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The effect of plaque eccentricity on blood hemodynamics and drug release in a stented artery

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ABSTRACT

Atherosclerosis in the coronary arteries is one of the leading causes of death in the world. Percutaneous coronary interventions (PCI) associated with the implantation of drug eluting stents (DES) is one of the most common forms of revascularization in patients with atherosclerotic coronary artery disease. The use of DES is considered as an effective tool to reduce restenosis after PCI. However despite all the progress made in DES procedures, the rate of restenosis remains relatively high. Mathematical modeling and numerical simulation are believed to play an essential role in identifying zones with a higher risk of in-stent restenosis. In this work the local delivery of a therapeutic agent, from a stent implanted in a coronary artery, is mathematically modeled and numerically simulated. The mathematical model includes the diffusion of the dissolved drug in the biodegradable polymeric coating of the stent, the diffusion and convection of the drug with reversible binding in the viscoelastic arterial wall with plaques of different morphology and the local hemodynamics. The study is an attempt to detect zones with a higher risk of in-stent restenosis and their relation to plaque eccentricity. The location of zones with highest risk of thrombosis and plaque rupture is also addressed. The results are in agreement with claims presented in clinical papers.

1. Introduction

Atherosclerosis is one of the most serious and common forms of cardiovascular disease which arises due to the accumulation of fatty deposits, cholesterol, and calcified materials in the arterial wall [1]. As a consequence of this accumulation, the lumen is occluded and the problem gets worse with age [2]. Different treatments, from invasive techniques such as coronary artery bypass grafting to safer and less invasive techniques like percutaneous coronary intervention (PCI), have been developed to prevent lumen occlusion [3].

Balloon angioplasty was the first nonsurgical procedure of mechanically widening the narrowed or obstructed arteries. After many years of clinical experience, balloon angioplasty is still far from being the perfect technique to minimize the occlusion of the lumen. A common problem called restenosis, that is the renarrowing of the artery, is the main drawback of balloon angioplasty [4]. Restenosis is the result of a complex series of biological events, in response to the initial injury to the arterial wall caused by balloon expansion [3]. Arterial injury induces cellular and subcellular mediators of restenosis that can be found in the arterial wall within hours, and which may persist for days to weeks. Bare metal stents (BMS) improved clinical and angiographic outcomes by reducing restenosis when compared to balloon angioplasty. However, despite their advantages, they are associated with an in-stent restenosis rate of more than 20% [5]. In an attempt to reduce this rate, drug-eluting stents (DES), which release an antiproliferative drug into the arterial wall with programmed pharmacokinetics, were first introduced in 2003. First generation DES consisted of a metallic scaffold - a BMS - coated with a polymeric layer which gradually delivers a drug that inhibits the proliferation of smooth muscle cells that cause restenosis. New generations of DES include polymer-free and bioabsorbable stents [6–8]. DES represented a breakthrough in the treatment of coronary artery disease owing to their ability to reduce the incidence of in-stent restenosis to less than 5% through the controlled release of drugs that inhibit

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intima proliferation [6]. However the delayed, or sometimes absent endothelialization of the arterial wall, can be the cause of late stent thrombosis that is the sudden occlusion of an artery due to thrombus formation. Summarizing, the two major causes of stent failure are in-stent restenosis and in-stent thrombosis [9].

Regarding in-stent restenosis, the main predictors are patient comorbidities, procedural characteristics and lesion characteristics as mechanical properties and plaques geometry. The first two predictors are object of a huge number of clinical studies. The influence of the mechanical properties of plaques has been studied by the authors previously ([10,11]). In the present paper we study a mathematical model that, while considering the viscoelastic properties of the arterial wall, includes the local hemodynamics, the geometry of plaques namely their eccentricity and its influence on drug distribution. A number of numerical and experimental studies have been done to address the importance of plaque eccentricity in different arteries ([12–15]). The novelty of our model is the fact that in-stent eccentricity of a deployed DES is considered. Once a stent is deployed and full dilatation is not achieved, mainly due to plaques stiffness, a post-stent picture of the vessel, with concentric lesions or lesions exhibiting different degrees of eccentricity, appears. The incidence of eccentric lesion is largely underestimated.

