Thrombosis Modulates Arterial Drug Distribution for Drug-Eluting Stents

Chao-Wei Hwang, MD, PhD*; Andrew D. Levin, MS*; Michael Jonas, MD; Pamela H. Li, BS; Elazer R. Edelman, MD, PhD

Background—Drug-eluting stents deliver potent compounds directly to arterial segments but can become clot laden when deployed. The question arises as to whether thrombi affect drug elution and arterial uptake.

Methods and Results—Paclitaxel transport and retention were assessed in clots of different blood components. Diffusivity, affected by clot organization, is fastest in fibrin (≈347 μm²/s), slower in fibrin–red blood cell clots (34.98 μm²/s), and slowest in whole-blood clots (3.55 μm²/s). Blood cells bind and retain paclitaxel such that levels in clot increase linearly with red cell fraction. At physiological hematocrit, clot retains 3 times the amount of paclitaxel in surrounding solutions. Computational models predict that the potential of thrombus to absorb, retain, and release drug or to act as a barrier to drug delivery depends on clot geometry and strut position in clot relative to the vessel wall. Clot between artery and stent can reduce uptake 10-fold, whereas clot overlying the stent can shield drug from washout, increasing uptake. Model assumptions were confirmed and predictions were validated in a novel rat model that introduces thrombosis within stented aortas where nonocclusive thrombus acts as capacitive space for drug and shifts drug levels to decrease tissue uptake 2-fold.

Conclusions—Thrombus apposed on stents creates large variations in drug uptake and can act to either increase or decrease wall deposition according to the clot and stent geometry. Arterial deposition of drug from stents deployed in clots will be highly variable and unpredictable unless the clot can be adequately controlled or removed. (Circulation. 2005;111:1619-1626.)

Key Words: stents ■ thrombus ■ thrombosis ■ drugs ■ restenosis

The reduction of intimal hyperplasia in an arterial segment by drug-eluting stents1–3 depends on appropriate drug dose distribution in the arterial wall over an extended period of time.4–7 Although several experimental and computational studies have examined the local pharmacokinetics of stent-based drug delivery,7,8 none have considered how thrombus affects drug uptake 2-fold.

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ad sorption on binding capacity was simulated with the addition of 4% bovine serum albumin (Sigma) to the drug solution. The clot was incubated with drug for 72 hours, a period determined in separate experiments to be sufficient to approach tissue equilibrium. Clots were washed in PBS, dissolved for 48 hours in 400 μL of aqueous-based solubilizer (Solvable, Packard-Canberra), and treated with 30% H2O2 (Mallinckrodt) in a 1:8 ratio. Drug content was measured with a liquid scintillation counter (Ultima Gold, Perkin-Elmer). Drug capacity of the clot was taken as the ratio of drug concentration in the clots referenced to final drug concentration in the source solution. Assuming that specific and nonspecific drug-binding interactions in tissue are independent of those in clot, we can estimate: $K_{\text{tissue:clot}}$ the ratio of tissue drug capacity relative to clot drug capacity, from $K_{\text{clot:solution}}$ as follows:

$$K_{\text{tissue:clot}} = K_{\text{clot:solution}} K_{\text{solution:clot}}$$

using previously reported values of $K_{\text{tissue:solution}}$ for paclitaxel.

### Drug Diffusivity

Fresh rabbit blood and fibrin–red cell mixtures were coagulated in 12-well tissue culture plates with a clot volume of 2 mL per well. Care was taken to minimize air bubbles, and larger well diameters were chosen to reduce the effects of meniscus formation. [3H]Paclitaxel (1.06×10^{-8} mmol/mL, 2 mL per well) in 7.5 U/mL hirudin was allowed to diffuse into the clot for up to 1 hour. After the diffusion phase, clots were washed in PBS and dissolved for 48 hours in 2.1 mL of Solvable. After treatment with 30% H2O2, clot drug content was measured with a liquid scintillation counter with 10 mL scintillation cocktail. Drug diffusivity was determined by fitting the measured total clot drug content with the numerical solution of the diffusion equation and a steady-release boundary condition.

