

# Impact of transport and drug properties on the local pharmacology of drug-eluting stents

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**Drugs released from stents are driven by physiological transport forces, principally solvent-driven flow (convection) and random molecular agitation (diffusion). The relative strength of these two forces determines drug penetration and distribution in the arterial wall. Drug physicochemical factors can induce critical modulations to the primary distribution, both transiently and at steady state. Hydrophobic interactions and non-specific binding, for example, can both result in tissue drug concentrations severalfold above administered concentration. Drug interaction with native proteins may also interfere with drug transfer at the stent-artery interface. These transport forces and tissue interactions can induce local drug concentrations even at steady state to vary by one or more orders of magnitude over the span of a few cells.**

To account for significant local variations in drug concentrations following stent-based delivery, rational design of vascular delivery systems requires consideration of drug distribution and tissue interactions on a local, continuum basis. Continuum analysis adapts traditional pharmacokinetics to the local environment by supplementing discrete global parameters of drug content with continuous local values of concentration, transport and binding. The interplay of these parameters with local flux conditions and drug and tissue properties defines the local drug distribution in space and over time. This type of analysis may well become increasingly relevant given the trend toward stent-based drug therapy in cardiovascular care. (Int J Cardiovasc Intervent 2003; 5: 7–12)

**Keywords:** stent – drug-eluting – continuum analysis

## Introduction

Stent-based drug delivery is a powerful approach intended to mitigate the dramatic insults of balloon angioplasty, the immune response and hyperplastic growth of smooth muscle in the restenotic state. Its success is therefore empirically associated with effective delivery of potent therapeutics to the target site at a sufficient concentration, for a sufficient time and in a biologically active state.<sup>1</sup> The distribution of any pharmacological agent within the arterial wall is dependent principally on physicochemical transport forces (for example, convection and diffusion) and local pharmacology effects (for example, proteolysis and internalization). Physiological transport forces are the primary determinants of drug transport, and indeed the relative importance of diffusion- versus convection-mediated transport is commonly used as an index for predicting drug penetration and distribution.<sup>2,3</sup> In contrast, local tissue factors can induce secondary but critical modu-

lations to drug distribution, both transiently and at steady state. Hydrophobic interactions, for example, can result in tissue drug concentrations of more than an order of magnitude above applied levels.<sup>4</sup> Protein-mediated transport and target tissue ultrastructure exert their own modulating influences, affecting drug uptake at the stent-artery interface and accelerating circumferential diffusion.<sup>5</sup> Additionally, local pharmacology interactions become important for novel drugs such as growth factors.<sup>6,7</sup> These effects are far more intricate and can result in subtle time-dependent changes between the primary (determined by transport alone) and active drug distributions.<sup>8</sup> Most intriguingly, the complex kinetics of the interplay between proteolysis, drug internalization and receptor recycling produce well-defined regimens in which sustained delivery is more advantageous than bolus delivery or vice versa.<sup>9</sup>

An appreciation of the dynamic interplay of physiological forces, tissue architecture and drug pharmacodynamics is especially pertinent to local delivery because the close

juxtaposition of drug-eluting stents and vessel wall can lead to a wide spectrum of biologic activity ranging from the absence of pharmacologic effect to outright toxicity, depending on the microscopic local concentration. Indeed, because the geometrical designs of stents and therapeutic window of many potent therapeutics now being considered for local delivery impose strict constraints on feasible drug delivery profiles, it is not unreasonable to find this spectrum of biologic activity just a few cell lengths apart. While the precise relationship between tissue response to local concentration has remained baffling, it has been possible to predict the expected drug distribution profiles based on qualitative and semi-quantitative considerations. Using continuum pharmacokinetics, an approach based on discretizing the local arterial wall into elements of microscopic length scales, one can examine the intricacies of local drug-tissue interactions, much in the same way that traditional pharmacokinetic analyses have been successful in providing insights for systemic drug administration.<sup>10</sup> Continuum pharmacokinetics describes the local environment as a spatial continuity of transport and binding potential. By supplementing macroscopic predictions of mean tissue content with analysis of the evolution and variation of drug distribution at a very local scale, continuum pharmacokinetics is able to account for the myriad local transport and pharmacology effects. As a result, this analysis has led to remarkable insights on stent-based delivery, and may well become routine for the rational design of drug delivery systems.

