AN *IN-SILICO* INVESTIGATION INTO THE INFLUENCE OF ENDOTHELIAL DENUDATION ON THE PROGRESSION OF IN-STENT RESTENOSIS

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Introduction

Cardiovascular diseases are a major cause of death worldwide, in Europe coronary atherosclerosis accounts for about 20% of all cardiovascular disease [1]. One common treatment for atherosclerosis is endovascular stenting, where a metallic mesh tube is expanded within a stenotic region of a vessel to restore normal blood flow conditions. A major limitation of stenting is in-stent restenosis, whereby vascular smooth muscle cells (VSMCs) proliferate into the lumen over time, re-blocking the vessel [2]. This response may be relatively mild, or may be severe enough to require a second intervention [2].

It has been established that there is a strong correlation between the degree of mechanical injury, or tissue damage, caused by the stent to the vessel wall and the magnitude of the restenotic growth [3]. Furthermore the survival of endothelial cells (ECs) post-stenting is critical to inhibiting restenosis [4]. Therefore it is vital to further elucidate the mechanobiological mechanisms of in-stent restenosis to inform future medical device designs.

Materials and Methods

A 2-D, quarter symmetry, coupled finite element (FE) – agent based model (ABM) simulation environment is established where the FE model computes the mechanical response of a coronary artery and passes the results to an ABM. The ABM simulates the collective response of VSMC and EC agents, which are seeded in the vessel wall and along the lumen, respectively.

The stresses computed by the FE model are used to compute a damage value (from 0 to 1) which serves as the primary stimulus of a rule-set for VSMC agents in the ABM. If a VSMC agent is damaged then it takes on a synthetic, proliferative phenotype, otherwise it has a contractile phenotype and is quiescent. The rule set for the VSMC agents is governed by a set of coupled ordinary differential equations which also incorporate the local proteinase concentration and local extracellular matrix density for VSMCs [5].

EC agents are included in the model and have the effect of quiescing local proliferative VSMC agents. To examine the effect of the degree of EC denudation on the subsequent restenotic growth patterns, a parametric study was conducted which varied EC denudation from 30 to 60 ECs. Furthermore complete EC denudation of the vessel was investigated.

Results

The results show that the degree of EC denudation has a significant impact on the timeframe and magnitude of restenosis post-stenting, see Fig. 1.

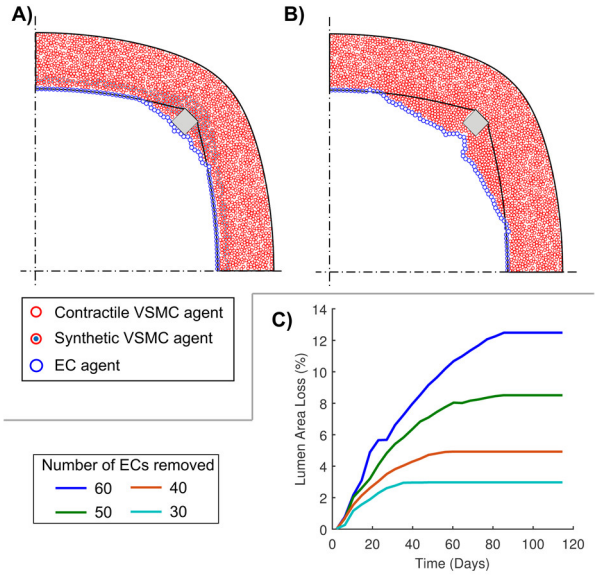

***Figure 1**: **A)** Restenosis predicted at 58 days with 30 ECs removed from the lumen. **B)** Restenosis predicted at 116 days with 60 ECs removed from the lumen. **C)** Plot of lumen area loss over time as a function of the total number of ECs removed from the lumen.*

Whilst removal of varying numbers of ECs does affect the restenosis timeline, even with full denudation the model still reaches a steady state condition predicting 26% lumen loss after 82 days.

Discussion and Conclusions

The current model uses VSMC proximity to ECs as a regulating factor, based on the assumption that nitric oxide (NO) released from ECs will quiesce nearby VSMCs (<60 μm). Future work will explicitly incorporate NO diffusion and be validated against cell experiments which have measured VSMC proliferation in the presence of different levels of NO. This framework will then be used to test various stent design parameters in order to inform, and optimize, next generation stent designs.

References

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