### Drug Convective Velocity

Although drug is efficiently transported through isolated clots, drug convective velocity in clots juxtaposed to the arterial wall is restricted at steady state by continuity to match the slower transport through the arterial wall. Paclitaxel convective velocity was determined in 4- to 5-mm segments of bovine carotid arteries connected to tubing on one end and sealed on the other. [3H]Paclitaxel (1.06×10^{-8} mmol/mL) was infused at pressures of 60 and 90 mm Hg. After 2 hours, drug content in a 6-mm-diameter biopsy punch of the arterial wall was measured. The source drug concentration, arterial drug content, convective time, biopsy punch dimensions, and tissue [3H]paclitaxel diffusivity and capacity were fit to a drug diffusion-convection model. Convective velocity increased 3-fold, from 3.2 to 9.2 mm/s, for a 50% increase in transmural pressure from 60 to 90 mm Hg.

### Continuum Pharmacokinetics Modeling of Thrombus Transport

Drug release from a stent and transport within the thrombus and arterial wall were modeled with the use of the diffusion-convection equation and a steady-release boundary condition. We limited our analysis to a 2-dimensional cross section of the artery and clot, a 100×100-μm strut, and assumed rapid luminal washout, no endothelial resistance, and a perivascular sink. We used zero concentration boundary conditions on the endovascular and perivascular aspects of the artery and symmetry boundary conditions in the planar directions. We further assumed an arterial wall thickness of 800 μm and a strut-to-strut distance of 1000 μm. Simulations were performed in Cartesian coordinates. In such a system, transport of soluble drug is described as follows:

$$\frac{\partial U}{\partial t} = \frac{1}{\partial x} \left( D_x \frac{\partial U}{\partial x} + D_y \frac{\partial U}{\partial y} \right) - V \frac{\partial U}{\partial y}$$

where $U$ is free drug concentration, and $V$ is the transmural convective velocity. $D_x$ and $D_y$ are diffusivities in the planar $X$ and transmural $Y$ directions, and within the arterial wall the former was...
3 orders of magnitude larger than the latter (37.2 versus 0.021 \( \mu m^2/s \)). Free drug concentration is related to total concentration \( C \) by the tissue capacity of the drug \( K \), so that \( C = K \times U \). Because of the multicomponent structure of the clot-artery system, \( K, D_s, \) and \( D_r \) are experimentally determined for each component of the system. \( V \) was taken as 9.2 mm/s, corresponding to our measured drug convective velocity at 90 mm Hg of transmural pressure. Simultaneous transport and binding were implemented with the use of operator splitting. During each time step, free drug released from the stent was allowed to diffuse and convect along with free drug already in the system. We thus first compute an intermediate transport-free drug distribution \( P \) and then calculate the free \( U \) and total \( C \) drug concentrations at the start of the next computation cycle to account for differential drug capacity:

\[
C(t + \Delta t) = C(t) + \Delta C = C(t) + [P - U(t)] = C(t) + P - C(t)/K
\]

\[
U(t + \Delta t) = U(t) + \Delta U = U(t) + \Delta C/K
\]

\[
= U(t) + [P - U(t)]/K = (C(t) + P)/K - C(t)/K^2
\]

We examined the theoretical total arterial drug content for a range of clot widths (100 to 900 \( \mu m \)), heights (50 to 450 \( \mu m \)), and strut strut distances from the arterial surface (0 to 350 \( \mu m \)), so that \( C = K \times U \). Because of the multicomponent structure of the clot-artery system, \( K, D_s, \) and \( D_r \) are experimentally determined for each component of the system. \( V \) was taken as 9.2 mm/s, corresponding to our measured drug convective velocity at 90 mm Hg of transmural pressure. Simultaneous transport and binding were implemented with the use of operator splitting. During each time step, free drug released from the stent was allowed to diffuse and convect along with free drug already in the system. We thus first compute an intermediate transport-free drug distribution \( P \) and then calculate the free \( U \) and total \( C \) drug concentrations at the start of the next computation cycle to account for differential drug capacity:

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= U(t) + [P - U(t)]/K = (C(t) + P)/K - C(t)/K^2
\]

We examined the theoretical total arterial drug content for a range of clot widths (100 to 900 \( \mu m \)), heights (50 to 450 \( \mu m \)), and strut strut distances from the arterial surface (0 to 350 \( \mu m \)). We considered clots composed of pure fibrin, 50% packed red blood cells, or whole blood, with clot transport and drug uptake properties based on our experimental measurements for paclitaxel. We further simulated clots with varying drug diffusivities and capacities to assess the specific effects of these parameters on arterial drug content.

