Localized Arterial Wall Drug Delivery From a Polymer-Coated Removable Metallic Stent

Kinetics, Distribution, and Bioactivity of Forskolin

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Background Coronary stenting is associated with two major complications: subacute thrombosis and neointimal proliferation resulting in restenosis. Our hypothesis is that the biocompatibility of metallic stents can be improved by coating with a polymer membrane that delivers agents that favorably modify the local arterial microenvironment. This study evaluates the kinetics, distribution, and bioactivity of the model drug forskolin delivered to the local arterial wall by a polyurethane-coated removable metallic stent.

Methods and Results Stents were used in rabbit carotid arteries (n=20) for as long as 24 hours. The quantity of forskolin bound to the stent decreased exponentially with a half-life of 5.8 hours. Blood concentrations peaked at 140±39 pg/µL at 4 hours. The adjacent arterial media contained 60±39 ng/mg, which was 380- and 460-fold greater than the contralateral carotid media and the systemic blood, respectively (P<.0001). Media forskolin concentrations declined exponentially over time with a tissue half-life of 5.0 hours. Drug distributed throughout the vessel wall with decreasing gradients in the radial and axial dimensions consistent with a diffusion process. Removal of the stent was associated with a 100-fold decline in media forskolin concentration within 2 hours. Forskolin release was associated with a sustained 92% increase in carotid blood flow and a 60% decrease in local arterial resistance compared with coated control stents (P<.005). In another set of rabbits (n=14) using a carotid crush injury, flow-reduction model, forskolin prolonged the time to flow variation and occlusion by 12-fold compared with the use of bare metal stents and 5-fold compared with the use of polyurethane-coated stents (P<.0001).

Conclusions A polymer-coated metallic stent can deliver forskolin to the local arterial wall in high concentrations relative to the blood or other tissues. High local drug concentrations are dependent on maintaining stent-to-tissue gradients. The delivered drug is biologically active, demonstrating vasodilating and antplatelet properties. (Circulation. 1994;90:1003-1011.)

Key Words • angioplasty • restenosis • thrombosis • stents

Our fundamental aim is to improve the biocompatibility of metallic coronary stents by developing a polymer membrane coating that can deliver pharmacological agents locally in high concentrations. Coronary stenting is associated with two major complications: subacute thrombosis and restenosis resulting from vascular smooth muscle cell proliferation.1-5 A successful method of preventing these complications in humans has not been found. The precise mechanisms through which metallic stents stimulate thrombus formation and neointimal hyperplasia are not fully understood. One reason that systemically administered pharmacological agents fail to prevent these complications may be that the tolerated dose is too low to achieve sufficient drug concentration at the targeted site. A stent capable of delivering effective agents precisely to the site of arterial injury for a sufficient time period may be advantageous for discovering and implementing successful treatment strategies.

The purpose of this study was to test the feasibility of local drug delivery from a polyurethane-coated metallic stent. We used a new type of stent called the heat-activated removable temporary stent (HARTS). This device functions like other permanent coronary stents but has the option of reliable percutaneous removal for at least 1 week after deployment.6 Removability allows assessment of persistence of delivered substances in tissue irrespective of the presence of the delivery system or maintenance of blood levels. We chose forskolin, a nonpolar adenylylate cyclase activator with antiplatelet and vasodilator properties, as a model drug.7-9 Using a rabbit carotid artery model of temporary stent implantation, our goals were to quantify the kinetics of forskolin release, distribution, and persistence in blood, local arterial wall, and distant tissues and to determine if the drug delivered by the stent is biologically active.

