Physiological Transport Forces Govern Drug Distribution for Stent-Based Delivery

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Background—The first compounds considered for stent-based delivery, such as heparin, were chosen on the basis of promising tissue culture and animal experiments, and yet they have failed to stop restenosis clinically. More recent compounds, such as paclitaxel, are of a different sort, being hydrophobic in nature, and their effects after local release seem far more profound. This dichotomy raises the question of whether drugs that have an effect when released from a stent do so because of differences in biology or differences in physicochemical properties and targeting.

Methods and Results—We applied continuum pharmacokinetics to examine the effects of transport forces and device geometry on the distribution of stent-delivered hydrophilic and hydrophobic drugs. We found that stent-based delivery invariably leads to large concentration gradients, with drug concentrations ranging from nil to several times the mean tissue concentration over a few micrometers. Concentration variations were a function of the Peclet number (Pe), the ratio of convective to diffusive forces. Although hydrophobic drugs exhibited greater variability than hydrophilic drugs, they achieved higher mean concentrations and remained closer to the intima. Inhomogeneous strut placement influenced hydrophilic drugs more negatively than hydrophobic drugs, dramatically affecting local concentrations without changing mean concentrations.

Conclusions—Because local concentrations and gradients are inextricably linked to biological effect, our results provide a potential explanation for the variable success of stent-based delivery. We conclude that mere proximity of delivery devices to tissues does not ensure adequate targeting, because physiological transport forces cause local concentrations to deviate significantly from mean concentrations. (Circulation. 2001;104:600-605.)

Key Words: stents ■ restenosis ■ pharmacokinetics ■ drugs ■ arteries

Stent-based drug delivery provides an intriguing paradox wherein the biological motivation for drug use does not necessarily predict efficacy. Such drugs as heparin and dexamethasone inhibit smooth muscle cell proliferation in culture and intimal hyperplasia in animal models. Clinically, however, they have only mixed success in limiting thrombosis and often little effect in controlling intimal hyperplasia. Their effects in reducing intimal hyperplasia seem far more profound, and yet they have refueled enthusiasm for stent-based therapies. The question, then, is whether drugs that have an effect when released from a stent do so because of fundamentally different biological effects or because of different physicochemical properties and targeting.

This issue has profound importance beyond the treatment of proliferative vascular diseases. Because blood vessels pose an excellent model in which to study how local delivery and transport determine and correlate with observed biological effect, however, we sought to examine the limitations to the efficacy of stent-based drug delivery imposed by local pharmacokinetics. Both hydrophilic compounds, like heparin, and hydrophobic compounds, like paclitaxel, as delivered from coated endovascular stents were considered. We found that stent-based delivery leads to large Peclet number–dependent concentration variability. Although hydrophobic drugs exhibited more heterogeneous local tissue concentrations across the vessel wall than hydrophilic drugs, they achieved higher mean tissue concentrations and remained closer to the intima. The importance of acknowledging this difference between local and mean tissue concentrations becomes increasingly important as stent designs evolve to more complex geometries with inherent inhomogeneity in the circumferential and longitudinal distribution of stent struts. Because local drug concentrations and concentration gradients are inextricably linked to the biological effect of a drug, our results provide a potential explanation for the variable success of stent-based delivery.

Methods

Stent Delivery Devices

Palmaz-Schatz Crown stents (Cordis, Johnson & Johnson, 15×4 mm) were spray-coated with 33% w/wt fluorescein sodium/
ethylenediyvinylacetate copolymer (Elvax 40P, Dupont Chemical Co) dissolved indichloromethane. Bovine carotid arteries were obtained from aslaughterhouse, and cylindrical segments 2 to 4 cm long were cleaned,inspected for leaks, and cannulated. Drug-coated stents were balloon-expanded into cannulated artery segments at 12 atm. Stented arteries were positioned in an ex vivo perfusion apparatus and immersed in a perivascular bath of PBS (Sigma-Aldrich). PBS was circulated in an open loop at 0.6 to 0.7 mL/s and 100 mm Hg pressure to simulate flows in coronary arteries. After a 3-hour perfusion, arteries were cut in half transversely for bulk elution and imaging. Arteries were cryosectioned into en face slices 20 μm thick (Cryotome SME, Shandon). The length and width of each slice were measured to compute the slice volume (V_slice).

To convert fluorescence intensities to tissue concentration, separate arteries were incubated in serial dilutions of fluorescein for 48 hours and imaged with the identical setup. The average fluorescence intensities, and thus concentrations of regions corresponding to unit stent cells, were compared with bulk elution measurements. To convert fluorescence intensities to tissue concentrations, separate arteries were incubated in serial dilutions of fluorescein for 48 hours and imaged with the identical setup. The average intensity of a 40 000-square-pixel region was correlated with fluorescein concentration. This was then converted to tissue concentration by multiplying the former by the fractional free space available to fluorescein in the media, measured in separate equilibrium incubation experiments.