## Outline of computational method

Drug transfer into the arterial wall is dependent principally on diffusion- and convection-mediated transport. Mathematically, this process is described by considering the change in drug content of a small arterial wall volume element due to the difference between the amount of drug entering and exiting that element because of these transport forces. The formal relationship is most naturally expressed using cylindrical coordinates, in which  $r$ ,  $\theta$ , and  $z$  specify a location in the radial, circumferential and longitudinal directions of the arterial wall, respectively. By convention, transport is taken as being vectorially positive when outward from the lumen. As such, the change in concentration  $C$  per unit time is governed by the classic transport equation:<sup>11</sup>

$$\frac{\partial C}{\partial t} = D_r \left( \frac{1}{r} \frac{\partial}{\partial r} \left( r \frac{\partial C}{\partial r} \right) \right) + D_\theta \left( \frac{1}{r^2} \frac{\partial^2 C}{\partial \theta^2} \right) + D_z \left( \frac{\partial^2 C}{\partial z^2} \right) - V_r \frac{\partial C}{\partial r} \quad (1)$$

where  $D$  is the diffusivity and  $V_r$  is the radial convective velocity. Drug within the arterial wall may bind to fixed tissue elements or remain free in solution within the tissue. Since only drug in solution is freely able to move, it is important to distinguish between the *solution drug concentration*, a measure of the free drug in solution, and the

*tissue drug concentration*, a measure of the total amount of drug (free and bound) per volume of tissue. Variable  $C$  in eqn (1) refers to the solution drug concentration in the arterial wall, and is related to tissue concentration  $C_{Tiss}$  by:

$$C(r, \theta, z, t) = \frac{C_{Tiss}(r, \theta, z, t)}{K(C, r, \theta, z, t)} \quad (2)$$

where  $K$  is a partitioning coefficient accounting for the concentration-, space-, and time-dependent specific and nonspecific binding processes. The spatial dependence accounts for the observation that drugs partition differently in different tissue elements. Hydrophobic drugs may favor the hydrophobic elastic laminae, for instance. Indeed, if binding kinetics are slow compared to drug transport, there can be a period when steady state is reached from a *transport* standpoint (that is, uniform concentration across the tissue), but not from a *binding* standpoint (that is, drug concentration continues to change).<sup>14</sup> Because of these multiple dependencies, compounds that exhibit significant partitioning are more intricate to model, especially in cases of rapidly fluctuating concentrations or if early transient distributions are desired. Several simplifications can be made however, first, when binding is much faster than transport, or when the time scale of interest is much longer than the time scale of binding (as is the case in drug delivery), the time-dependence of  $K$  can be neglected. Secondly, when binding is insignificant,  $K$  becomes negligible and can be included in a measure of 'fractional free space', the physical space accessible to drug molecules in the arterial wall. Thirdly, when the partitioning coefficient (or fractional free space) is constant across the arterial wall, as may be for small hydrophilic molecules,  $K$  becomes important only at the wall boundaries where it determines drug transfer into and from the luminal bulk phase. The intima and adventitia at these boundaries are effectively described as series resistors  $R_{int}$  and  $R_{adv}$ <sup>12-15</sup> and the movement of drug is described as drug fluxes  $J_{int}$  and  $J_{adv}$ :

$$J_{int} = \frac{1}{R_{int}} \left( C_{ev} - \frac{C_{im}}{K_{im}} \right) + V_r C_{ev}$$

and

$$J_{adv} = \frac{1}{R_{adv}} \left( \frac{C_{am}}{K_{am}} - \frac{C_{pv}}{K_{pv}} \right) + V_r \frac{C_{am}}{K_{am}} \quad (3)$$

where  $C_{ev}$ ,  $C_{pv}$ ,  $C_{im}$ ,  $C_{am}$ ,  $K_{pv}$ ,  $K_{im}$  and  $K_{am}$  are tissue drug concentrations and partitioning coefficients in the endovascular (*ev*) and perivascular (*pv*) spaces and in the media adjacent to the intima (*im*) and adventitia (*am*). The partitioning coefficient of the endovascular bulk phase is defined to be unity and is used as a relative measure for all other partitioning coefficients.