Methods

Drug Delivery System

A prototype HARTS (Advanced Coronary Technologies) was selected as the drug delivery device for this study (Fig 1A). The technical details of this stent have been previously reported.6 The stent is constructed from 0.009-in-diameter wire segments of the shape-memory nickel-titanium alloy nitinol. The stent is percutaneously implanted into the vessel wall by balloon expansion and subsequently recovered to its predeployment dimensions by transiently heating it to the selected thermoelectric transition temperature of 55°C. This property permits percutaneous extraction, which has been accomplished as long as 1 week after deployment in canine coronary arteries.
Fig 1. A, Uncoated prototype heat-activated removable temporary stent device, on balloon, and on recovery catheter. B, Polyurethane-coated, forskolin-loaded stent after 4-hour implantation in low-flow, thrombosis model (group 2). A small, nonobstructive red thrombus (graded as minor) was adherent to a stent strut (arrow).
Forskolin, a diterpene (molecular weight, 410 Da) isolated from the roots of the Indian Coleus forskohlii, was chosen as the model drug for local delivery. Forskolin activates adenylate cyclase directly bypassing cholinergic and adrenergic receptors.\textsuperscript{10,11} Binding sites have been described in platelet, smooth muscle, and cardiac muscle sarcolemmal membranes.\textsuperscript{12,13} It produces disaggregation of platelets, coronary and peripheral vasodilatation, and cardiac inotropic effects that are quantitatively where the stent was recanalized to rise in cyclic AMP (cAMP).\textsuperscript{10-12,14} These properties make assessment of the biological activity of locally delivered drug straightforward. In addition, one report suggests that forskolin may have a role in inhibiting smooth muscle cell proliferation.\textsuperscript{15} Forskolin has limited utility for systemic administration because of poor water solubility, but it can be readily dissolved by organic solvents and incorporated into nonpolar polymers. Polytetrafluoroethylene vascular grafts impregnated with forskolin have been shown to inhibit platelet uptake and prevent graft thrombosis in sheep.\textsuperscript{16}

A commercially available polyurethane (Tecoflex, Thermetics) was selected for its properties of membrane formation, flexibility, biocompatibility, and lipophilic drug incorporation. Stents were fabricated with polyethylene terephthalate (PET) to a thickness of approximately 50 \(\mu\)m (Fig 1B). Unlabeled and tritiated forskolin (Calbiochem and New England Nuclear, respectively) with a specific activity of 25 \(\mu\)Ci/mg was incorporated in the polyurethane membrane by incubating the coated stents for 6 minutes at 29°C. Stents were dried in a partial vacuum at 40°C for 24 hours to remove solvent and then rinsed with saline just before use. The amount of drug loaded on the stent depends on its concentration in solution and the weight of the polymer coating. Such treatment incorporated 1580±600 \(\mu\)g (n=6) of forskolin per stent.

Animal Models

The animal experiments conformed with the guiding principles of the American Physiological Society and were approved by the Cedars-Sinai Medical Center Institutional Animal Care and Use Committee. The first animal experiment (group 1) was designed to quantify forskolin uptake, persistence, and effect on hemodynamics. New Zealand White rabbits (n=20; weight, 3.5 kg) were anesthetized with intravenous xylazine and ketamine. After left femoral and right carotid surgical exposure, a 6F introducer sheath was placed in the left femoral artery and connected to a pressure transducer. The right common carotid was inspected for anomalous branches that were ligated, and a 22-gauge cannula was placed in the external carotid. A 2.5-mm transit-time flow probe (Transonic) was placed just proximal to the carotid bifurcation, and heparin (1000 IU intra-arterially) was given. A forskolin-loaded stent mounted on a 3.0-mm-diameter, 20-mm-long percutaneous transluminal coronary angioplasty (PTCA) balloon catheter was used in the right carotid artery at a maximum of 6 atm for 30 seconds. Serial carotid blood flow measurements and blood samples distal to the stent site and from the systemic arterial blood were collected.

In experiments where the stent was recanalized on all 3F catheter with multiple distal sideholes was passed over a guide wire until it was coaxial within the stent. Five milliliters of normal saline heated to 65°C was rapidly injected, resulting in immediate collapse of the stent to its predetermination shape, tightly gripping the catheter. The stent and catheter were then withdrawn percutaneously. Previous experiments (unpublished data) in canine and porcine coronary arteries have shown no histological evidence of short- or long-term thermal injury with this recovery procedure.

