Drug Delivery from Coated Balloons: Drug Loading Density and Transfer Rate Determine Peak Tissue Content, Binding Determines Sustained Tissue Retention

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Statement of Purpose: Translating the success of drug eluting coronary stents to other vascular beds has been difficult. Angioplasty with drug-coated balloons (DCBs) is emerging as a potentially viable strategy demonstrating clinical efficacy at inhibiting restenosis after angioplasty in the lower extremities. DCBs are particularly attractive as they concomitantly open occluded vessels and deliver drug to target lesions, but avoid the risks of chronic inflammation and incomplete healing associated with permanent implants such as stents. Studies with DCBs have demonstrated a strong dependence of drug delivery and efficacy on drug type as well as on excipients that are used to bind the drug to the coating and facilitate drug transfer to the artery wall. Optimization by trial and error is inefficient and results in variable drug delivery and efficacy. As an alternative, we are developing mechanistic computational models of drug transfer and tissue distribution to optimize the development and preclinical evaluation of DCBs. Our use of such modeling based on measured tissue constants of binding and diffusion recently[1] explained the local pharmacokinetics of Zotarolimus-coated balloons (ZCBs), while highlighting the active role of the coating in minimizing luminal washout of the drug. This calibrated computational model is now used to examine *in silico* the sensitivity of tissue retention to the delivered drug load, its release kinetics and its non-specific tissue-binding interactions.

Methods: Model equations were implemented and solved numerically using the finite element package COMSOL (Comsol, Burlington MA). Drug (coating) transfer to the subjacent artery wall during balloon expansion was modeled as an exponentially declining mural flux[1] $A \cdot exp(-t/t_{1/2})/(t_{1/2} \cdot Z_{MW})$, where A is the load density per unit area of the coated drug, t is the time since expansion, $t_{1/2}$ is a half-life time of release, and Z_{MW} is the molecular weight of the drug. Simulations evaluated the effect of varying A and $t_{1/2}$ from published baseline estimates[1], respectively, 24 µg/cm^2 and 75 s. Though drug transfer theoretically ceases upon balloon deflation and retraction, the delivered coating is assumed to remain adherent and impede luminal clearance of drug[1], modeled as a zero flux mural boundary condition. Transferred drug molecules distribute in the artery wall by diffusion and binding, and are cleared at the peri-adventitial surface, modeled as a perfect sink boundary condition 500 µm away from the lumen. Simulations evaluated the effect of increasing the density of non-specific drug binding sites (B_{max}) relative to our published estimate for Zotarolimus (356 µM) while setting their affinity at the published value[1] (2.6 µM).

Results: Previously[1] we had shown that 30 s expansions of ZCBs with a release half life of 75 s provides a peak tissue content of 118 µM, and kinetics that are consistent with in vivo measurements (Fig 1A). Such coatings only release 33% of their load at the end of 30 s. Decreasing the half life of drug transfer from 75 s to 25 s or 7.5 s results in, respectively, a 2.3-fold or 3.9-fold higher drug transfer at the end of 30s of balloon expansion and commensurately higher predicted peak tissue contents (Fig 1A). Yet the benefit of faster drug transfer is predicted to be short lived, as higher transfer rates saturate deeper binding sites during balloon expansion (Fig 1B), thereby hastening the onset of adventitial clearance of excess free drug. Simulations that consider reformulated coatings with 2.3-fold and 3.9-fold load densities of transferable drug show similar transiently elevated tissue concentrations (Fig 2A) though saturation of binding sites at 30 s (Fig 2B) is less extended relative to the fast release cases. By contrast, increasing the density of drug binding sites in the tissue does not affect peak tissue content (Fig 3A) but dramatically reduces the rate of drug clearance as though a larger fraction of the transferred drug is bound at the end of balloon expansion, such binding is more localized to the delivery site (Fig 3B). Similar results were obtained for 180 s balloon expansions (not shown).

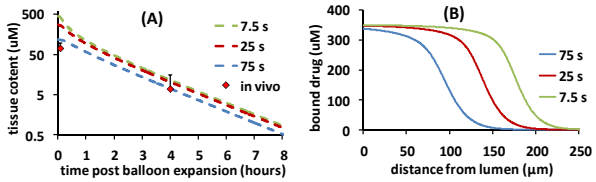

Figure 1 Predicted influence of drug transfer half life on tissue content (A) and the distribution of bound drug at 30 s DCB expansion (B). Panel A also depicts in vivo data (diamonds) for a 75 s drug transfer half life[1].

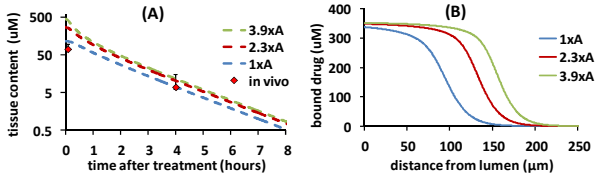

Figure 2 Predicted influence of transferable drug load density on tissue content (A) and the distribution of bound drug at 30 s DCB expansion (B). Panel A also depicts in vivo data (diamonds) for the baseline loading density[1] A=24 µg/cm^2.

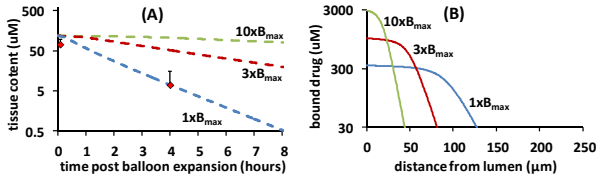

Figure 3 Predicted influence of binding site density on tissue content (A) and the distribution of bound drug at 30 s DCB expansion (B).

Conclusions: Simulations of a calibrated model explain that there is a limit beyond which increasing drug transfer through modulation of release half life or drug load provides diminishing returns due to earlier adventitial clearance of excess free drug. In such cases, strategies that extend drug retention, for example through optimization of drug binding, are expected to provide vastly favorable results.

References:

1. Kolachalama V. et al. Circulation. 2013; 127:2047-2055.