Arterial drug content was expressed as an arterial drug ratio, defined as the total arterial drug deposition achieved by a specific stent-thrombus configuration normalized to the total arterial drug deposition achieved by a nonclotted drug-eluting stent directly apposed against the arterial wall. An arterial drug ratio greater than unity implies a greater amount of drug in the arterial wall relative to that achieved by a nonclotted drug-eluting stent. Simulations were run at a resolution of 50 \( \mu m \) per computational node. Finer mesh resolutions were tested for a number of cases and did not qualitatively change the simulation results. The model was run until steady-state drug levels were achieved both in the thrombus and in the arterial wall.

### In Vivo Thrombus Model

Paclitaxel uptake was evaluated in stented abdominal aortas of adult male Sprague-Dawley rats (n = 4; weight, 500 to 700 mg; Charles River Laboratories, Wilmington, Mass) in the presence and absence of controlled induced mural thrombus. Procedures were in accordance with the guidelines of the American Association for the Accreditation of Laboratory Animal Care and the National Institutes of Health. Under inhaled isoflurane anesthesia, the right femoral artery was exposed, ligated, and incised proximally to allow passage of a 0.014-inch angioplasty guide into the aorta. The abdominal aorta was exposed, and a 15-mm segment above the origin of the renal arteries was ligated proximally and distally. Thrombus formed within 10 minutes in the isolated aortic segment, and the proximal aortic ligature was removed. A 2.625-mm steel stent (MULTI-LINK PIXEL, Guidant) was rapidly passed into the thrombosed segment and deployed for 15 seconds at 10 atm. The distal ligature was removed, and after we visually ensured adequate blood flow in the aorta with no macroscopic evidence of aortic ischemia, the balloon and wire were removed, the femoral artery was ligated proximally to the arteriotomy, and both incisions were closed.

Control animals underwent abdominal aortic stenting with the use of a similar technique without aortic thrombus formation. Heparin (100 U/kg) was administered intravenously before stenting only to the control rats. Aspirin (5 mg/kg per day, per standard practice in this type of procedure) was added to drinking water immediately after surgery to all animals for the duration of the experiment. Paclitaxel was administered intraperitoneally 3 times at 5 mg/kg every 12 hours with the first injection immediately after stenting. Animals were euthanized 30 hours after stenting with inhaled CO2.

The aorta was pressure perfused with isotonic saline and cleared of adherent fat and connective tissues, and the stented segment was detached. The stent was carefully removed, and the tissue, stent, and overlying thrombus were snap-frozen with liquid N2. Paclitaxel in the arterial wall and excised thrombus was determined with the use of a commercial immunoassay (Hawaii Biotech). Paclitaxel uptake in the stented region was normalized to uptake in a nonstented region and compared for cases with clot absent and clot present. Additionally, segments of the stented vessels were excised and histologically processed with Verhoeff’s tissue elastin stain.

### Results

#### Influence of Thrombus Geometry on Arterial Paclitaxel Uptake

Arterial paclitaxel distribution is exquisitely sensitive to changes in the local geometry of the overlying thrombus. Strut position within the clot determines uptake (Figure 2). When there is a greater mass of clot over the strut, the strut sits close to the wall, and the overlying clot shields against systemic washout. Arterial drug uptake can rise 30-fold higher than if clot were not present. Conversely, when the bulk of the clot is interposed between the strut and artery, a barrier to transport is created that decreases arterial drug uptake. For some geometries, these forces balance. Indeed, the clot can grow in height, surface area, or both to alter
uptake. Arterial drug uptake peaks at a clot height to width ratio of \(\approx 0.3\), when clot dimensions were varied and clot volume was kept constant (Figure 2D). Radial and longitudinal washout increases at other ratios, lowering drug uptake. Given the natural variability of thrombosis in vivo, such sensitivity to geometry implies that arterial drug uptake from drug-eluting stents deployed in clotted arterial segments may also be highly variable.