To quantify tissue uptake, we implanted drug-impregnated stents, and euthanized with rabbits under anesthesia was performed with stents remaining in situ after 2 hours in two rabbits, 4 hours in six rabbits, and 24 hours in three rabbits (group 1a, n=11). To quantify tissue persistence of drug, stents were percutaneously removed after 2 hours (group 1b, n=4). Two of the rabbits were euthanized while under anesthesia at 4 hours and two at 24 hours (ie, 2 and 22 hours after stent removal). To assess whether hemodynamic changes were mediated by local forskolin action, additional rabbits underwent implantation with stents containing no drug but coated with the polymer membrane (group 1 control, n=5). Otherwise, the protocol was identical to group 1a with euthanasia at 4 hours.

In a single experiment to evaluate the uniformity of tissue uptake of a lipophilic drug, a coated stent was similarly impregnated with rhodamine B (2.5 mg) and used in one rabbit carotid artery for 4 hours. Frozen sections (10 \(\mu\)m) of the stented arterial segment and the contralateral artery were examined with light and fluorescent microscopy.

Another series of rabbit experiments (group 2) was performed to evaluate the antithrombotic activity of locally delivered forskolin using a carotid artery crush injury, reduced-flow model modified for stent implantation.\textsuperscript{17} New Zealand White rabbits (n=14) underwent the same anesthesia, surgical, and blood flow-monitoring protocol described for group 1 with the following differences. Systemic anticoagulants were withheld. Crush injury was performed with a plastic occluder fitted on the right common carotid artery. After 5 minutes, stents (five bare metal, four polyurethane-coated, and four forskolin-loaded) were advanced to straddle the area of injury, and the balloon was expanded to a diameter of 3.0 mm. A perivascular constriction balloon was placed 1 cm proximal to the stent, followed by a 15-minute equilibration period. The occluder was inflated to reduce flow to 4 mL/min (averaging 49% of baseline flow). To ensure maintenance of consistent stenosis, a pressure transducer was placed in-line with the flow-constricting balloon. If the flow remained <0.5 mL/min for 5 minutes, the artery was considered occluded. If the artery exhibited flow <0.5 mL/min but returned to flow >0.5 mL/min, intermittent occlusion or flow variation was determined to be present. Experiments were terminated at the time of artery occlusion, or at 4 hours. The time from flow restriction until flow variation and experiment termination was recorded. After euthanasia with the rabbits under anesthesia, the artery was explanted and cut longitudinally with a scalpel, and the stent was removed. The polyurethane coating was inspected for defects under a dissecting microscope at X10, and the presence of white or red thrombus was recorded. The amount of thrombus present was qualitatively assessed as occlusive if no lumen remained through the stent, nonocclusive if thrombus partially occupied the lumen, and minor if present on the stent or artery wall without encroachment of the lumen.

Forskolin Distribution and Kinetics

In group 1 experiments, samples of adventitia were removed, and the carotid artery was sectioned into 1-cm segments from the stented region and the segments proximal and distal to the stent. Additional samples were obtained from the sternocleidomastoid muscle, uninvolved contralateral carotid artery, liver, and kidney. Tissue samples were weighed (10 mCi for carotid artery media/intima, 12±7 mCi for adventitia, and 23±12 mCi for other tissues) immediately after collection and digested in 1.0 mL of BTS-450 (Beckman) at 40°C for 24 hours and counted for 1 minute in 10 mL of Ready Organic scintillation fluid (Beckman). Blood samples (0.5 mL) were digested in 1.5 mL of 1:2 BTS450/isopropanol at 40°C for 24 hours, decolorized with H2O2, and counted in 18 mL of Safety Sol scintillation fluid (RPI). Scintillation fluid contained 0.7% acetic acid to reduce chemoluminescence. Scintillation counts were then adjusted for measured background and efficiency. The amount of forskolin present was calculated by comparison of tissue activity with a 25-\(\mu\)Ci/mg standard. For comparison of tissue and blood forskolin concentrations, blood levels were divided by specific gravity of rabbit blood (1.050 g/mL). The
forskolin content of stents before use and after explantation was measured by scintillation counting of aliquots of the stent coating dissolved in tetrahydrafuran.

