Endovascular Drug Delivery and Drug Elution Systems: First Principles

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KEYWORDS

• Controlled release • Drug-eluting stents • Drug-filled stents • Polymer-free stents • Diffusion • Dissolution • Distribution • Retention

KEY POINTS

- Because the effects of combination drug-eluting devices are multifactorial, designs abound and there is still room for innovation.
- Drug concentrations in tissues are predictive of effect and are not synonymous with delivered dose.
- Thus, although promising drug pharmacology is requisite, achieving adequate drug distribution and retention is key.
- Understanding and computationally modeling the determinants of drug release kinetics and tissue distribution can help further drive innovation at reduced cost.

INTRODUCTION

Endovascular drug-eluting stents (DESs) and more recently drug-eluting balloons, have revolutionized, and continue to revolutionize, the treatment of atherosclerosis in coronary and peripheral vasculature. The key has been to identify biologic agents that can counter the hyperplastic tissue responses to device expansion/implantation and to develop effective local delivery strategies that can maintain efficacious drug levels across the artery wall over the course of device effects (Fig. 1). This article reviews the various local drug delivery strategies implemented in approved and emerging endovascular devices, explains the mechanisms they use for drug release, and provides a mechanistic basis for relating drug release mode to arterial drug distribution and effect.

TISSUE PHARMACOKINETICS CAN LIMIT DRUG EFFICACY

Restenosis was recognized early as a clinical syndrome and a range of systemic pharmacologic therapies showed promise in vitro but failed in animals or humans. It became apparent (see Fig. 1) that the lesions to be combated were focal not diffuse and that systemic delivery not only exposed the great mass of unaffected tissues but diluted the desired target effects. Local therapy, once embraced, required a different mindset than other administration modes because issues of targeting, penetration, and retention now dominated rather than dosing. Administered dose is less important than these other forces, necessitating not simply a change in perspective but obviating qualitative, inferential approaches. The complexity of

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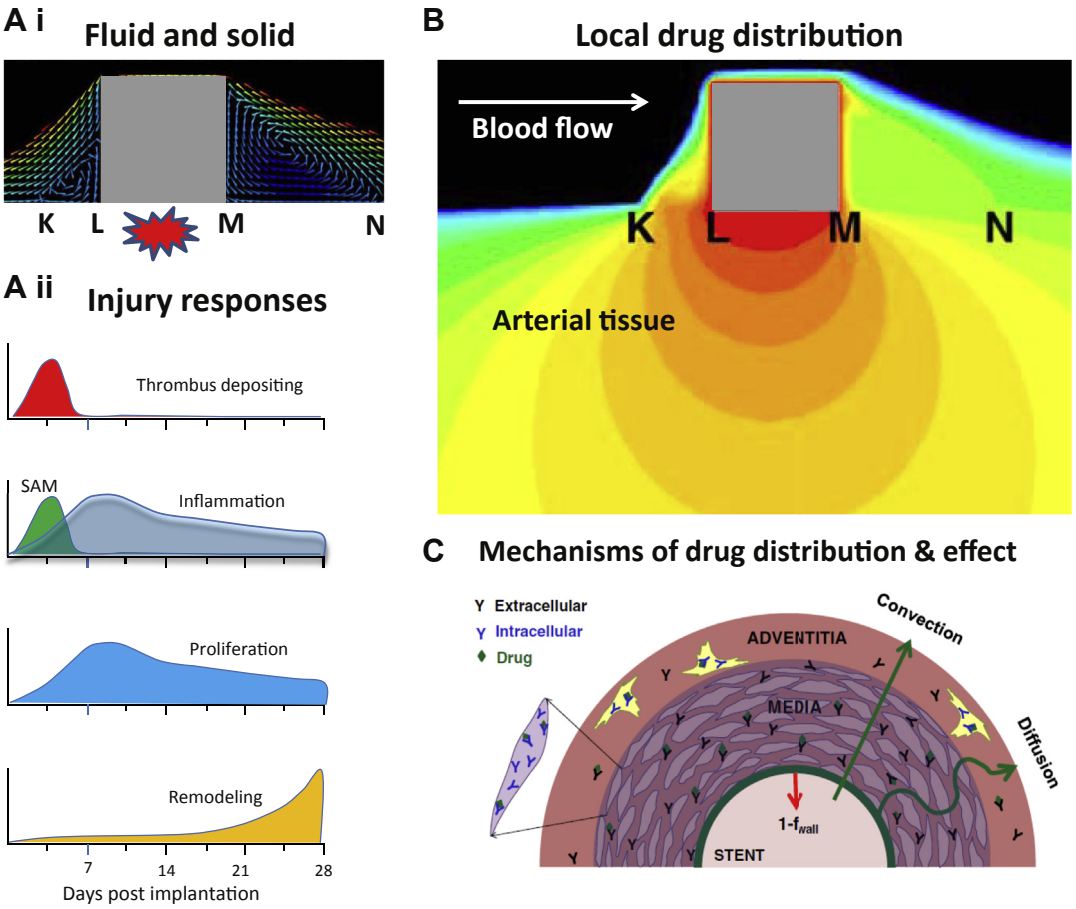

Fig. 1. Endovascular drug delivery occurs in the context of tissue response to mechanical forces. (*A.i*) Stent implantation mechanically injures the arterial wall and induces strut-proximal (K-L) and strut-distal (M-N) recirculation zones. (*A.ii*) This process triggers 4 phases of vascular repair: platelet-rich thrombus accumulates at areas of deep strut injury, accounting for most early luminal loss. Coincident with thrombus deposition, inflammatory cells, predominantly surface-adherent monocytes (SAM), are recruited to the injury site, both at and between the struts, before migrating into the neointima as tissue-infiltrating monocytes. Proliferation of smooth muscle cells and monocyte/macrophages within the neointima peaks at 7 days after implantation and continues at greater than baseline levels for weeks thereafter. Collagen deposition in the adventitia and throughout the tunica media and neointima leads to arterial shrinkage, or remodeling, causing compression of the artery on the stent struts from without. (*B*) Model predicted drug distribution surrounding the square strut depicted in *A.i*. Maximal concentrations (*red*) occur immediately beneath the strut, minimal concentrations (*blue*) occur between struts. (*C*) Depiction of the processes governing arterial drug distribution and effect: transmural drug convection along a pressure gradient, diffusion driven by concentration gradients, drug binding to nonspecific binding tissue proteins and intracellular receptors. (*Adapted from* [*A.i*, *B*] Kolachalama VB, Levine EG, Edelman ER. Luminal flow amplifies stent-based drug deposition in arterial bifurcations. PLoS One 2009;4:e8105, with permission; and [*A.ii*] Edelman ER, Rogers C. Pathobiologic responses to stenting. Am J Cardiol 1998;81:6E, with permission; and *Reproduced from* [*C*] Tzafriri AR, Groothuis A, Price GS, et al. Stent elution rate determines drug deposition and receptor-mediated effects. J Control Release 2012;161:920, with permission.)

the issues required experimental and computational modeling analyses, which created a quantitative framework by which to evaluate temporal and spatial extents of drug distribution in the arterial wall and correlate patterns with successful tissue effects (Fig. 2).

The challenge of optimizing local delivery increases dramatically given the innovations and complexity in modern stent designs, because tissue distribution after stent delivery tends to mirror stent coating geometry (see Fig. 2A). Different designs differentially affect luminal washout relative to drug diffusion in the tissue, and can result in peak drug concentrations and toxicity immediately adjacent to stent struts (see Fig. 2B). The disparity between peak and