Mathematical models are often simplified and their validity demonstrated through dimensionless parameters. By grouping variables related by natural physical scales, dimensional analyses enable results calculated for one set of physical measurements to apply to others, allowing trends to be appreciated more clearly. A critical dimension-

less parameter in vascular biology is the Péclet number,  $Pé = V_r L / D_r$ , the ratio of convection to diffusion for an artery of thickness  $L$ . Physiological Péclet numbers range typically from 0.1 to 10. Larger  $Pé$  applies to drugs driven by convection and conversely, smaller  $Pé$  implies a greater diffusive influence.

## Results and discussion

### Extensive drug distribution heterogeneity

Computational models show that substantial drug concentration inhomogeneities persist for different strut placements and in all geometric directions (Figures 1(A–D)).<sup>2</sup> Indeed, radial washout is accompanied by steep circumferential gradients that are most significant near the struts and that decay outward before becoming more prominent again near the adventitia. While geometric constraints of strut placement can principally determine drug distribution, it is not the sole determinant of drug distribution, however. Both drug and tissue properties may dramatically affect local concentrations. For instance, between stent struts and close to the luminal surface, smaller hydrophilic drugs mix more readily with flowing blood, lowering local concentrations. Locally, hydrophilic tissue or injured endothelium may further enhance this washout. Thus, tissues deeper into the artery, away from the drug source, may actually have a *greater* net amount of drug than tissues closer to the drug source. Hydrophobic drugs manifest similar variation patterns but undergo less luminal and perivascular washout. As a result, they distribute more

fully in the vessel wall, with regions devoid of drug 60% smaller than those of hydrophilic drugs.

To illustrate the implications of these results for stent-based delivery, stents coated with sodium fluorescein were implanted in bovine arteries cannulated in a perfusion apparatus.<sup>2,13</sup> Drug delivery was allowed to reach a steady state before the extent and distribution of drug within the arterial wall was analyzed. Drug content assessed by bulk elution revealed a mean concentration of  $0.24 \pm 0.02$  mg/mL. However, this result neglected the extensive heterogeneity in drug concentration that was apparent by quantitative fluorescent microscopy (Figure 2(A)).<sup>16</sup> The average concentration measured by quantitative microscopy,  $0.22 \pm 0.03$  mg/mL, was identical to that determined by elution but the striking pattern of high and low drug zones corresponded to concentration variations spanning from 0.06 to  $> 0.97$  mg/mL (Figure 2(B)). The scale of this heterogeneity is even more remarkable considering that rapid diffusion of sodium fluorescein should dampen spatial gradients considerably compared to other potential therapeutic compounds which are much less hydrophilic. Together with the computational studies, these results demonstrate the importance of supplementing measurements of mean drug content with measurements of concentration variations at a very local scale.

### Transport effects

#### Diffusive versus convective considerations

Complex drug distribution profiles are intrinsically affected by arterial transport properties of each drug. In particular, the relative susceptibility of the drug to