Instantaneous net rate or flux of forskolin accumulation in the carotid arterial blood was calculated using the conservation of mass principle with the fickian assumptions of instantaneous mixing and insignificant spatial distribution affects.\(^{(1)}\)

\[
\frac{dM}{dt} = Q(C_{\text{carotid}} - C_{\text{systemic}})
\]

where \(M\) is the amount of forskolin, \(Q\) is carotid blood flow, and \(C\) is the concentration of blood forskolin in the carotid distal to the stent and in the systemic arterial blood.

First-order kinetic modeling was performed by a least-squares fit of a monoeponential function of the general form

\[
Y = a_0 e^{(-a_1t)}
\]

where \(Y\) is the measured variable that can be the drug mass, tissue concentration, or blood flux; \(a_0\) is the amplitude at time zero; and the decay half-life is \(a_1/0.693\).

The forskolin content of the stent coating was also compared with previous observations of diffusion from membranes with slab geometry.\(^{(18,19)}\) These studies show that fractional drug release \(M/M_0\) can be expressed as

\[
M/M_0 = (4/h)(D/\pi)^{0.5}t^{0.5}
\]

for \(0 \leq M/M_0 \leq 0.6\)

where \(M\) is the cumulative amount of drug released in time \(t\), \(M_0\) is the total amount of a drug incorporated in the polymer membrane, \(h\) is the thickness of the membrane, and \(D\) is the diffusion coefficient of the drug through the membrane. This equation is accurate for up to approximately 60% of the total drug released.

**Hemodynamic Measurements**

Serial mean aortic blood pressure (MAP) and carotid blood flow measurements were used to calculate the resistance of the right carotid circulation, so that

\[
R_{\text{carotid}} = \frac{\text{MAP (mm Hg)}}{\text{Q (mL/min)}} \times \frac{8 \times 10^5 \text{ dynes} \cdot \text{s} \cdot \text{cm}^2}{\text{mm Hg} \cdot \text{cm}^2}
\]

**Statistical Analysis**

Data in the text and figures are expressed as mean±SD. Assessment of differences between the multiple sites of the tissue samples in group 1a and for comparing uncoated, coated, and drug-loaded stent thrombosis in group 2 was by one-way ANOVA. If significant differences were found \((P<.05)\), pairwise comparisons were then performed using the \(t\) test within ANOVA corrected for multiple comparisons (Bonferroni/least significant difference tests). Hemodynamic values before and after stent implantation were pooled for each experiment and compared by paired Student’s \(t\) test.

**Results**

Inspection of group 1 animals after they were killed revealed patent carotid arteries without gross evidence of thrombosis. In group 1b, all four stents were successfully recovered at 2 hours after implantation. Visualization by dissecting microscope of in situ stents (group 1a) and percutaneously explanted stents (group 1b) did not reveal thrombosis. In each instance, the polyurethane coating was intact without rupture or sloughing.
Fig 4. Semilog plot of the net forskolin flux (rate of accumulation) in the carotid arterial blood as a function of time with curve fit of the first-order single exponential model function. Flux was determined using Equation 1 operating on the data set displayed in Fig 3.

Fig 4 shows the net flux of forskolin into the carotid artery blood as a function of time after stent implantation. The rate of forskolin entering the carotid artery blood, initially 6.9±1.9 µg/min, declined monotonically and was closely described by a single exponential decay function with a half-life of 1.2 hours. The total mass of forskolin entering the carotid blood in the first 4 hours was 649 µg, or 61% of the forskolin released from the stent.

Fig 5 shows the distribution of tissue forskolin concentration at 4 hours after implantation. The carotid media of the stented segment contained 60±39 ng/mg, which averaged 380-fold higher than similar tissue from the contralateral carotid artery and 460-fold higher than the concentration of forskolin in the systemic arterial blood. Media and adventitia lying the stent and sections proximal and distal to the stent all had significantly higher concentrations of forskolin compared with blood, contralateral artery, liver, and kidney (P<.0001).

