

Numerical Simulation of Restenosis in a Stented Coronary Artery

Weronika Kurowska-Nouyrigat, Jacek Szumbariski

Abstract—Nowadays, cardiac disease is one of the most common cause of death. Each year almost one million of angioplasty interventions and stents implantations are made all over the world. Unfortunately, in 20-30% of cases neointimal proliferations leads to restenosis occurring within the following period of 3-6 months. Three major factors are believed to contribute mostly to the edge restenosis: (a) mechanical damage of the artery's wall caused by the stent implantation, (b) interaction between the stent and the blood constituents and (c) endothelial growth stimulation by small (lower than 1.5 Pa) and oscillating wall shear stress. Assuming that this last factor is particularly important, a numerical model of restenosis basing on wall shear stress distribution in the stented artery was elaborated. A numerical simulations of the development of in-stent restenosis have been performed and realistic geometric patterns of a progressing lumen reduction have been obtained.

Keywords—Coronary artery disease, coronary blood flow, in-stent restenosis.

I. INTRODUCTION

NOWADAYS, cardiac disease is one of the most common cause of death. In fact continuous stress, lack of exercise, bad diet and other similar phenomenon can damage the heart or other elements of the circulatory system.

Blood vessels have living and deforming walls, which internal surfaces are covered by a layer of endothelial cells. The endothelium has a various metabolic properties, but mainly forms an interface between circulating blood in the lumen and the rest of the vessel wall. It constitutes an anticoagulation barrier preventing platelets deposition and clotting. The localization of the endothelial cells in such a strategic place exposes them also to mechanical stimulation from the flow. This stimulation of the endothelium by the wall shear stress may cause damage leading to morphological changes. In consequence, functioning of the endothelium can be disturbed and pathology may develop.

In the places of the endothelial cells' damage, a gradual accumulation of platelets deposit occurs, reducing the lumen's diameter and blood delivery to the cardiac muscle. In case of a healthy person during strenuous physical exercise, the coronary arteries enlarge so that an increased supply of

reach-oxygen blood is possible. In case of a person with coronary artery disease, the stenosed and rigidified vessels are not able to fulfil this growing demand for oxygen and nutritive substances, leading to a cardiac muscle ischemia.

Apart of a pharmacological treatment, non-surgical interventions are applied. This technique consists on mechanical widening of the obstructed blood vessel. Tightly folded balloons are passed into the stenosed locations and then inflated to a fixed size using water pressures some 75 to 500 times normal blood pressure (6 to 20 atmospheres). Often this intervention is enriched by placing a stent, which is a metallic tube playing the role of a scaffolding. Each year almost one million of angioplasty interventions and stents implantations are made all over the world. Unfortunately, in 20-30% of cases neointimal proliferations leads to restenosis occurring within the following period of 3-6 months.

The mechanism of restenosis formation is very complex, and still not entirely known, nevertheless there is no doubt, that the factors contributing to its development are:

- mechanical damage of the artery's wall caused by the stent implantation,
- interaction between the stent and the blood constituents
- endothelial growth stimulation by small (lower than 1.5 Pa) and oscillating wall shear stress.

The last mentioned factor seems to be particularly important. In the last two decades, a number of investigations have been done in order to determine the correlation between wall shear stress distribution and the tendency of the endothelial cells to boost neointimal proliferation. It has been proved in the 90's that low and oscillating wall shear stress stimulate endothelium in such way that cellular growth is generated [1-2]. In fact, endothelial cells release substances responsible for the control of the endothelium growth rate and the intensity of this process depends on the local wall shear stress. When mechanical stimuli is high, the amount of nitric oxide secreted increases significantly leading to an inhibition of cellular growth. At weak wall shear stress the production of trombomodulin, as well as nitric oxide decreases, which may lead to cellular proliferation and at the end to restenosis [3].

It is commonly known, that during stent implantation the endothelial layer is damaged. This entrails physiological response that can be divided into two stages. The first stage that occurs immediately after tissue trauma, is thrombosis. A blood clot forms at the site of damage and further hinders blood flow. This is accompanied by an inflammatory immune response. The second stage tends to occur 3-6 months after surgery and is the result of cells proliferation.

