On the influence of non-uniform binding site density in determining arterial drug distribution following stent-based delivery

Javier Escuer(1), Bryan Scullion(2), Christopher McCormick(3), Sean McGinty(2)

[1]University of Zaragoza, Spain. [2]University of Glasgow, Glasgow, United Kingdom. [3]University of Strathclyde, Glasgow, United Kingdom

Introduction

Many mathematical models have been developed to try to understand drug release from stents and subsequent redistribution in the arterial wall[1]. Models have highlighted the importance of accounting for specific and non-specific binding[2], concluding that for sirolimus-eluting stents it is more important to sustain release than to increase dose. Modelling has also been used to explain how differences in the binding properties of paclitaxel and sirolimus lead to different retention, suggesting that the optimal delivery strategy is drug-dependent[3]. However, these conclusions have been made based on the assumption that the density of binding sites is *uniform* across the arterial wall. This is despite experimental evidence to the contrary, suggesting a variation across the wall thickness, with noticeable differences between and within the media and adventitia[4-5]. Target receptor densities for paclitaxel and sirolimus do not follow the same spatial pattern[5] and when components of disease are present, the picture is further complicated[6]. The aim of this study is therefore to investigate the role of non-uniform binding site density in determining arterial drug distribution following stent-based delivery.

Methods

We develop a 2D axisymmetric model of coupled stent drug release and redistribution in the arterial wall, similar to that employed by Bozsak et al.[3] but with two important differences: we model binding to both specific and non-specific binding sites, and we consider the density of binding sites to be a function of radial distance. The form of the function is derived from experimental data, by relating binding site density to the partition coefficient. We simulate a number of cases including different drugs and initial drug loadings.

Results

Whilst plots of time-varying normalised mean concentration are similar for the range of cases considered, our results highlight clear differences in spatially-varying concentration of bound and free drug in the arterial wall.

Discussion

By assuming a uniform density of binding sites across the wall, current models may be misguiding the optimal drug delivery strategy. Accounting for spatial variation in binding site density can have a significant influence on local drug concentrations and binding site saturation levels. Since the distribution of binding sites will vary from artery-to-artery and from patient-to-patient, our results

may help in the development of optimal drug delivery strategies and open up opportunities for personalised stent treatments.

Acknowledgements

We acknowledge funding provided by the Spanish Ministry of Economy, Industry and Competitiveness (Project DPI2016-76630-C2-1-R and grant BES-2014-069737).

[1]McGinty, S. *Math. Biosci*. **2014**,257:80-90.

[2]Tzafriri, A.R., et al. *J. Control. Release*. **2012**,161(3):918-926.

[3]Bozsak, F., et al. *Biomech. Model. Mechanobiol*. **2014**,13(2):327-47.

[4]Creel, C.J., et al. *Circ. Res*. **2000**,86:879-884.

[5]Levin, A.D., et al. *Circ. Res.* **2004**,101(25):9463-7

[6]Tzafriri, A.R, et al. *J. Control. Release*. **2010**,142(3):332-338.

Accepted manuscript of the following research output: Escuer, J., Scullion, B., McCormick, C., & McGinty, S. (2018). *On the influence of non-uniform binding site density in determining arterial drug distribution following stent-based delivery*. Abstract from 8th World Congress of Biomechanics, Dublin, Ireland.