Fig 6 shows the distribution of rhodamine B in the ipsilateral and contralateral arteries 4 hours after stenting. Fluorescent microscopy showed intense uptake of rhodamine throughout the media and adventitia of the stented artery. Light microscopy revealed that the intensity of staining varied circumferentially and radially with respect to the lumen. The most intense staining was at the sites of stent contact along the inner circumference. Staining diminished in between these sites and with distance radially outward from the lumen surface but extended throughout the media and adventitia. The contralateral unstented artery contained no rhodamine by either method of microscopic examination.

Fig 7 shows the time course of forskolin concentration in the media of the ipsilateral carotid artery: in group 1a, with the stent present as a drug reservoir, and in group 1b, where the stent was removed at 2 hours. With the stent continuously present, tissue forskolin decreased from 134±2 ng/mg at 2 hours to 4.9±1.2 ng/mg at 24 hours but remained 77-fold greater than the simultaneous blood concentration. Arterial media concentrations followed a time course similar to drug bound to the stent with a half-life of 5.0 hours. After stent removal, media washout was brisk, decreasing to 1.2±0.2 ng/mg after 2 hours and further declining to 0.2±0.1 ng/mg after 22 hours.

**Biological Activity**

Fig 8 shows the effect of implanting forskolin-loaded stents on carotid blood flow, mean aortic blood pressure, and local carotid resistance in group 1a rabbits with forskolin-loaded stents compared with group 1 control coated stents. Carotid blood flow increased immediately after implantation of forskolin-containing stents and remained elevated by an average of 92±46% for the duration of the experiment. This change was significant compared with controls, in which blood flow declined by 21±26% (P<.005). Mean aortic blood pressure decreased modestly after forskolin-loaded stent implantation compared with controls, but this difference was not significant (−27±20% versus −6±15%, respectively; P=.11). Local carotid resistance fell significantly after implantation of forskolin-loaded stent compared with controls (−60±10% versus 44±59%, respectively; P<.005).

The Table summarizes the results of the crush injury, flow-reduction model in group 2 animals. Implantation of forskolin-loaded stents was associated with a significant increase in the time to flow variation and the time to occlusion compared with the use of bare metal (>12-fold) and polyurethane-coated (>5-fold) stents. There was also a mild but significant increase in time to occlusion for the non-drug-containing coated stents compared with the bare metal stents. On inspection, all bare metal stents had occlusive mixed red and white thrombi; all polyurethane stents were obstructed by predominantly white thrombi. Only one of five forskolin-loaded stents had a nonocclusive thrombus, which was red. The four other forskolin stents had minor amounts of thrombi (Fig 1B).

**Discussion**

The present study demonstrates the potential of a polymer-coated metallic stent for short-term local arterial wall delivery of biologically active lipophilic agents. Four hours after implantation, the arterial media of the stented rabbit carotid segment had 460-fold higher concentrations of forskolin compared with blood and 380-fold higher concentrations than the control contralateral artery.
Fig 6. Light photomicrographs of frozen cross sections of ipsilateral and contralateral carotid arteries (A and B, respectively) 4 hours after implantation of stent containing rhodamine B. A, Deformity of arterial wall created by stent strut contact (arrows), which contains the most intense rhodamine staining. The lower portion is from a region in between struts. B, No staining in the unstented, contralateral vessel.

Drug Release From Stent Coating

The kinetics of forskolin release from the HARTS device can be approximated by an exponential decay function with a half-life of 5.8 hours. By 24 hours after implantation, more than 95% of the original forskolin mass was no longer detected in the stent coating. This exponential temporal dependency suggests that forskolin release is largely proportional to the mass of drug remaining in the polymer matrix and can be modeled as a first-order or diffusion-limited system. Moreover, the data are consistent with an empirically derived model of diffusion from membranes with slab geometry.

Forskolin transit into the carotid blood was immediate (Fig 3) with a peak concentration gradient between the distal carotid blood and the systemic circulation developing within 1 minute. This gradient progressively narrowed and was nearly abolished after 4 hours. The net flux of forskolin entry into the carotid blood was also very closely predicted \((r=.997)\) by a monoexponential decay function with a half-life of 1.2 hours. The shorter half-life is most likely indicative of drug distributing from the blood into tissue compartments such that by 4 hours, the net amount of forskolin entering the blood was 61% of the drug eluted off the stent.