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This may explain, why restenosis often develops inside the stent[4-9], but does not show why in many cases it occurs mostly at the stent edges. In fact, in the clinical practice, it is accepted to implant stents whose diameter exceeds the arteries one [10]. This precaution is taken, to avoid stent displacement after the intervention. This generates a sudden geometry change and related regions of low wall shear stress may appear. Another important issue is the curvature of the vessel [11].

In the current study, we consider a simple mechanical model of the restenosis development. The key idea is based on the observation that stent implantation leads to significant increase of the local bending stiffness and thus sharp changes of curvature will typically appear near the ends of the stented vessel's segment. Such geometrical modification (accompanied by strong flow pulsations) is expected to generate persistently low-WSS flow, with the possibility of massive separations in the regions near the inlet and outlet of the stented segment. The main goal of the current study is to substantiate the above scenario by means of numerical simulation.

II. MODEL AND SIMULATION ASSUMPTIONS

A. Coronary artery model

Based on coronarography results, a 3D realistic model of the left main coronary artery, including the LAD and LCX branches, has been prepared. The presence of stent is realistically simulated by a cylinder (Fig.1). The modelled stent is 15mm long and its diameter exceeds the LAD's one by 5%.

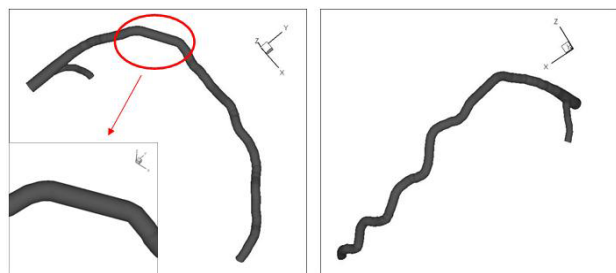


Fig. 1 Left main coronary artery model with implanted stent

The geometrical model of the artery has been generated with the use of the author's own computer code and then meshed by means of the commercial tools (TGrid, Gambit). The typical computational grid consists of about 1 million tetrahedral finite volumes.

B. Computation model

In this work, blood is considered a newtonian fluid with a viscosity of $3.5 \cdot 10^{-3}$ kg/m·s, and with a density of 1060 kg/m³. Blood flow at the inlet has been given a realistic time variation (Fig. 2) and a constant-in-time split between LAD (70%) and LCX (30%) branches has been assumed. The diameter at the inlet of the left main coronary artery is 5 mm, LAD diameter is 4 mm, and LCX – 3 mm.

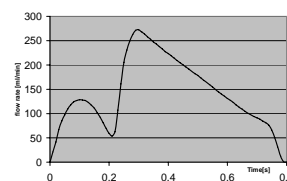


Fig. 2 Inlet flow rate to the left main coronary artery

All flow simulations have been performed by means of the commercial CFD solver Fluent 12.0.7.

C. Modeling of endothelial growth

The characteristic time of restenosis development is measured in months. In contrast, the flow effects are governed by a time scale of the cardiac pulse. This makes the time scale of the endothelial growth to be at least six orders of magnitude larger than characteristic time scale for flow phenomena. It is then reasonable to assume that the process of endothelial growth is sensitive only to time-averaged flow characteristics and thus the quasi-static approach to the restenosis development is plausible.

The main idea consists in performing the sequence of flow simulations inside a gradually changing geometric models of the stented artery with progressing stenosis. In each step of this procedure, several cardiac cycles of pulsatile flow in a fixed domain are performed to determine reliably the time-averaged characteristics of the wall stress distribution. Next, the geometric change of the vessel wall is determined and the finite volume grid for the next step is prepared.