Computational Model

Transport in the arterial media is described by the convection-diffusion equation:

\[
\frac{\partial C}{\partial t} + V_r \frac{\partial C}{\partial r} + V_z \frac{\partial C}{\partial z} + D_r \nabla^2 C = \frac{1}{\eta_m \eta_q} \frac{\partial}{\partial \eta} \left( \frac{\partial C}{\partial \eta} \right) + D_z \frac{\partial^2 C}{\partial \eta^2}
\]

where C denotes local tissue drug concentration. Both diffusion (D_r, D_z) and convection (V_r, V_z) are directionally dependent. The only significant pressure drop occurs across the arterial wall, however, and therefore convection in all but the radial direction can be neglected. Hydrophobic drugs are modeled with a partition coefficient k(r), defined as the ratio of tissue to bulk phase concentration, which is dramatically different for hydrophilic and hydrophobic drugs and can be spatially dependent. The intima flux is

\[
J_n = \frac{1}{R_m} \left( \frac{C_{ev}}{\kappa_m} - C_m \right) - V_r C_{ev},
\]

where C_{ev} is the endovascular drug concentration and C_m and \kappa_m are the tissue drug concentration and partition coefficient in the media adjacent to the intima. The advective flux has a similar form.

Assuming a media thickness L and defining dimensionless variables \( \kappa = C/C_m \) and \( \eta = \eta/L = \zeta/L, \) \( \tau = D_t/L^2, \) the model can be reduced to a finite-difference form as:

\[
\frac{\Delta C_{mnq}}{\Delta \tau} = \frac{K_{mn-1,nq} + K_{mn+1,nq}}{2} + \frac{1}{\eta_{mn,q}} \frac{K_{mn-1,nq} - K_{mn+1,nq}}{2 \Delta \eta} + \frac{D_r}{\eta_{mn,q}^2} \frac{1}{(\Delta \eta)^2} \left( K_{mn-1,q} - 2K_{mn,q} + K_{mn+1,q} \right) - \frac{D_z}{\Delta \eta} \left( K_{mn,n-1,q} - 2K_{mn,n,q} + K_{mn,n+1,q} \right) - \frac{D_t}{\Delta \eta} \left( K_{mn,q-1} - 2K_{mn,q} + K_{mn,q+1} \right) \frac{K_{mn,n,q}}{\eta_{mn,q}^2}.
\]

Figure 1. A, Concentration profile obtained by bulk elution of serial en face sections. B, En face image of fluorescein distribution at 200 μm from luminal surface of bovine carotid artery.
where the only relevant transport parameters are now the dimensionless diffusivity ratios $D_u/D_r$ and $D_z/D_r$, and the transmural Peclet number, $Pe = V_r L/D_r$, the ratio of convection to diffusion. The dimensionless strut concentration, $C_{sd}$, was defined as the maximal exposed tissue dose. Experimental measurements and order-of-magnitude analysis suggest an anisotropic media diffusivity, $D_u' \approx 10D_r$ (data not shown). This result was implemented without loss of generality because the solution for other degrees of anisotropy can be obtained by scaling the $\theta$ and $z$ coordinates by appropriate factors.

**Simulation Parameters**

Stents were modeled as comprising variably spaced drug-eluting struts with steady zero-order release. Transmural Peclet numbers were from 0 to 100, spanning beyond the physiological range of drugs as determined from experiments previously performed with heparin$^{10,14}$ and paclitaxel$^{13}$. Drug entering the lumen was presumed to be washed out, resulting in the luminal condition $C_{ev} = 0$.

Endothelial denudation with stenting was assumed to reduce luminal resistance to $0 \, \text{s/\mu m}$. The perivascular condition was defined by an adventitial resistance, $R_{adw}$, of $5 \, \text{s/\mu m}$. Hydrophobic compounds have spatially dependent partition coefficients, and in this study, data accumulated with paclitaxel were used$^{13}$. To examine how inhomogeneous strut placement affects drug distribution, Monte Carlo simulations ($n=90$) were conducted by randomly placing struts in nonoverlapping positions. The concentration variability was then assessed by use of the coefficient of variation, defined as the standard deviation of local concentrations referenced to the overall mean concentration. All simulations were run to steady state, defined as a change in overall drug concentration of $<0.0005$ dimensionless drug units per second.