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One potential problem with this type of local drug delivery device was that mechanical deformation of the polyurethane or loosely bound drug on the surface of the coating could create a substantial bolus effect on deployment, resulting in untoward systemic effects. Christenson et al documented a bolus effect after implanting polytetrafluoroethylene grafts impregnated
with forskolin into the femoral circulation of sheep. Five minutes after placement, there was a fourfold overshoot compared with steady-state levels, which were achieved only 10 minutes later. By 30 minutes, more than 90% of the drug had eluted off the grafts.

In the present study, inspection of explanted stents by dissecting microscope revealed that the polyurethane coating was intact without rupture or sloughing. The observation that systemic arterial levels increased immediately, reaching $57 \pm 26 \text{ pg/mL}$ within 1 minute after deployment, which was 41% of the steady-state concentration at 4 hours, may represent a small bolus effect. The robustness of the fit of the exponential model to the blood flux data, especially of the 1-minute samples (Fig 4), strongly suggests that the bolus effect related to stent deployment was minor. In addition, the absence of early hypotension or transient changes in flow or resistance argues against a sizable bolus effect.

**Tissue Distribution**

The most important observation of our study was the demonstration of high local arterial wall concentrations of drug compared with systemic blood or other organs. There was a decreasing concentration gradient of forskolin with distance from the stent in both radial and axial dimensions. The time dependency of arterial media forskolin levels closely paralleled the amount of drug remaining on the stent with half-lives of 5.0 and 5.8 hours, respectively. The frozen sections of vessel implanted with a stent containing the lipophilic fluorescent dye rhodamine B showed that drug deposition is relatively higher near the location of the struts and confirmed that there was uptake of drug throughout the media and adventitia. These data suggest that this class of small lipophilic molecules diffuse directly from the stent, although distribution involving the vasovasorum cannot be excluded. Removal of the stent was associated with a $>100$-fold decline in adjacent tissue levels within 2 hours. Tissue washout over the next 20 hours was slower with a half-life of about 8 hours. These observations indicate that high local drug concentrations are dependent on maintaining stent-to-tissue gradients.

Although delivery of pharmaceuticals directly to the arterial wall has been reported using perforated balloons and balloon occlusion systems, few studies have quantified tissue drug levels. Van Lierde et al. infused ridogrel through a microporous balloon. Within minutes after injection, a peak tissue level of 167 ng/mg was reported, a 34-fold increment compared with blood. By 40 minutes, however, tissue concentrations were less than systemic blood levels. In a dose-response experiment, Hong et al. delivered angiopeptin with a porous balloon for 1 minute to the aorta of rabbits. Autoradiography at 30 minutes revealed areas of intense radioactive particles throughout the vessel wall interspersed by adjacent areas devoid of radioactivity. This pattern of distribution may be related to the jet injury created by this delivery system. At 24 hours, the arterial wall angiopeptin concentration was 3.2 pg/mg of tissue. Taken together, these reports suggest that it is possible to achieve early but relatively nonsustainable tissue concentrations by porous balloon local delivery. A potential advantage of using stents for drug delivery is that they prolong tissue contact with a relatively large drug mass. Moreover, as demonstrated in the present study, the highest concentration of drug is delivered...
precisely to the site of arterial injury where the stent has been embedded into the arterial wall. The HARTS stent or similar devices may confer an additional advantage in that they can be removed once therapeutic goals are achieved or if there are untoward effects. The choice of a removable or permanent stent for local drug delivery will depend on to-be-determined factors such as the cost versus benefit of each procedure.