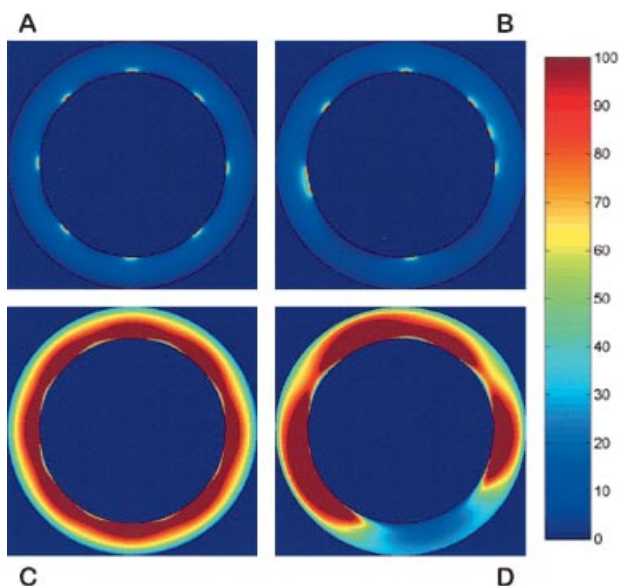


Figure 1

Large concentration variations resulting from stent-based drug delivery in a simulation modeling balanced convective and diffusive forces from eight-strut stents with homogeneous (hydrophilic (A), hydrophobic (C)) and inhomogeneous (hydrophilic (B), hydrophobic (D)) strut distributions. Scales are in dimensionless units.

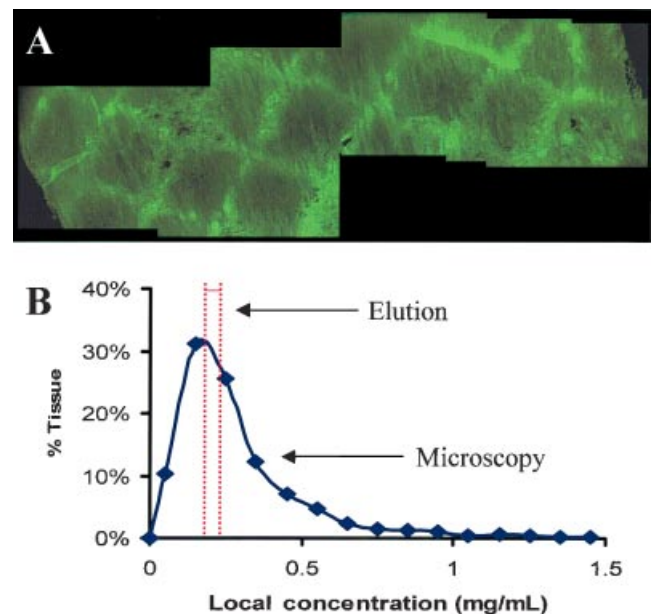


Figure 2

(A) *En face* image of fluorescein distribution at 200  $\mu$ m from the luminal surface of the bovine carotid artery. (B) Range of local tissue drug concentration distribution in the arterial wall as measured by bulk elution and quantitative fluorescence microscopy.

diffusion- and convection-mediated transport dictates the delicate balance between effective and ineffective delivery.<sup>2,3,17</sup> As shown in quantitative models of drug transport, drug distribution is best described using the Péclet number, a dimensionless parameter that reflects the ratio of convective to diffusive forces on drug transport. In computer simulations, the spatial variability in drug concentrations and mean drug concentrations near the intima are smallest and greatest respectively at low Péc. These results change minimally with increasing Péc while overall concentrations rise. At Péc ~ 10, where convective forces are approximately tenfold greater than diffusive forces, robust penetration into the arterial wall and decreased luminal washout maximize overall drug concentrations with minimal effects on intimal drug concentrations. With increasing susceptibility to convection-mediated transport, perivascular washout of drug predominates, consequently resulting in increased variability in drug concentration overall and decreased intimal and overall drug concentrations (Figures 3(A–B)). At the extreme where convection dominates exclusively, intimal and overall concentrations converge due to a streaming effect that results in drug being streamlined into alternating bands of radial high and low drug zones. Since only solubilized drugs freely diffuse, hydrophilic drugs are far more sensitive to these transport effects than hydrophobic drugs. Indeed, although hydrophobic drugs qualitatively manifest similar variation patterns, they accumulate far more and remain significantly closer to the intima than hydrophilic drugs (Figures 3(C–D)).