**Results**

**Concentration Variability**

We focused on the initial impact of local drug delivery on the arterial wall and drug redistribution thereafter. Initial attempts...
using bulk elution to determine uniformity of drug targeting after stent-based delivery revealed a flat radial drug concentration profile in the media that was indicative of convective transport with an average tissue concentration of 0.24±0.02 mg/mL (Figure 1A). On more detailed studies using quantitative fluorescence microscopy, however, dramatic spatial heterogeneity in tissue concentrations was observed. Microscopic imaging of the arteries revealed zones of high and low fluorescein concentrations throughout the media that identically followed stent geometry. These zones corresponded to tissue concentrations ranging from 0.06 to >0.97 mg/mL (Figure 1B). Average media concentrations determined by microscopy were 0.22±0.03 mg/mL, matching bulk elution. Together, these results suggest that compartmental pharmacokinetics does not document the heterogeneous drug distribution as accurately as continuum pharmacokinetics.

Models of Transport
We developed theoretical models of stent-based drug delivery to account for our experimental observations. These models demonstrated that for both hydrophobic and hydrophilic compounds, considerable variation of drug concentration in the arterial wall is present after stent-based delivery (Figure 2A and 2B). Large areas of high and low drug levels, relative to mean concentration, exist simultaneously at steady state and are very close to one another. Such variations are present in both the circumferential and longitudinal directions. For hydrophilic drugs, some regions of the superficial layers of the media are nearly devoid of drug, whereas deeper layers have levels of drug several times the mean concentration. High-drug regions increase in area with depth into the tissue. Although hydrophobic compounds manifest similar variation patterns, they nevertheless distribute better, because regions with nearly no drug relative to mean concentration are in some cases 60% smaller than those of hydrophilic agents, depending on strut configuration. Both circumferential and radial concentration gradients are greatest near the struts and decay rapidly away before increasing again near the perivascular space. For hydrophilic drugs, peak circumferential gradients approach a concentration change of 20% Csd per cell length and are independent of strut number in diffusion-dominated systems.

Transport Forces
Drug distribution is mediated first, by the use of struts as sources, and second, by the balance between convective and diffusive forces on the specific compound. Strut-adherent release dictates sharp circumferential concentration gradients near the superficial layer, where high-drug zones are juxtaposed to stent struts with low-drug zones in the interstrut spaces. The superficial drug distribution variation and mean concentration, which were lowest and highest, respectively, at low Pe, change minimally until Pe≈10, whereas overall tissue concentrations actually increase. Beyond this value, convection dominates, the variation increases, and both superficial and overall concentrations drop significantly (Figure 3A and 3B). At very large Pe, where drugs move exclusively by convection, superficial and overall mean tissue concentrations converge as alternating bands of transarterial high- and low-drug zones form. Although hydrophobic drugs exhibit a higher overall variability than hydrophilic drugs, they preferentially remain significantly closer to the intima than hydrophilic drugs at all Pe (Figure 3C and 3D).

Stent Geometry
As stent designs evolve toward more complex and more inhomogeneous strut configurations, we assessed how strut placement affects drug delivery. Monte Carlo simulations were conducted by randomly assigning strut positions without overlap. Mean arterial wall concentrations were independent of strut arrangement but increased with strut number (n=90). Hydrophobic drugs distributed significantly more into the arterial wall than hydrophilic drugs (Figure 4A). Uniformity of drug distribution also increased with strut number but, conversely, was significantly dependent on strut arrangement. For hydrophilic drugs, the average difference in uniformity between homogeneous and inhomogeneous stent strut placement increased from 11% for a 4-strut stent to 33% for a 12-strut stent. Conversely, the distribution of hydrophobic compounds was slightly less dependent on strut arrangement, with the difference in uniformity increasing from 8% for a 4-strut stent to 21% for a 12-strut stent before decreasing for higher strut numbers (Figure 4B).

Discussion
Continuum Pharmacokinetics
The lackluster performance of stent-based delivery systems for hydrophilic drugs may arise in part from the inability to effectively distribute drug at the target site at therapeutic concentrations for a sufficient period of time. To appreciate the pharmacokinetic limitations of drug efficacy, detailed information about drug tissue interactions and drug
transport mechanisms is required. Several studies have applied traditional pharmacokinetics to examine the distribution of stent-delivered drugs at a gross level by assaying for tissue average drug content.1,4,17,18 Yet, it appears that stent-based delivery can produce high tissue average concentrations relative to plasma but simultaneously less than optimal therapeutic effects.4 In contrast, other studies with far less mobile compounds, such as paclitaxel, have shown more promising data in reducing intimal hyperplasia.9 These confounding results might be explained first, by the relatively enhanced targeting of hydrophilic compared with hydrophobic agents, and second, by the large spatial concentration variations observed for both drug types in the arterial wall. Our results suggest that control of drug delivery concentrations that can vary from nearly nil to several times the tissue average concentration over very short distances, resulting in local concentrations that may be both toxic and inadequate. As such, compartmental pharmacokinetics needs to be augmented by a continuum pharmacokinetic evaluation for optimizing local delivery.