Paclitaxel Deposition and Transport in Fibrin, Fibrin–Red Blood Cell, and Whole-Blood Clots

Paclitaxel diffusivity is retarded by fibrin clots once organized by addition of thrombin. Diffusivity decreases by half to \(347\pm 14\ \mu m^2/s\) when thrombin sufficient to induce cross-linking is added to fibrinogen and by an additional order of magnitude when red blood cells are present (Figure 3A). Until red blood cells are present, the paclitaxel capacity of fibrin clots is no different from the capacity of buffer solution \((K_{\text{fibrin:solution}}=0.94\pm 0.11)\), irrespective of thrombin concentration and degree of cross-linking thrombin induces (data not shown). Clots with 50% red cells retain nearly 3-fold more drug than pure fibrin clots \((K_{\text{clot:solution}}=2.92\pm 0.26; P<0.05; \text{Figure 3B})\). Paclitaxel capacity increases dramatically and in a linear fashion as the red cell fraction in the clot increases.

Mature or chronic thrombotic masses are more heterogeneous than fibrin–red cell clots. The fibrin meshwork in these clots contains platelets and other blood elements, adding further restrictions on drug transport. Paclitaxel diffusivity in whole-blood clots is an order of magnitude lower than that in 50% fibrin–red cell clots \((D_{\text{fibrin-red cell clot}}=34.98\pm 10.3\ \mu m^2/s\) versus \(D_{\text{whole-blood clot}}=3.55\pm 0.75\ \mu m^2/s\); Figures 3A and 4A). The paclitaxel capacity of whole-blood clots is, however, remarkably close to that expected of a fibrin–red cell clot with physiological hematocrit \((K_{\text{clot:solution}}=2.63\pm 0.17; \text{Figure 4B})\). Thus, non–red cell components of blood delay drug transport but do not add substantially to the ability of fibrin and red cells to retain drug within the clot. The protein-binding nature of paclitaxel has an effect as well. The presence of albumin in the drug solution reduced the binding of drug by red blood cells. Whole-blood clot paclitaxel diffusivity increased when albumin was present (Figure 4A), whereas capacity was reduced to near unity (Figure 4B).

Influence of Clot Diffusivity and Capacity on Arterial Paclitaxel Uptake

Modeling allows us to investigate how drug retention capacity and diffusivity independently influence arterial drug uptake for stent struts adjacent to the arterial wall in the midline of an invariant clot. This type of analysis can be used
to understand how drugs with transport and capacity characteristics different from paclitaxel will behave. Drug levels are maximal when drug diffusivity in the clot is at or below transmural drug diffusivity in the arterial wall (0.021 μm²/s for paclitaxel). Arterial drug uptake will decrease in a sigmoidal fashion if drug can diffuse more freely in the clot (Figure 5A). This prediction is consistent with heightened arterial drug uptake for arteries embedded with stents surrounded by whole-blood clots where diffusivity is lowest and low uptake for stents surrounded by fibrin clots where diffusivity is maximized. Arterial drug loading is determined by more than diffusivity. For 2 drugs of identical clot diffusivities, arterial uptake is delayed for the one that is more highly retained in the clot. Greater interactions of drug with clot components retard drug release from the clot (Figure 5B). Nevertheless, with a continuous drug source from the stent, identical steady-state arterial drug content is eventually reached, independent of clot drug retention capacity, albeit at different time points.

