A multiscale mechanobiological model of in-stent restenosis

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Introduction

Arterial injury due to surgical interventions such as stenting initiates a complex cascade of inflammatory events within the arterial wall which ultimately lead into the development of intimal hyperplasia and arterial stenosis. Accumulation of mitogens, disruption of endothelial cells (ECs) and their denudation and also changes occurring within the extracellular matrix (ECM), specifically within the basement membrane, have been found to be the key regulators of medial vascular smooth muscle cells (VSMCs) activation, migration and neointimal growth [1]. Computational modelling can be used as a means to model the biological response of arteries to different stent designs using mechanobiological models whereby the mechanical environment may be used to dictate the growth and remodelling of vascular cells.

In this study a mechanistic multiscale mechanobiological model of in-stent restenosis using finite element models and agent based modelling is presented which allows quantitative evaluation of the ECM turnover following stent induced arterial injury and the subsequent development of in-stent restenosis.

Materials and Methods

A mechanobiological modelling framework was developed which comprises of two main coupled modules, (i) a module based on finite element method (FEM) that quantifies stresses to determine the level of arterial damage due to surgical intervention (ii) a biological modelling module based on a lattice free agent based model (ABM) that simulates the key responses of VSMCs and ECs, i.e. migration, proliferation, and ECM degradation and synthesis in response to the mechanical damage quantified using the FE analysis. The simulation starts in the FE module where the value of the initial damage is quantified and is transferred to the ABM where the growth of VSMCs is simulated. The measured stresses within the arterial wall were correlated to a damage level index ranging from 0 to 1. Damage upregulated MMP synthesis by VSMCs and as a result increased ECM degradation which ultimately caused activation of the medial VSMCs. Full endothelial denudation was assumed in the site of injury. The activated VSMCs proliferated and synthesised ECM within the arterial lumen leading to stenosis.

Results and Discussion

Following arterial damage due to high stent induced mechanical stresses, neointimal growth started with degradation of ECM by MMPs which were upregulated due to the damage accumulation, see Fig. 1. The neointimal growth continued until full re-endothelialisation occurred and ECM value increased to normal values. The neointimal growth dynamics predicted by the model was consistent with the findings of *in-vivo* studies such as [2]. The model results on collagen changes were found to be consistent with the outcome of organ culture studies on damaged human saphenous vein which showed that although in the first 2 days following injury there was a significant increase in degradation compared to uninjured veins, at days 12-14 there was no significant difference in degradation when compared to healthy tissue [3].

The model demonstrates that there exists a direct correlation between the stent deployment diameter and the level of in-stent restenosis. In addition, investigating the influence of stent strut thickness using the mechanobiological model reveals that thicker strut stents induce a higher level of in-stent restenosis due to a higher extent of arterial injury. The presented model has been successfully applied to capture remodelling of vascular grafts and also in-stent restenosis as previously published [1,4].

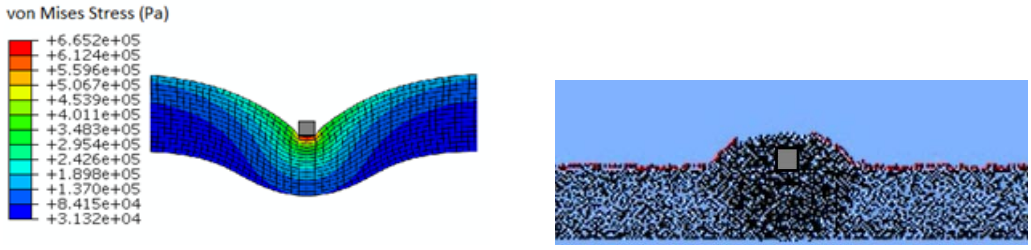

Figure 1. (Left) Axisymmetric FE model of a stent strut expanded in an artery and (right) the ABM consist of VSMCs in the arterial wall and ECs lining the lumen of the artery simulating the response of artery to stent induced stresses and injury.

Conclusion

In this study a mechanistic multiscale mechanobiological model using agent based models coupled with FE analysis was used to decipher the role of ECM turnover and endothelium in development of in-stent restenosis. The mechanobiological model allows new hypotheses on the mechanisms underlying the development of in-stent restenosis to be tested quantitatively and hence helps to generate key knowledge and insights into the mechanisms underlying the pathophysiology of in-stent restenosis. Specifically, the model corroborates the hypothesis that changes occurring within the collagen matrix following stent induced damage due to VSMC-collagen interaction play a key role in the long-term outcome of stent deployment procedures.

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