The need for a microscopic appreciation of the forces of drug distribution and transport is substantiated by recent studies that directly correlate local concentrations of therapeutic agents with ensuing biological response.19,20 Although it is clear that absolute concentrations can determine biological effect, gradients in concentrations may also affect biological behavior. For instance, morphogens direct tissue formation in embryos by specifying cell fates along a concentration profile,21,22 whereas the graded distribution of cytokines leads to the directed recruitment of inflammatory cells to sites of injury, minimizing their activities. Enhanced targeting of hydrophilic compared with hydrophobic agents, and second, by the large spatial concentration variations observed for both drug types in the arterial wall. Our results suggest that control of drug delivery concentrations that can vary from nearly nil to several times the tissue average concentration over very short distances, resulting in local concentrations that may be both toxic and inadequate. As such, compartmental pharmacokinetics needs to be augmented by a continuum pharmacokinetic evaluation for optimizing local delivery.

Concentration Gradients Depend on Drug Physicochemical Properties

Physicochemical properties remain important determinants of drug distribution even in local delivery. Charge, molecular weight, and drug partitioning determine the relative difference of convective versus diffusive forces on drug transport.13,25 Compounds that partition significantly into tissues will have smaller low-drug regions, because these drugs would be less prone to both diffusive backwash into the endovascular space and convective washout into the perivascular space. Paclitaxel, rapamycin, and other drugs currently being considered for stent-based release partition extremely well into arterial tissues as a result of hydrophobic and vascular wall protein interactions.13,26 These drugs are consequently retained more effectively than heparin.

Our simulations indicate that there is an intimate dependence of the variability of drug distribution on the Peclet number, a dimensionless ratio of convective and diffusive forces. If spatially uniform drug distribution remains a clinical goal of local delivery for restenosis, designer drugs might be chemically modified or genetically engineered to capitalize on the intrinsic balance of transport mechanisms. For example, our studies suggest that when a hydrophilic drug is subject to almost equivalent forces of convective versus diffusive transport characterized by a Pe between 1 and 10, there is decreased overall concentration variability without adverse effects on superficial concentration variability. Moreover, although hydrophobic drugs achieve significantly higher tissue levels in the arterial wall than hydrophilic drugs, they tend to do so with relatively larger concentration variability and remain in regions closer to the intima. Given their lower concentration variability, the hydrophilic nature of a drug may be advantageous when that drug possesses a small therapeutic window, whereas the hydrophobic nature of a drug may be advantageous to maintain high therapeutic doses close to the intima.

Concentration Gradients Depend on Expanded Stent Configuration

In addition to the physicochemical properties of the drug, geometric characteristics of the delivery device must be considered. Simple proximity of the target tissue to the coated stent does not ensure adequate distribution, because our results show unequivocally that distribution is most nonuniform in the layers of the artery closest to the stent. The potential difference between local drug distribution and mean tissue concentration actually becomes increasingly important as stent designs evolve to progressively more complex forms. Although the mean tissue concentration of a stent-released drug is independent of stent strut position, local concentrations, which ultimately govern biological effect, are highly spacing-dependent. Newer stent designs will inherently produce inhomogeneous arrays of stent struts in the circumferential and longitudinal directions. This variance in distance between stent struts will amplify the vicissitudes in concentrations and the areas of overlap toxicity where struts are close together and subtherapeutic areas between widely spaced struts. Taken together, inhomogeneous stent strut placement can lead to suboptimal drug delivery. Disparity in drug distribution between stents with homogeneous and inhomogeneous strut designs increases with strut numbers and is more apparent for hydrophilic drugs than for hydrophobic drugs. Optimization of drug distribution therefore requires symmetric expansion of stents with homogeneous distributions of struts.

Conclusions

Local drug delivery from stents probably remains a promising option for the treatment of atherosclerosis and restenosis, with the caveat that important issues regarding distribution and targeting be addressed. Device proximity to target tissue does not ensure adequate distribution, and most importantly, mean tissue concentrations can be misleading indicators of delivery efficiency. By understanding local pharmacokinetics, including physiological transport forces and drug physicochemical properties, we might rationally capitalize on the many advances made in the field of controlled-release technologies.
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References


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