### Diffusive resistance

Endoluminal diffusive resistance in areas where the endothelium remains uninjured after stenting can significantly decrease concentration variations in the intimal region of the arterial wall for some drugs.<sup>12,13,18</sup> For example, in an eight-strut stent delivering drug with Péc ~ 1, transport resistance of 100 s/μm reduces intimal region concentration variation by 83% and throughout the arterial wall by 35% compared to arteries with denuded endothelium (Figure 4). This effect, however, is less prominent for drugs which move predominantly by convection. Moreover, computer simulations demonstrate that significant increases in luminal resistances beyond 100 s/μm do not lead to significant additional improvements in distribution, irrespective of Péc. Thus, optimizing balloon or stent design to minimize endothelial injury is likely to be valuable for drug delivery considerations only for small hydrophilic drugs.

### Drug physicochemical properties

#### Molecular weight and charge

The mechanisms by which drugs transport through the arterial wall are highly dependent on the size and charge of the drug. These physicochemical properties determine the predominant mode of transport and endoluminal resistance, and have been demonstrated by measuring the transport of anionic, cationic, and neutral dextrans across native and denuded rat carotid arteries.<sup>12</sup> Drug diffusivity

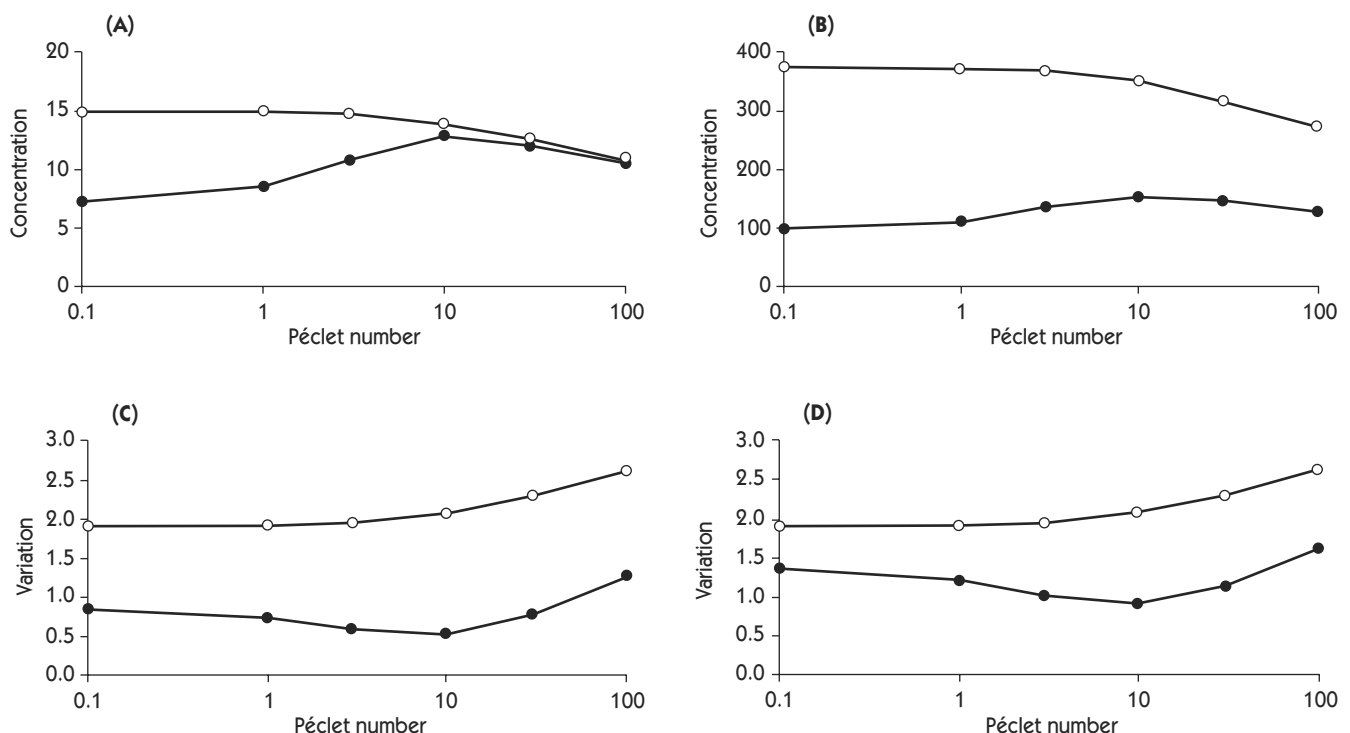


Figure 3

Mean drug concentration in the superficial layer (O) and throughout the arterial wall (●) for a homogeneously distributed eight-strut stent as a function of the Péclet number (Péc) for hydrophilic (A) and hydrophobic (B) drugs. Concentration variation (SD/mean) in the superficial layer (O) and throughout the arterial wall (●) for a homogeneously distributed eight-strut stent as a function of Péc, for hydrophilic (C) and hydrophobic (D) drugs.

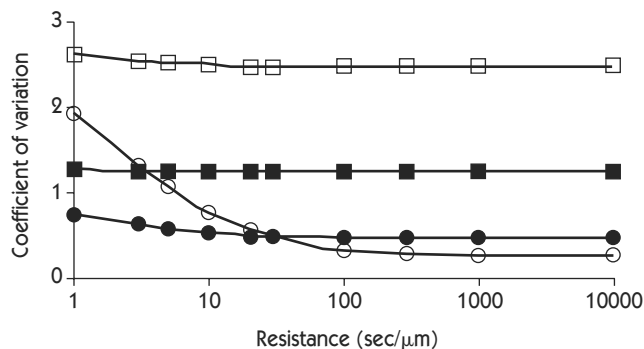


Figure 4

Effects of increasing endoluminal resistance on concentration variability for a symmetrically expanded eight-strut stent. For  $Pê \sim 1$ , endoluminal resistance decreases concentration variability in the superficial layer (O) more than throughout the arterial wall (●). For  $Pê \sim 100$ , endoluminal resistance has little effect on concentration variability either in the superficial layer (□) or throughout the arterial wall (■).