**Thrombus and Paclitaxel Uptake In Vivo**

A novel model of controlled in vivo thrombus was developed for this study. These experiments in rats confirm that clot possesses capacitive properties for sequestering paclitaxel. Clot does not simply pass drug through to the underlying artery after stent release; rather, it alters arterial wall uptake. All stented aortas, control (Figure 6A) and clot laden (Figure 6B), appeared viable, with no evidence of necrosis or ischemia at time of euthanasia. Control animals had no notable thrombus in stented aortas at implantation, and on device excision no clot was present on the stent or the luminal surface of the vessel wall. Mural thrombus was present only after controlled induction, covering the stent struts without occluding the aortic lumen or affecting blood flow. A visible thrombotic meshlike mass was attached to the stent struts and was excised with the stent. The thrombus was a heterogeneous composite of fibrin, platelets, and red blood cells. The control and thrombosed stents were placed in a 20% ethanol solution with Tween 20 and vortexed for 15
minutes, a time period sufficient to dissolve the clot. The drug content on the thrombosed stents was significantly \((P<0.05)\) greater than the control devices (Figure 7A). This capacitive action of clot can both limit transport at the arterial wall interface and retard systemic washout, depending on clot geometry. In our in vivo studies, arterial drug uptake in the presence of clot was significantly \((P<0.05)\) reduced by \(\sim50\%\) in stented vessels in comparison to the control devices (Figure 7B).

Systemic delivery via intraperitoneal administration is equivalent to a non-zero Dirichlet luminal loading condition, a situation most analogous to the computational model with the stent strut adjacent to the lumen (Figure 2C). When the in vivo clot dimensions were determined and used as boundary conditions and input parameters, the model predicted an arterial drug ratio of 0.56, strikingly close to the 50\% decrease in arterial uptake seen in the animal model. In this case, drug recycles between the thrombus and the lumen more effectively than it passes from the clot to the tissue wall, reducing arterial drug uptake. As predicted, thrombus is not merely a passive medium but rather a capacitive space to retain drug and shift the drug deposition distribution.

**Transport Forces in the Clot Affect Arterial Drug Uptake**

There exists a balance between the capacity of an artery to absorb a drug and the rate at which the drug is presented to the arterial tissue. Clot alters this balance by absorbing drug and retarding transport. Alterations in both capacity and diffusivity will likely change arterial drug levels during therapeutic delivery by modifying the amount and the rate at which drug can enter the vessel wall. Paclitaxel moves more slowly through clots with higher red cell content because of repeated binding and release from nonspecific and specific cellular components like tubulin,\(^{21}\) which are ubiquitous within tissue and red cells. Whole-blood clots present a denser platelet-fibrin meshwork, which further hampers drug transport. Diffusivities change with clot content and drug. The steady-state arterial uptake of a given drug will be maximized when the drug diffusivity through a specific clot is slower than its diffusivity in arterial tissue. In this case, clot retains drug within the local vicinity of the vessel wall, allowing for increased contact time and potential infiltration and distribution through the arterial wall. At higher clot diffusivities, drug is delivered to the artery more quickly than can be absorbed, and a greater fraction of the drug cannot be bound before it is lost to the circulation.

Clot is therefore a double-edged sword for drug-eluting stents. In some scenarios the capacitive and binding phenomena will increase tissue uptake, and in others it will reduce it. The problem is that thrombosis is unpredictable and irregular. Indeed, the DELIVER trial of nonpolymeric rapidly eluting paclitaxel stents supports the potential beneficial impact of clot on drug-eluting stents. Patients who received paclitaxel-eluting stents and glycoprotein-IIb/IIIa inhibitors had significantly higher rates of restenosis than those patients who received only the drug-eluting stent without the inhibitor.\(^{22}\) It is possible that the glycoprotein inhibitor removed or reduced thrombus around the stent struts. In this specific case in which the drug was so rapidly eluted off of the stent, the capacitive-like properties of clot might serve as a secondary release platform. Here clot may reduce systemic washout and preserve drug for presentation to the arterial wall. In systems in

**Discussion**

Thrombosis is a feature of the acutely occluded artery and a catastrophic failure mode for endovascular devices. Drug elution increases the potential for subacute stent thrombosis. We now show that clot, even nonobstructing microthrombi, can affect drug deposition. Our physiological and computational models demonstrate that clot changes the local environment of the stent strut and physiological transport forces\(^{7,8}\) to alter arterial wall drug uptake and retention.\(^{6,17,20}\) Small amounts of local thrombus produce significant variations in arterial drug levels depending on clot geometry and composition. Because of the unpredictability of these factors in the clinical setting, deployment of a drug-eluting stent in a clot-laden arterial segment will inevitably lead to variability in arterial drug distribution, potentially affecting clinical outcome.
which polymeric coatings are designed specifically to elute drug into tissue over time, extended retention in clot may enhance systemic dilution. More consistent clinical results may thus be expected if clots are both removed from the target arterial segment before stent deployment and carefully regulated after interventions.