Drug Effects

The bioactivity of forskolin delivered by the stent was demonstrated in two phases of this study. In controlled experiments, implantation of forskolin-containing stents was associated with an immediate, sustained, and significant 92% increase in carotid blood flow and a 60% decrease in carotid resistance, consistent with the known vasodilatory effects of forskolin.17 The observation that mean systemic blood pressure decreased slightly suggests that local changes in resistance accounted for the increase in carotid blood flow. Second, in the crush injury–thrombosis model (group 2), forskolin-loaded stents were associated with a 12-fold prolongation in the time to cyclic flow variations and total occlusion compared with the uncoated stent, whereas polyurethane coating alone mildly prolonged the time to stent thrombosis. The absence of occlusive platelet-rich white thrombus in the forskolin-treated rabbits is consistent with the antiplatelet aggregation properties of forskolin.19

Study Limitations

This study has several important limitations. The simple linear kinetic model for forskolin release, blood flux, and tissue retention should be considered a rough approximation. Although it suggests a first-order or diffusion-limited mechanism, it may be applicable only within a narrow range of drug concentrations tested. Forskolin uptake is likely a much more complex kinetic process involving multiple, spatially distributed compartments and transport and receptor mechanisms. Mechanical factors, including the degree of stent strut contact with the vessel wall and the geometry of the polymer membrane, may also be important considerations.

We did not evaluate the biocompatibility of the polyurethane coating or the potential for the high local concentration of drug to be cytotoxic to the arterial wall. Preliminary studies suggest that a commonly used bioactive polymer, polyurethane-urea, induces a marked chronic inflammatory response when used as a coating on permanently implanted stents.2324 There are no reports of inflammatory responses to the type of polyurethane coating used in our study. Tocoflexol may be more biocompatible because it lacks reactive aromatic side chains, but this requires further evaluation. Polyurethane membranes can be made more hemocompatible by surface treatments with crosslinked albumin, poly(ethylene-oxide), or heparin.25

The effect of forskolin on intimal hyperplasia was not evaluated. The distribution of forskolin into atherosclerotic plaque is unknown. Despite the dramatic prolongation of the time to stent thrombosis in the crush-injury, low-flow model, no inference can be made about inhibition of subacute thrombosis, an event that occurs several days after implantation in humans. Prevention of subacute thrombosis or the proliferative component of restenosis may require maintenance of high tissue levels for days to weeks. With the current method of drug incorporation, the stent coating as a forskolin reservoir was 95% exhausted by 24 hours, and the adjacent medial concentration had decreased to 4.9 ng/mg. Even so, this level is still 12-fold greater than the effective concentration or EC50 of forskolin, which has been reported to be approximately 1×10−6 mol/L for canine and porcine coronary vasodilation.11,26 Moreover, vascular grafts impregnated with forskolin inhibit platelet accumulation for up to 4 days and graft patency at 3 months is significantly improved, despite the fact that graft forskolin content is 90% depleted within 30 minutes.19,21 These data suggest that there may be sufficient forskolin present on the stent to exert an effect for several days, but this too requires specific testing. Drugs with high binding affinities for the stent coating or tissues or with poorer water solubility may persist in the arterial wall for longer periods. Covalent crosslinking of the polymer membrane surface may further retard the rate of drug release. As such, the pharmacokinetics and duration of bioactivity of different drugs delivered by a polyurethane coated stent are likely to vary substantially and need to be documented for each combination of therapeutic agent and coating.

A further limitation is that polyurethane does not absorb water-soluble drugs. This limitation might be overcome by modification of the polymer matrix with aqueous channels or surfactant molecules that ionically bind polar molecules. Water-soluble molecules can be made more nonpolar by the addition of lipid side chains. These modifications may broaden the number of therapeutic compounds that can be delivered by this system.

In conclusion, this report demonstrates that a polymer-coated metallic stent can deliver forskolin to the local arterial wall in high concentrations relative to the blood or other tissues. Delivery of forskolin can be modeled as a simple diffusion process. High local concentrations are dependent on maintaining stent-to-tissue gradients. The delivered drug is biologically active, demonstrating vasodilating and antiplatelet properties. These data suggest the feasibility of a hybrid stent/local drug delivery system to improve the biocompatibility of metallic stents by modification of the microenvironment. Further research is required to determine the pharmacokinetic and biological effects of various candidate drugs delivered by this system and whether stent removal hours to days after implantation confers any clinical advantages.

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References


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