remained constant for neutral compounds at low molecular weights, and only fell significantly above 40 kDa (Figure 5). Cationic dextran diffusivity was found to be similar to the neutral compounds. However, anionic dextran diffusivity was 39.8% and 44.4% smaller than its neutral and cationic counterparts, respectively.<sup>2</sup> The effective resistance posed by the endothelium was measured for neutral compounds to increase 27.8-fold from 10 to 282 kDa, with a dramatic increase above 40 kDa (Figure 5). In terms of charge, resistance was 19.5-fold higher for neutral than cationic dextran, and 213-fold higher for anionic than cationic dextran.<sup>12</sup> These data suggest that one aspect of effective drug design might be through controlling either charge or molecular weight such that optimal arterial delivery is achieved.

### Partitioning

The arterial wall can serve as an effective drug reservoir for drugs that partition well to minimizing washout and regions of either sub- or supratherapeutic doses. Studies thus far with highly hydrophobic drugs demonstrate this enhanced dosing effect.<sup>4,19-21</sup> In one study, paclitaxel uptake in bovine carotids was quantified to examine these effects.<sup>4</sup> At equilibrium, paclitaxel concentrations greatly exceeded the applied dose, suggesting that paclitaxel binds to elements throughout the vessel wall (Figure 6(A)). In particular, paclitaxel was found to concentrate specifically in the intima and adventitia, reflecting the higher densities of binding sites in these regions. In the arterial media, binding sites densities were also inhomogeneously distributed, with a gradient extending inward from the intima and adventitia. As a result, paclitaxel deposition in these studies was dependent on site of administration, and nearly twofold greater with endovascular than perivascular application. Paclitaxel deposition was also time-dependent, suggesting that partitioning is highly dynamic (Figure 6(B)). Thus, the distribution of paclitaxel likely reflects an intricate combination of transport and binding events with inhomogeneous binding sites. These interac-

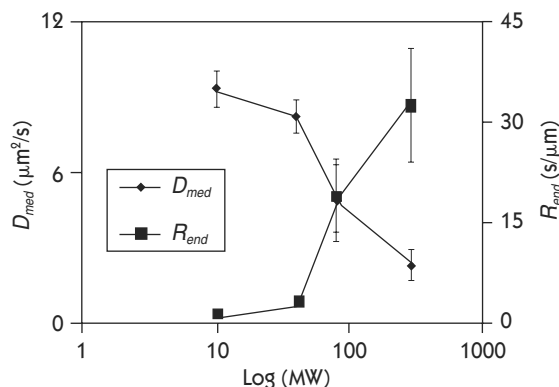


Figure 5

The effective diffusivity in the arterial media ( $D_{med}$ ) and the endoluminal resistance to transport ( $R_{end}$ ) as a function of dextran molecular weight.