Eccentric stenosis of the coronary artery is associated in some clinical papers with plaque disruption and acute coronary syndrome. A number of studies suggested that patients with these cardiovascular pathologies tend to present eccentric plaques rather than concentric ones [16,17]. Regarding neo-intimal growth, that is intimately related with in-stent restenosis, several clinical studies claim that there were no consistent correlations between eccentricity and neo-intimal growth [18,19]. We propose a mathematical model that suggests an explanation for the previous clinical claims: the relation between stent eccentricity, thrombus formation or plaque disruption; and the apparent no relation between stent eccentricity and in-stent restenosis. The mathematical model, composed by a system of Partial Differential Equations linked by interface conditions, describes the local hemodynamics, the diffusion of the dissolved drug in the biodegradable polymeric coating of the stent, and the diffusion and convection of the drug with reversible binding in the viscoelastic arterial wall with plaques of different morphologies. The inclusion of the local hemodynamics not only provides a pattern of the local wall shear stress but also largely influences the drug distribution into the arterial wall and the lumen [20,21].

When we investigate how eccentricity influences the flow behavior we are ultimately interested in its influence on the wall shear stress. The vessel walls are exposed to the frictional force of the blood flow, acting on the tangential direction, and also to the blood pressure that acts perpendicularly to the wall. Laboratorial experiments have suggested that a high wall shear stress, not belonging to the physiological range, damages the endothelium and can cause its denudation and eventually a plaque rupture or a thrombus formation. On the contrary, laboratorial and clinical studies show that low wall shear stress affects the migratory and proliferative behavior of smooth muscle cells, leading to atherosclerotic plaque formation [22,23]. Interpreting simultaneously the patterns of local wall shear stress and the local distribution of drug, eluted from a DES, provides us with a possible explanation of the previous medical findings.

To the best of our knowledge the novelty of the present approach is the analysis of the coupled effect of the eccentricity of post-stenting plaques, the mechanical properties of plaques, the frictional force of the blood flow and the drug distribution. The simultaneous consideration of these effects lead to a more complete description of local phenomena and provides an explanation for the medical findings described in the literature. The model presented in this paper may also be viewed as a predictive tool to detect the location of thrombus formation, plaques rupture and in-stent restenosis areas in the case of eccentric and concentric lesions. Namely, as outcomes of the model, we provide explanations for:

- The location of the zones with higher risk of thrombus formation and plaque rupture in the case of concentric and eccentric post-stenting stenosis;
- The relation between in-stent eccentricity and thrombus formation and plaque rupture;
- The possible no-relation between the clinically observed eccentricity and in-stent restenosis.

These outcomes have been established through numerical studies carried on with COMSOL Multiphysics 5.1 (COMSOL AB, Burlington, MA, USA).

We believe that the study presented here may act as a predictive tool to detect the location of in-stent restenosis areas and plaque rupture or thrombus prone areas. To the best of our knowledge, the previous questions have not been investigated in the literature previously.

The paper is organized as follows. In Section 2, we describe the mathematical model of drug release from the stent coating into the arterial wall and the lumen. Section 3 is devoted to studying the effect of plaque eccentricity on blood hemodynamics and drug distribution in the stented artery. In Section 4 some comments are presented and finally in Section 5 the relations between the model results and the claims in the medical literature are addressed.

2. Mathematical modeling

In this section, we present a mathematical model that describes the integrated process of drug release from a biodegradable stent coating, the transport of drug in the coating and the arterial wall and the local hemodynamics. The mechanical properties and the morphology of the plaques are considered.

2.1. Geometry of the model

We consider a two-dimensional longitudinal section of a stenosed coronary artery containing a stent with a biodegradable polymeric coating (S) and an impermeable metallic core, concentric or eccentric plaques (P), the healthy part of the arterial wall (H) and the lumen (L) (Fig. 1). The diseased condition is taken into account by the geometric and structural modifications caused by the progression of atherosclerosis. For a sake of simplicity, we consider that there is no remodeling of the arterial wall during the period of analysis, which is a simplification of the complex dynamics of tissue healing and regrowth that takes place after stent implantation [24,25]. The stent in both cases (concentric or eccentric lesions) is underexpanded which means that it is not fully expanded. This is due to the high stiffness of the plaques and/or inadequate balloon pressure during inflation.

We have assumed that concentric and eccentric plaques in Fig. 1 have the same volume. An eccentricity index was calculated using the following formula: $\mathrm{EI} = \frac{A-B}{A}$, where A indicates maximum wall thickness and B stands for minimum wall thickness. A common criterion to define eccentric plaques is $\mathrm{EI} \geq 0.5$.

2.2. Drug release from a biodegradable stent coating

We study a DES coated with a PLGA, poly(lactic-co-glycolic acid), where a drug (Sirolimus) is dispersed. The drug is initially available in the solid phase and gradually dissolves and diffuses through the polymer in the presence of plasma.

Dissolution, diffusion and degradation are the main mechanisms of drug release from polymeric coating [25,26]. When the

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