Understanding the Influence of Stent Design on Arterial Drug Distribution and Effect through Computational Modeling

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Statement of Purpose: Drug eluting stent (DES) designs abound and yet the dependence of arterial patterns of drug distribution and effect on stent and coating design remains unclear. *In vivo* evaluation of DES is costly and time-consuming, rendering computational modeling a viable alternative for examining this question and leveraging data on approved devices. Computational models that match *in vivo* drug release and tissue content for existing DES designs can be used to predict associated distributions of drug and receptor mediated effects within stented tissue and to quantify the influence of design modifications. To this end we refined and validated a computational model of arterial pharmacokinetics (Tzafriri 2012) to also account for strut and coating geometry and used it to predict the influence of alterations in conformal coating design.

Methods: We developed a 2-dimentional computational model to evaluate the influence of coating design and drug elution kinetics on tissue distribution patterns relative to a representative strut pair. Strut dimensions (140x140 µm), interstrut distance (3.1 mm) and drug dose per metal surface area (140 µg/cm^2) correspond to published values for the CYPHER® Sirolimus-eluting Coronary Stents (Cordis Corporation, Bridgewater NJ). Model struts were assumed embedded in a 1.5-strut thick neointima, confirmed by histology of CYPHER stented arteries (Suzuki 200). Time dependent flux modeled drug elution from coated strut surfaces based on a fit of release kinetics (Fig 1, inset). Sirolimus transport in the tissue was modeled using validated equations of convection, diffusion and binding to receptors and non specific hydrophobic tissue sites (Tzafriri 2012). Sink boundary conditions accounted for luminal and periadventitial washout. Model equations were solved numerically using the finite element package COMSOL 3.5a.

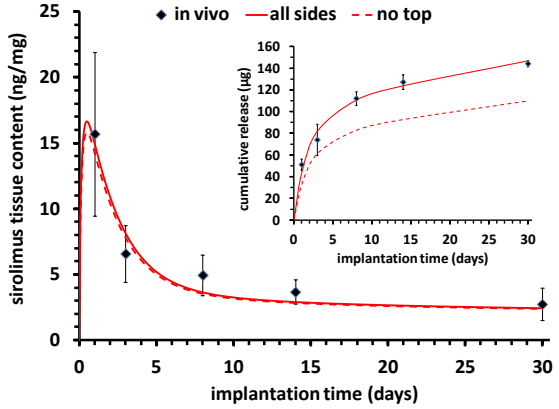

Figure 1. *In vivo* (diamonds) sirolimus tissue content and cumulative release (inset) versus model for fully coated struts (lines) and struts that are uncoated on lumen facing strut surfaces (dashes).

Results: Published *in vivo* kinetics of sirolimus release and tissue content in CYPHER stented porcine arteries (Tzafriri 2012) were closely matched by model predictions for fully coated struts (Fig 1). Near strut concentrations were 1-2 log orders larger than midway between struts (Fig 2A). Drug concentration gradients over-estimated gradients in bound receptors, a measure of drug effect (Fig 2B). Rendering strut tops uncoated reduced drug release while only minimally altering tissue content (Fig 1) and distribution patterns (Fig 2), speaking to strong luminal washout of drug in the neointima.

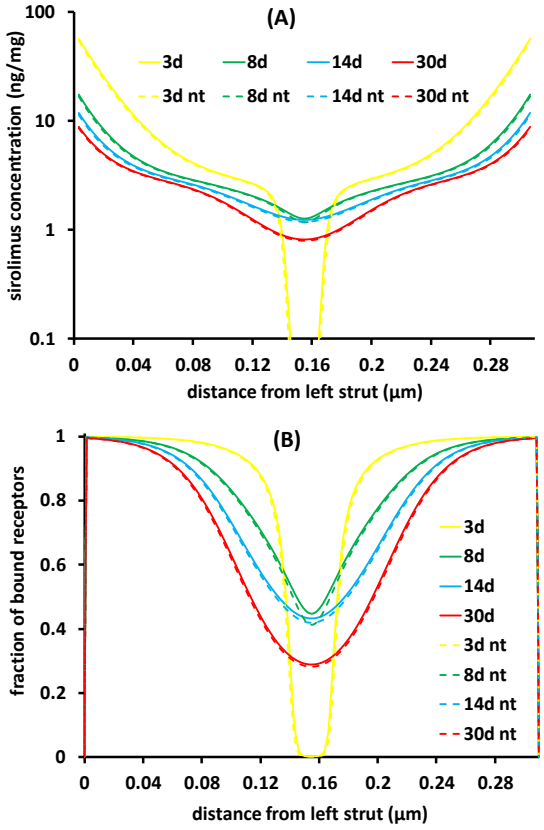

Figure 2. Predicted interstrut distribution of drug (A) and bound receptors for arteries stented with CYPHER (lines) or a hypothetical formulation that is uncoated on lumen facing strut surfaces (dashes, denoted as 'nt').

Conclusions: Computational modeling revealed significant drug effects in seemingly drug poor regions midway between struts and efficient washout of drug in the neointima that minimizes the contribution of lumen facing strut surfaces to tissue distribution of drug.

References:

Suzuki T. Circulation. 2001; 104:1188-1193.
Tzafriri AR. J Control Rel. 2012; 161: 918-926.