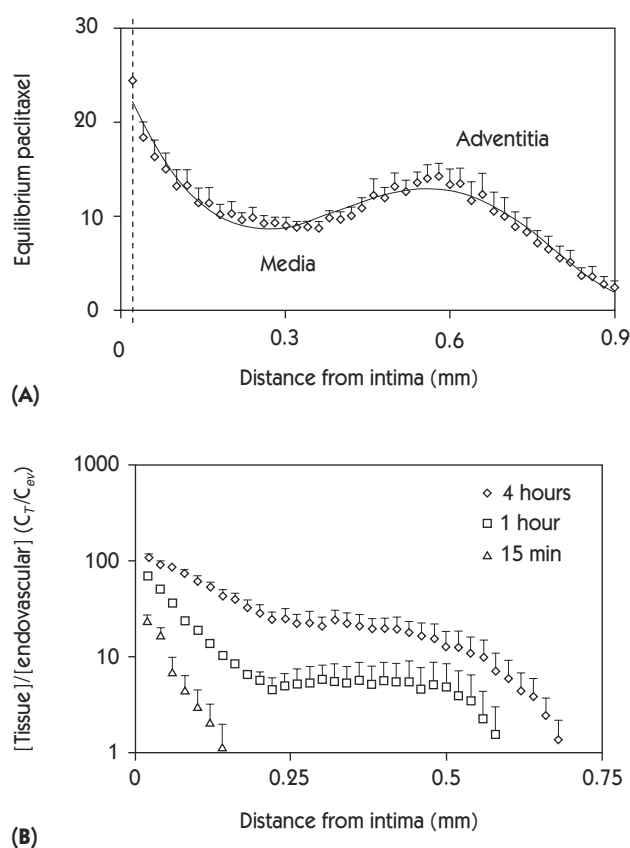


Figure 6

(A) Equilibrium distribution of paclitaxel in the arterial wall reveals drug uptake above and beyond administered concentration, and a spatial gradient of drug across and within the intima, media, and adventitia. (B) Tissue concentration normalized by the endovascularly applied concentration as a function of time in the presence of a physiological transmural hydrostatic pressure gradient of 90 mmHg.

tions must be considered particularly if perturbations to drug distribution due to transport occur on a timescale faster than the time for binding to reach equilibrium.

### Protein-mediated transport

Another layer of complexity is added when interactions of

drug with serum proteins are considered. In one study, protein-mediated transport of paclitaxel was characterized by determining, in the presence or absence of carrier proteins, drug solubility in aqueous solution, diffusivity in free solution and diffusivity in arterial tissues.<sup>5</sup> While the solubility of paclitaxel in aqueous solutions was increased in the presence of  $\alpha_1$ -acid glycoproteins, albumin and calf serum, its effective diffusivity in solution was reduced. More significantly, when paclitaxel was applied to cannulated bovine arteries in a flow system, drug deposition was more abundant at the tissue interface, with protein carriers tending to retain the drug in the lumen. Once within the tissue, proteins did not affect the rate at which drug traversed the tissue as the drug interacted with abundant fixed binding sites. These observations are likely to be important for modeling and predicting optimal dosing of highly hydrophobic compounds.

## Conclusion

With the rapid ascent of stent-based drug elution in the treatment of vascular diseases, important issues regarding drug distribution and targeting need to be addressed. Transport forces and drug physicochemical properties contribute in varying degrees to vascular drug distribution. Device proximity to target tissue thus does not assure adequate distribution, and a detailed grasp of local pharmacokinetics is a prerequisite for the rational design of drug delivery systems.

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