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Drug deposition in coronary arteries with overlapping drug-eluting stents

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ABSTRACT

Drug-eluting stents are accepted as mainstream endovascular therapy, yet concerns for their safety may be under-appreciated. While failure from restenosis has dropped to below 5%, the risk of stent thrombosis and associated mortality remain relatively high. Further optimization of drug release is required to minimize thrombosis risk while maintaining therapeutic dose.

The complex three-dimensional geometry of deployed stents together with the combination of diffusive and advective drug transport render an intuitive understanding of the situation exceedingly difficult. In situations such as this, computational modeling has proven essential, helping define the limits of efficacy, determine the mode and mechanism of drug release, and identify alternatives to avoid toxicity.

A particularly challenging conformation is encountered in coronary arteries with overlapping stents. To study hemodynamics and drug deposition in such vessels we combined high-resolution, multi-scale ex vivo computed tomography with a flow and mass transfer computational model. This approach ensures high geometric fidelity and precise, simultaneous calculation of blood flow velocity, shear stress and drug distribution.

Our calculations show that drug uptake by the arterial tissue is dependent both on the patterns of flow disruption near the wall, as well as on the relative positioning of drug-eluting struts. Overlapping stent struts lead to localized peaks of drug concentration that may increase the risk of thrombosis. Such peaks could be avoided by anisotropic stent structure or asymmetric drug release designed to yield homogeneous drug distribution along the coronary artery and, at the least, suggest that these issues need to remain in the forefront of consideration in clinical practice.

1. Introduction

Drug eluting stents (DES) suppress neointimal hyperplasia and reduce angiographic restenosis seen in their bare metal stent (BMS) counterparts, but are not free of these disease processes [1–4]. DES angiographic and clinical restenosis increase with lesion complexity, and especially when multiple and overlapping stents are implanted [5]. The use of multiple stents and the intervention on long lesions virtually necessitate stent overlap, and is indeed present in more than one in three patients undergoing percutaneous coronary intervention (PCI) [6,7]. Overlap is the one major category of interventions where new designs have not had as great an impact as seen in other use domains [8–10]. While some investigators have reported the safety and effectiveness of overlapping DES being comparable to those experienced with single long or multiple short stents [11–13], more recent publications have raised concerns about negative outcomes [14–18]. Regardless of stent type, stent overlap has been associated with increased in-stent restenosis (ISR) and lumen loss due to delayed healing and increased inflammation [6,19,20].

Stent overlap interferes with the two major goals of placement optimization – reduction in interference with luminal flow and minimization of mural injury. It is simply impossible to have complete apposition without exacerbating vascular injury, and/or minimal vascular injury without significant alteration in arterial hemodynamics. Stacking of stents creates regions of stagnation, separation and recirculation, the extent of which depends on stent geometry, asymmetric change of stent cell structure due to implantation and relative geometric configuration of overlapping struts [21–23]. These effects may result in wide variations in mural drug concentration with areas of depletion and excessive concentration [22,24] exactly where precise control of drug delivery and retention is needed most – in the areas of injury. Overlapping struts or multiple struts in close proximity may increase the risk of local

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cytotoxicity, persistent inflammation [25], amplification of thrombogenic effects as a hypersensitivity reaction of the local vasculature to a specific polymer and/or drug [25,26], stent thrombosis and in-stent restenosis [6,21,27] as a consequence of increased arterial injury, poor endothelization and delayed healing [18,25,28].

The issues are thus profoundly complex, as we must now account for a balanced integration of drug delivery, vascular injury and flow disruption – considerations that defy intuition and are too costly to embrace in all its permutations in any experimental setting. This situation calls for a computational modeling approach with which the number of parameters as well as their scope can be reduced to experimentally tractable sizes.

Previous computational models have employed isolated struts devoid of complete designs, theoretical constructs and primarily two-dimensional systems [21,24,29,30]. While they make a point, they fail to integrate the complete interactions between adjacent struts and the limitations imposed by real systems. More intricate designs of strut cells provide stents with more flexibility and ease of deployment and enhance the apposition even in case of stent overlap. However, in the presence of complex target lesions, malposition of struts is more pronounced especially in case of overlap, which results in greater disruption of near-wall flow [31]. Thus, simple consideration of two-dimensional primary systems, e.g. [24,29,30], will not allow for accurate modeling of the three-dimensional patterns of violated flow in arteries with overlapping stents.

Here we present a combined experimental and computational framework for the determination of hemodynamics and drug elution in stented arteries. Following a methodology we have developed and previously described in detail [32], we resolve the precise three dimensional geometry of stented arteries from microscale computed tomography data, ensuring high geometric fidelity both at the whole stent as well as at the individual strut scale. In conjunction with computational modeling, this allows prediction of drug distribution and deposition in anatomically accurate arteries under physiologic and pathophysiologic flow conditions. We show that taking into account the relative positioning of overlapping struts as well as arterial deformation warrants more realistic estimation of drug uptake by the tissue and highlights several hemodynamic and consequent pharmacodynamics outcomes which are the predecessors of reported clinical events.