The key ingredient of the above procedure is the way how the change of the wall shape is determined. The general assumption in this work is that the absolute value of the endothelial growth is basically not known; the only information available is the relative rate of growth, which is determined by some time-averaged characteristic of the WSS distribution. In other words, we can determine the consecutive shapes of the stenosed vessel, but we do not know exactly when such shape will actually be assumed. We will also assume that the growth occurs only in the spatial direction normal to the wall. As for the WSS characteristics which "translates" to the endothelial growth, we have at least two options. One possibility is to base the cellular growth of the wall distribution of the time fraction in which the WSS remain smaller than the dangerous value of 1.5 Pa. An alternative method is to assume that the growth rate is sensitive directly to the time-averaged WSS. Although these two approaches are nonequivalent, they are not so much different. Indeed, it can be expected that low value of the time fraction in the first method corresponds typically to larger values of time-averaged WSS, while high values of the time fraction will typically correlate to small time-averaged WSS. The numerical tests performed by the authors revealed that both methods give essentially the same picture of the early stages of the restenosis development, but the second method (based on time-averaged WSS) is easier to implement and it exhibits much less tendency for grid degeneration in the

advanced stages of the computations. All results discussed below have been obtained with the use of this approach. The maximal displacement p_{max} of the wall surface in the normal direction per one step of the simulation has been assumed. Then, the actual radial displacement of the each grid node at the wall has been defined as the averaged-WSS dependent fraction of the maximal displacement - the plot of the corresponding function has been depicted in Fig.3. The range of WSS where the relative displacement increases from 0 to 1 has been arbitrarily chosen to be [0.6 Pa, 1.5 Pa]. In other words, it assumed that WSS larger than 1.5 Pa are essentially inactive in the process, while WSS smaller then 0.6 Pa lead to exactly the same growth rate of the endothelial cells in wall-normal direction.

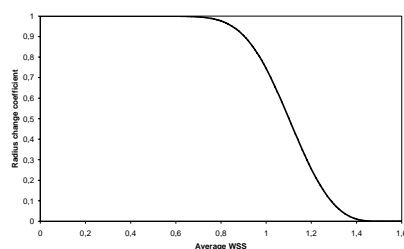


Fig. 3 Radius change coefficient in function of average wall shear stress

III. RESULTS

A. Simulation of pulsatile flow on the stented artery

In the first step, a blood flow simulation in the model was made, as well as a study of the wall shear stress distribution and the velocity profiles. The aim of this study was to determine whether “dangerous” regions of low wall shear stress persist during the whole cardiac cycle. The presented results show only WSS in the dangerous range, in three different time instants of the cardiac cycle: at minimum, average and maximum flow (Fig.4).

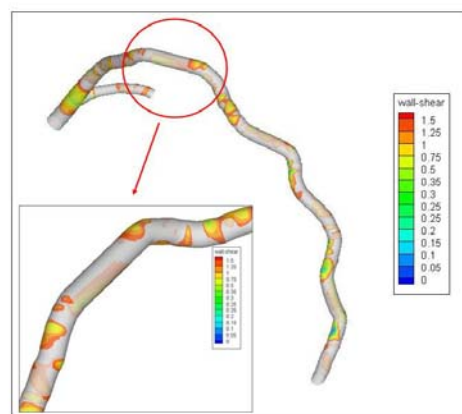
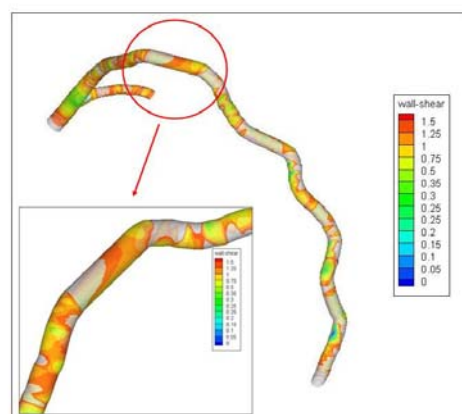
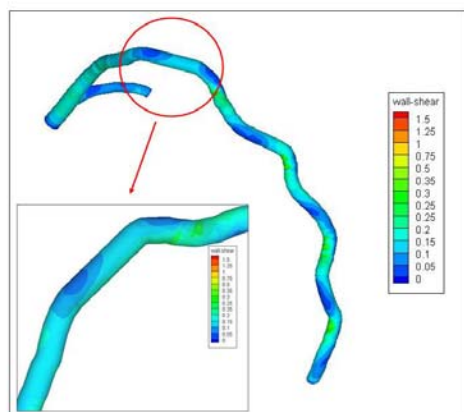
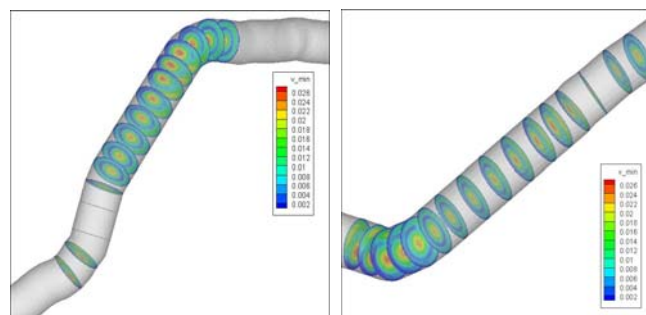