**Drug Interactions With Clot**

Just as arterial ultrastructure influences arterial drug uptake, the organization of thrombus affects the capacity to store and release paclitaxel to the arterial wall. Clots with more red cells absorb greater amounts of drug as a result of an increase in both nonspecific and specific interactions. These same interactions, however, also retard arterial drug uptake kinetics. Most of the paclitaxel in high-capacity clots is bound, and because only free drug can diffuse, delivery to the artery slows when drug passes through clot before it contacts the arterial wall. Drug capacity in clot thus helps to determine drug uptake kinetics in arteries. The rate of drug transport in clot influences the extent to which the clot can retard systemic drug washout. Effective drug transport distances are determined both by the drug transport coefficients within the clot and by the geometric dimensions of the clot. Net arterial drug uptake is governed by a balance of drug retention in the clot and drug transport from the clot to the systemic circulation and from the clot into the artery. Clot-stent geometry determines which of these competing processes dominates. This fundamental mechanism must be considered for optimizing drug-eluting stent therapies.

The importance of binding was demonstrated further by the competition established by bovine serum albumin. High levels of circulating proteins can act as an enhanced sink for drug that does not interact with the arterial wall beneath a strut or with clot. The competition for drug between blood and blood vessel is amplified in vivo, and the ability of clot to retain and retard drug is all the more critical for protein binding compounds. In this regard, specific and nonspecific binding in arterial systems are major determinants of tissue transport and uptake for both paclitaxel and rapamycin. Polymerized microtubules in red blood cells and smooth muscles bind paclitaxel with nanomolar specificity. At similar concentrations in the same cell types, the FK506 binding protein also shows nanomolar binding specificity to rapamycin. With such similar cellular concentrations of binding proteins and nearly identical pharmacokinetic and physicochemical properties, rapamycin-eluting stents will likely behave in a manner very similar to that of paclitaxel in the setting of thrombus.

**Drug Uptake and Stent Positioning**

Our simulations demonstrate intriguing relationships between stent positioning and arterial paclitaxel uptake. The effects of positioning are primarily mediated by the local transport forces that drive the migration of drug through the clot to the arterial wall. Macromolecular transport in thrombus has been a fertile area of research in thrombolytic therapy, as researchers have sought ways to enhance clot uptake of thrombolytic drugs and enzymes to maximize clot dissolution. Controlling the thrombus is a delicate issue in stent-based drug delivery because efforts to modulate uptake must be balanced with concern for creating local zones of toxic or subtherapeutic drug levels. In general, arterial drug uptake is decreased for clot configurations with larger luminal surface area, for stent positioning that increases the strut-to-intima distance, and for narrow clots that allow for a steep stent-lumen concentration gradient that washes drug out to the circulation. In some instances, even changes in stent positioning of just tens of microns have dramatic effects in raising or lowering arterial drug uptake. Two cases in which these effects may be realized are deploying a stent in a preexisting thrombus and deploying a stent in a thrombus that develops after implantation.

**Conclusions**

Clots can modulate stent-based drug elution to significantly alter arterial drug levels and potentially efficacy. Thrombus composition influences uptake kinetics through changes in its retention capacity for drug. Clot geometry mediates arterial drug levels through the balance of local transport forces. The exquisite sensitivity of tissue uptake to geometry and composition implies that drug deposition will be highly variable and difficult to predict in a thrombotic microenvironment. As such, the full power of drug-eluting stents in clinical practice may not be realized entirely until local thrombosis is tightly controlled.

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