The Impact of Sex-Based Differences in Atherosclerotic Plaque on the Response to Drug Eluting Stent (DES) Implantation

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Introduction

Drug-eluting stents (DES) treat atherosclerosis by structurally opening diseased arteries followed by controlled release of anti-inflammatory drug to prevent in-stent restenosis. Because drug diffusivity and solubility depend upon material properties of the surrounding tissue or plaque, variations in plaque composition influence drug elution and dispersion.

It is well established that the atherosclerotic plaque and vessel structure in women are physiologically different from those in men [1-3]. For example, women's coronary plaque contains a greater proportion of cellular fibrous tissue, and less dense fibrous tissue, relative to coronary plaque in men. Men tend to have softer, more lipid-rich plaque than women, a trend which increases with age. Additionally, plaque composition also differs between pre-menopausal and post-menopausal women. Therefore, treatments with the same device may have different clinical outcomes. Thus, elucidating the extent of the impact of these differences may be important to ensuring the safety and effectiveness of DES implantation.

To elucidate sex-based differences in atherosclerotic plaque on drug elution from drug-eluting stents, we designed and combined computational and experimental approach to identify critical physiological differences between men and women and implemented these approaches using a model drug, tetracycline.

Methods

We developed plaque surrogates to approximate the various components of typical diseased vasculature illustrated in Fig. 1. Next, we measured the solubility and transport properties of tetracycline drug molecules in surrogates representing each of the plaque components with Haglund Method [4]. The surrogates were contacted with a concentrated drug solution such that only the surface was exposed to the drug solution. Figure 2 showed one example of diffusion profile of tetracycline. Based on the spatial distribution of the drug within the gel, both the solubility and diffusion coefficient of the drug can be determined.

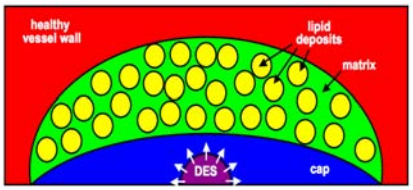

Figure 1. Schematic of DES strut in contact with plaque on the arterial wall illustrating the components of typical diseased vasculature.

These measured thermodynamic and kinetic properties were then used in a computational model to predict the release and distribution of drug in diseased vasculatures with varying plaque geometry and composition.

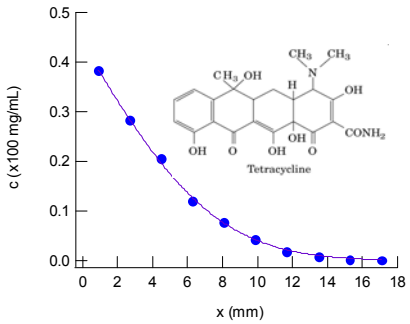

Figure 2. Example diffusion profile of tetracycline

Results

The diffusion curves of tetracycline in different plaque surrogates were measured and calculated (see Table 1) and utilized in the computational model to predict the transport behavior of the drug into the local vasculature as a function of time. Three compositions were investigated for the plaque core: 1) high density, 2) low density and 3) elevated lipid content.

Table 1. Diffusion coefficients of tetracycline in different plaque surrogate systems

	Diffusion Coefficients (cm^2/s)
Fibrous Cap	10^{-10}
Plaque Core	11×10^{-7} 4.4×10^{-7} 6.9×10^{-7}
Healthy Vessel	2.4×10^{-7}

By incorporating the measured properties into the computational model, we find that the release and distribution of drug is sensitive to the plaque tissue density, lipid content and geometry of plaque in the diseased vessel. These observations suggest that drug eluting stents may perform differently in men and women.

References

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