Fig. 4 WSS distribution in the left coronary artery with stent for minimum, middle and maximum flow rate at the inlet

As shown in the pictures, the numerical simulations confirm that the regions of a permanently low WSS exist inside the stented part of the vessel, especially at the stent's ends. In order to give a better idea of the flow character, the velocity distribution in the cross-sections located all along the stented segment are presented. For the minimum flow rate at the artery's inlet the velocity is small and the region of reversed flow appears. For the middle and maximum flow rates the main flow stream is shifted closer the upper (or external) side of the vessel wall and again the regions of low velocity appear near the stents edges. This phenomena is a consequence of a locally high curvature of the artery and the action of the centrifugal forces. Small values of the velocity field “translate” further into permanently low wall shear stress.



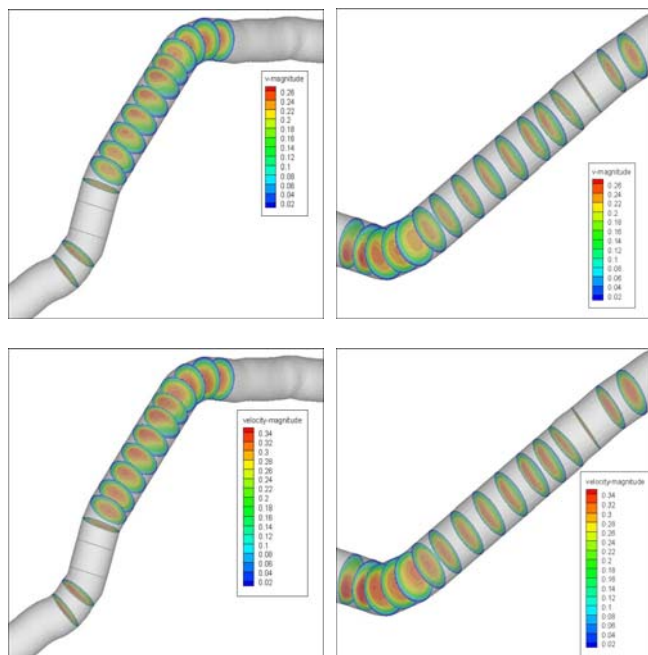


Fig. 5 Velocity distribution in planes situated in the stent area, for minimum, middle and maximum flow rate at the inlet

B. Simulation of the growth of the restenosis

The simulation of the development of the restenosis has been carried out in a number of steps as described in the point II.C. In each step, the flow field has been determined for the fixed geometry and wall distribution of time-averaged WSS has been calculated. Then, the wall grid nodes have been moved along the wall-normal direction. The length of displacement of each particular node has been determined as the WSS-dependent fraction of the admissible displacement p_{max} . New locations of the wall grid nodes are used to define the new shape of the wall and the computational domain. The obtained results show that this simple procedure is capable of generating a qualitatively realistic picture of the restenosis growth. The results presented in Fig. 6, show the comparison between the initial geometry of the stented artery and the artery with developed restenosis after 10 steps of the endothelial growth simulation. The admissible wall displacement applied in this case was of $p_{max} = 0.00002$ m per each step of the procedure, which is equal to 5% of the LAD's diameter. The changes of the cross-section shape along the stent are also shown. Figure 7 illustrates the geometry changes computed for the smaller admissible displacement $p_{max} = 0.00001$ m (2.5% of the LAD's diameter) and obtained after 20 steps of growth simulation. It can be noticed that for the smaller value of p_{max} the geometry is smoother and more regular than in the first case. Nevertheless, the overall shape of developed restenosis is similar. In both cases the largest rate of the lumen reduction is observed at the ends of the stented segment leading gradually to characteristic "candy-wrapper" effect. The maximal lumen reduction is nearly 50%.

