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Influence of proximal drug eluting stent (DES) on distal bare metal stent (BMS) in multi-stent implantation strategies in coronary arteries

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ABSTRACT

The aim of this study was to investigate the drug distribution in arteries treated with DES-BMS stenting strategy and to analyze the influence of proximal DES on distal segments of BMS. A straight artery model (*Straight Model*) and a branching artery model (*Branching Model*) were constructed in this study. In each model, the DES was implanted at the proximal position and the BMS was implanted distally. Hemodynamic environments, drug delivery and distribution features were simulated and analyzed in each model. The results showed that blood flow would contribute to non-uniform drug distribution in arteries. In the *Straight Model* the proximal DES would cause drug concentration in BMS segments. While in the *Branching Model* the DES in the main artery has slight influence on the BMS segments in the branch artery. In conclusion, due to the blood flow washing effect the uniformly released drug from DES would distribute focally and distally. The proximal DES would have greater influence on the distal BMS in straight artery than that in branching artery. This preliminary study would provide good reference for atherosclerosis treatment, especially for some complex cases, like coronary branching stenting.

1. Introduction

1.1. Background and problem

Drug eluting stents (DES) supports the narrow artery to its original section and gradually releases certain pharmacologic agent (drug) to interfere restenosis. DES have demonstrated excellent effects in prevention of angiographic restenosis and therefore brought percutaneous coronary intervention (PCI) to a new stage [1,2]. Currently, commercially available DES can reduce restenosis rate to approximately 15–30%, compared to 30–60% after balloon dilatation [2–4].

However the DES is still far from perfect. Although the restenosis rate was successfully reduced by the introduction of the DES, it is not completely diminished [4]. Stenting treatment of stenosed coronary would result in arterial injuries including severe damage of the endothelium and initiate a complex cascade of inflammatory processes, which may lead to the development of in-stent restenosis (ISR). Many clinical and biological factors involved in the progression of restenotic lesions have been studied over the past few years. But the mystery behind the pathophysiological mechanisms is still unresolved [5–8].

Many studies have reported that postoperative problems after DES intervention, like restenosis and endothelial dysfunction, were likely to be focal [9]. But the problematic locations after stenting in specific cases were depended. Pedro A. Lemos and colleagues reported that after sirolimus-eluting stents (SES) intervention, edge restenosis occurred more frequently in the proximal than in the distal stent border [10]. However Shin et al. got opposite results that SES implantation may induce significant impairment of the endothelium-dependent vasomotor function in the distal and far distal portions of the treated vessel [11].

1.2. Hypothesis

The reasons for those focal problems are to be clarified. The authors hypothesized that flow induced non-uniformly distributed drugs (locally low dose or over dose) would conduct insufficient effect or impairment to local artery tissues. Although drug releases evenly from the stent, the drug deposition will be non-uniform due to the blood flow interference. The mechanic effect of longitudinal flow will deliver drugs to the distal segments or the distal branching

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arteries [12]. This distally delivering effect (DDE) may cause drug distribution non-uniform, either insufficient or overdoes in arterial segments.

But for diffuse lesions the DDE would become beneficial. Obata et al. [13] reported that less luminal lumen loss, greater minimal lumen area and less in-stent neointimal hyperplasia happened in BMS segments distal to a DES in DES–BMS group when compared with BMS–BMS group. This result was likely related to DDE of blood flow.

Some numerical studies have been carried out to investigate hemodynamic features and drug delivery patterns at coronary bifurcations. For example, Demosthenes et al. investigated flow patterns at stented coronary bifurcations using ideal geometries models [37]; Chiastra et al. simulated hemodynamics of image-based stented coronary bifurcation [38]; Cutrì et al. investigated drug delivery patterns for different stenting techniques in coronary bifurcations [39]. However, to the authors' knowledge, no study has focused on analyzing drug delivery features of DES–BMS stenting strategy previously.

1.3. Objective

The objective of this study was to investigate the drug distribution in arteries treated with DES-BMS stenting strategy. We then numerically simulated drug delivery features of DES–BMS strategy in two typical models, namely the *Straight Model* and the *Branching Model*.

1.4. Advantages and clinical significance

The purpose of this study was to investigate the drug distribution in arteries treated with DES-BMS stenting strategy, particularly to investigate the influence of proximal DES on distal segments of BMS. The results would provide good reference for atherosclerosis treatment, especially for some complex cases, like diffuse lesions treatment and coronary branching stenting.