2. Methods

2.1. Ex vivo preparation of model: Stent implantation, vascular corrosion casting

The left coronary artery of an ex vivo porcine heart was cannulated, and an interventional cardiologist implanted two absorbable magnesium alloy scaffolds of 10 mm length and 3 mm diameter (Biotronik AG, Bülach, Switzerland) under angiographic guidance. Care was taken to ensure reproducible 20% overlap of the stents. Note that in the computational model the scaffolds are treated as permanent drug eluting stents (see Section 2.3).

A radio-opaque casting material was prepared by mixing the low-shrinkage epoxy-based Biodur E20 resin (Biodur Products GmbH, Heidelberg, Germany) and iodine-saturated methyl ethyl ketone solvent. Using a pneumatic apparatus, the casting material was injected under physiological pressure of 90 mm Hg (120 mbar) to accurately capture the arterial tree. The heart was maintained at room temperature for 36 h, and then macerated for 12 h at 55 °C in a 7.5% w/v solution of potassium hydroxide. The final product was rinsed with water several times to remove remaining adherent tissue.

A more detailed description of the ex vivo preparation can be found in [31,32].

2.2. Scanning and image processing: μCT imaging of casts, segmentation and registration

The overall geometry of the arterial tree was captured using micro-computed tomography (μCT 80, Scanco Medical AG, Brüttisellen, Switzerland) with an isotropic voxel size of 74 μm (energy 70kVp, integration time 300 ms, tube current 114 μA, and two times frame averaging). The stented arterial segment was dissected and re-scanned (μCT 40, Scanco) with an isotropic voxel size of 6 μm (energy 70kVp, integration time 300 ms, tube current 114 μA, and two times frame averaging) to obtain higher resolution images. This strategy enabled us to resolve the individual stent struts as well as the overall arterial geometry while keeping scan time and associated costs at bay.

To partly suppress noise in the raw μCT volumes, a constrained 3D Gauss filter was applied ($\sigma = 1.2$, $s = 1.0$). Using a semi-automatic, intensity-based approach in Avizo 6.2 (Visualization Sciences Group SAS, Merignac, France), both μCT datasets of low and high resolution were independently segmented to obtain the lumen geometry. The resulting 3D geometry was exported to Geomagic Studio 12 (Geomagic, Inc., Morrisville, NC, USA), wherein the high resolution geometry of the stented segment and the lower resolution remainder of the arterial tree were registered and merged. Assuming 500 μm as a nominal value of a coronary artery wall thickness (smaller than human vascular thickness [33]), the vascular wall was generated by numerical expansion of the segmented lumen boundary. The obtained geometry was exported in STL format for subsequent computational grid generation.

2.3. Computational set-up and governing equations

ANSYS ICEM CFD (ANSYS, Inc., Canonsburg, PA, USA) was used to generate a computational grid of approximately 85 million tetrahedral elements in the merged geometry. A sequential CFD and mass transfer model was applied to conduct steady-state blood flow and mass transfer analysis for determining the blood velocity inside the artery and drug distribution in the lumen and the arterial wall. The following mass and momentum conservation equations were solved inside the lumen:

$$\nabla .\ \vec{V_l} = 0 \tag{5.1}$$

$$\rho\left(\vec{V_l}.\nabla\vec{V_l}\ \right) = -\nabla P + \nabla.\left(\mu\ \nabla\vec{V_l}\right) \tag{5.2}$$

where $\vec{V_l}$, ρ, P and μ are the blood flow velocity vector inside the lumen, density, pressure and dynamic viscosity, respectively. Blood was modeled as a non-Newtonian incompressible fluid with constant density of 1050 kg/m^3 and shear-dependent dynamic viscosity according to the Carreau model [34]. Blood was assumed to enter the coronary artery at a flow rate of 0.95 mL/s at the ostium [35]. No slip boundary conditions were set at the stent wall, while on the vessel wall the transmural velocity of plasma was applied in the normal direction according to the pre-calculated luminal pressure distribution and resistance of the tissue excluding endothelial resistance as explained in [36,37]. Murray's law was applied at the outlets, to where the outlet with the largest diameter was set to 70 mm Hg relative pressure, and the remaining outlets were assigned outflow rates according to their cross-sectional area [32,38]. Drug transport inside the lumen was determined by the advection-diffusion equation

$$\vec{V_l}.\nabla C_l = D_l.\nabla^2 C_l \tag{5.3}$$

where C_l is the drug concentration within the fluid domain and D_l denotes the diffusivity of the drug. Paclitaxel served as the model drug, with its diffusivity of 3.89×10^{-11} m^2/s in blood [39]. Zero drug concentration was assigned at the ostium. Open boundary conditions as well as