MR., Foster, M., Bacharach, JM., Maini, B., Turco, M., Myla, S., Eles, G. and Ansel, GM. 2006. Protected Carotid Stenting in High-Risk Patients with Severe Carotid Artery Stenosis. Journal of the American College of Cardiology. 47 (12):2384-2389.

Song, CX., Labhasetwar, V., Murphy, H., Qu, X., Humphrey, WR., Shebuski, RJ. and Levy, RJ. 1997. Formulation and characterization of biodegradable nanoparticles for intravascular local drug delivery. Journal of Controlled Release. 43:197-212.

Tortoriello, A. and Pedrizzetti, G. 2004. Flow-tissue interaction with compliance mismatch in a model stented artery. Journal of Biomechanics. 37:1-11.

Wu, W., Qi, M., Liu, XP., Yang, DZ. and Wang, WQ. 2007. Delivery and release of nitinol stent in carotid artery and their interactions: A finite element analysis. Journal of Biomechanics. 40:3034-3040.

Zunino, P. 2004. Multidimensional Pharmacokinetic Models Applied to the Design of Drug-eluting Stents. Cardiovascular Engineering: An International Journal. 4: 181-191.