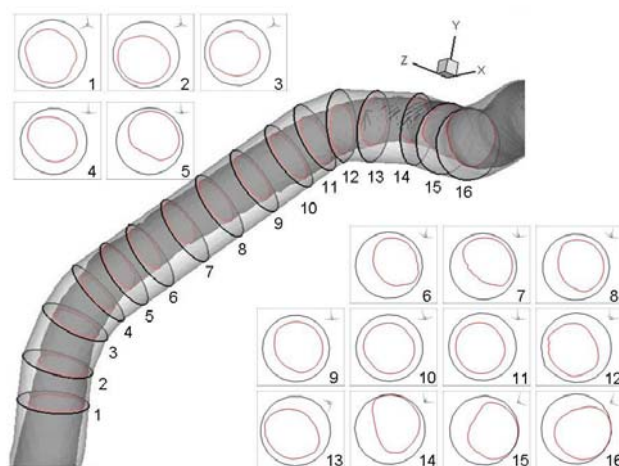


Fig. 6 Comparison between the stented artery, and the artery with developed restenosis for $p_{max} = 2 \cdot 10^{-4}$ m

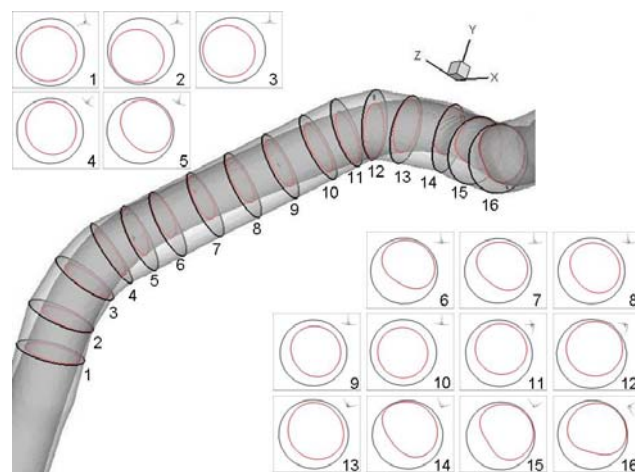


Fig. 7 Comparison between the stented artery, and the artery with developed restenosis for $p_{max} = 10^{-4}$ m

IV. CONCLUSION

Applying CFD methods, the flow simulations in stented LAD have been performed. Regions of permanently low WSS and thus especially prone to intimal proliferation have been localized. According to this results, a simple restenosis development model has been used to obtaining the shape of the obstructed artery. The quasi-static approach to the endothelial growth applied in this work seems to be justified by the fact that characteristic time scale of the blood flow (seconds) is by several orders of magnitude smaller than the time of growth of restenosis. In the proposed model, the value of the maximal displacement of the wall points in each step of the growth simulation is arbitrarily assumed, without any direct connection with the real dynamic of the studied phenomena. In spite of this obvious weakness, this model seems to be quite successful in predicting the sequence of shapes that might be attributed to the consecutive stages of the restenosis. Numerical computations demonstrate also that the interplay between geometry and flow can lead naturally to emergence

of the “candy-wrapper” structures. On the other hand, even if predicted forms of restenosis look realistically, the actual dynamics of the process is completely missing. The real and clinically useful prediction (if possible at all) might be provided only by a full model which accounts for cellular physiology and its full (not only mechanical) interaction with the blood flow. To the author’s best knowledge we are still quite far way from such model.

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