2. Methods

2.1. Models

Two simplified 3D models were constructed using computer-aided design software, SolidWorks, namely the *Straight Model* and the *Branching Model*. Both the two models were idealistic and gave the general features of stenting in straight and branching arteries. The two models represented the blood domains in the arteries after stenting. The stents in the two models were simplified and resembled general geometries rather than specific ones. All stent struts were supposed to be fixed on the arterial inner wall (outer wall of the two models for computation). The diameter of the main vessels in two models is 3*mm*, referring to the typical diameter of the left anterior descending coronary [14]. The side vessel in *Branching Model* was 2.5 mm in diameter. Two stents were deployed into each model. In the *Straight Model*, two stents (S1, S2) were implanted adjacently, with every stent 12 *mm* in length. In the *Branching Model*, one stent (B1) with 12 mm in length and 3 mm in diameter was implanted in the main vessel and the other stent (B2) with 9 mm in length and 2.5 mm in diameter was implanted distally to the branching. All stents in the two models had 0.15 mm × 0.15mm cross-sections. Both the main vessel and the side branching vessel were extended axially to ensure sufficient length for exit flow to be stabilized (Fig. 1).

To quantitatively analyze the influence of DES on distal BMS, series of areas in the stenting segment were defined. In the *Straight Model*, series of faces along the artery were selected, including 6 faces (S1-1 to S1-6) in the DES and 6 faces (S2-1 to S2-6) in the BMS. In the *Branching Model*, also series of faces were selected, including 6 faces (B1-1 toB1-6) in the DES and 6 faces (B2-1 to B2-6) in the BMS.

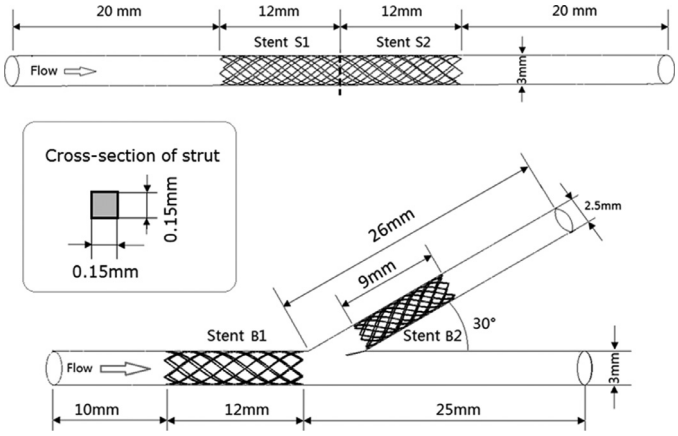

Fig. 1. The *Straight Model* (up) and the *Branching Model* (bottom).

2.2. Assumptions

In the present study, blood was assumed to be homogeneous, incompressible Newtonian fluid [15–17]. Blood viscosity $\mu = 3.5 \times 10^{-3}$ kg/m s and density $\rho = 1050$ kg/m^3.

2.3. Governing equations

The numerical simulations were based on the three-dimensional incompressible Navier-Stokes equations:

$$\rho\left(\vec{u}\cdot\nabla\right)\vec{u} + \nabla p - \mu\Delta\vec{u} = 0 \tag{1}$$

$$\nabla\cdot\vec{u} = 0 \tag{2}$$

and the mass transport equation:

$$\frac{\partial C}{\partial t} + \left(\vec{u}\cdot\nabla\right)C = D\nabla^2 C \tag{3}$$

where $\vec{u}$ and p represent fluid velocity vector and the pressure respectively. C is the concentration of the drug. D is the diffusion coefficient of the drug (sirolimus) in blood flow.

2.4. Boundary conditions for blood flow simulation

(1) *Inlet*: Uniform inflow velocity profile for the axial velocity component and a zero transverse velocity component were used in the numerical simulation [40]. According to the study by Ofili et al. [14], we chose 273 as Reynolds number (Re) in the present simulation, and hence the inflow velocity applied at the inlet was 0.3 *m/s*.

(2) *Outlet*: Outflow flow condition was used at the outlets of two models. For *Branching Model*, the flow ratio through the side branch was estimated as follows [18]:

$$\frac{q_{D2}}{q_{D1}} = \left(\frac{d_{D2}}{d_{D1}}\right)^{2.27} \tag{4}$$

with q_{D1} and q_{D2} the flow rate through, d_{D1} and d_{D2} the diameters of the branches. Then the flow ratio through the main vessel and the side branching vessel was 3:2.

(3) The vessel wall was assumed to be rigid and non-slip [19,20].

2.5. Boundary conditions for drug transport simulation

As drug deposition occurs less via contact between drug coating and the arterial wall than via flow-mediated deposition [21], we only simulated the drug transport in the flowing blood in the present study.