A New Approach for Local Intravascular Drug Delivery
Iontophoretic Balloon

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**Background**
Catheter-based systems are being developed to deliver drugs directly into the vessel wall. Pressure-mediated trauma and lack of homogeneous delivery are key limitations of these approaches.

**Methods and Results**
We studied a new catheter-based delivery system that uses electrical current to force the drug into the vessel wall. The in vivo feasibility of this approach has been assessed by delivering 125I-hirudin into porcine carotid arteries. Vascular levels of hirudin after active iontophoresis (4 mA/cm², 5 minutes) were 80-fold greater than those achieved by passive diffusion (without electricity). Tissue hirudin levels declined over time; by 1 hour after delivery, 80% of the drug had left the vessel wall, and by 3 hours later, the levels of hirudin within the wall were similar to those achieved by passive diffusion. Autoradiography revealed distribution of the drug throughout the entire circumference of the arterial wall within the intima, media, and adventitia. Iontophoresis-mediated vessel wall trauma was minimal (less than 10% endothelial denudation and medial smooth muscle cell damage). Balloon injury after local delivery changed neither kinetics nor distribution of the drug into the arterial wall.

**Conclusions**
1. High local concentrations of hirudin in the arterial wall may be achieved with the iontophoretic balloon catheter. (2) The drug is distributed throughout the entire vessel wall without significant damage. (3) The retention of hirudin in the arterial wall is time dependent. (4) This technique might be useful to deliver therapeutic agents before or after percutaneous vascular interventions. *(Circulation, 1994;89:1518-1522.)*

**Key Words** • restenosis • catheters • angioplasty

Restenosis, which occurs in 30% to 40% of cases, continues to be the “Achilles’ heel” of percutaneous transluminal coronary angioplasty. Restenosis is a complex process of injury-induced events triggered by vessel wall damage. Mechanisms contributing to restenosis include elastic recoil, smooth muscle cell migration and proliferation, extracellular matrix synthesis, vessel wall remodeling, and, possibly, thrombus incorporation and organization.1-4 Although newly developed devices such as stents may partially prevent elastic recoil,5 no other therapeutic interventions have been consistently successful in reducing the overall incidence of restenosis. Pharmacologic approaches to inhibit smooth muscle cell migration and proliferation have been effectively used at supraphysiologic doses in animal research studies.6 However, such high concentrations may be impractical for clinical use because of the risk of systemic side effects and the lack of specific targeting of drugs given systemically. Therefore, there is considerable interest in the development of drug delivery systems that would allow high concentrations of pharmacologic agents to be delivered directly to the site of angioplasty without exposing the entire circulation to the medication. In the present study, we evaluated for the first time the in vivo feasibility of a newly developed delivery system based on the use of low levels of electrical current to force the drug into the arterial wall. We have chosen for this initial study a specific thrombin inhibitor, recombinant hirudin (r-hirudin), to be delivered into porcine carotid arteries, because of the pivotal role of thrombin in the pathogenesis of acute thrombosis after vascular injury.1

**Methods**

**Local Drug Delivery Cathether**
The local drug delivery catheter used in the present study incorporated an iontophoretic mechanism to facilitate drug delivery. Iontophoresis is a form of drug delivery that uses electrical current to enhance the movement of charged molecules across or through tissue. The catheter system was developed by CorTrak Medical, Inc. It consists of a 7F catheter that includes a porous balloon with impermeable ends. The balloon used in this study was 5 mm in diameter, and its working length (permeable region) was 30 mm. An inflation pressure of 2 to 3 psi (0.1 to 0.2 atm) was used to expand the balloon, thus allowing contact of the porous membrane with the vessel wall. During the delivery procedure, the drug solution was recirculated through the balloon catheter at a flow rate of 1 to 2 mL/min with the use of a Masterflex peristaltic pump model 7013 (Cole-Parmer Instrument Co). The balloon includes an Ag-AgCl electrode that serves as the cathode. An adhesive electrode patch (10×16 cm) placed on the skin serves as the anode. A constant-current density of 4 mA/cm² was used to drive the charged drug molecules through the porous membrane into the arterial wall.

**Experimental Procedure**
All procedures performed in this study were approved by the appropriate institutional review committee and conformed

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Radiolabeling of r-Hirudin

Recombinant desulfatohirudin (r-hirudin, CG39393, CIBAGEIGY) was labeled with 125I using the chloramine-T method. In brief, 1 mCi of carrier-free 125I in 50 µL of 1 mol/L sodium acetate (pH 4) and 30 µL of 0.1% chloramine-T were added to 0.1 mg of r-hirudin dissolved in 100 µL of distilled water. The reaction was stopped by the addition of 50 µL of sodium metabisulfite. Unreacted iodine was separated from the labeled r-hirudin by gel filtration on a prepacked Sephadex G-25 cartridge (PD10) from Pharmacia. While they were washed with Tris buffer saline, 20 1-mL fractions were collected and counted in a dose gamma calibrator (AtomLab 100). The major radioactive eluates, representing 89.2% of the original activity, were pooled (fractions 3 to 5) and added up to 10 mL of a solution of unlabeled r-hirudin in distilled water (final concentration, 5 mg/mL).

Protocol

Animals were sedated with intramuscular ketamine (20 mg/kg, Ketalar, Parke-Davis) followed by intravenous injection of sodium pentobarbital (10 mg/kg, Sodium Pentobarbital Injection C, Anpro Pharmaceutical). Adequate anesthesia was confirmed by the absence of a limb-withdrawal reflex. Animals were intubated and ventilated with a volume ventilator (Searle). The ECG was continuously recorded. introducer sheaths (9F and 8F) were placed into the right and left femoral arteries, respectively. Thereafter, each animal received intravenous heparin for anticoagulation (100 IU·kg⁻¹·h⁻¹ bolus plus infusion). The iontophoretic balloon was advanced under fluoroscopic guidance through the 9F introducer over a 0.014-in. guidewire into either the right or left carotid artery. The balloon was fully inflated to a pressure of 2 to 3 psi by pumping the radiolabeled r-hirudin solution, and complete vessel occlusion was verified by contrast injection through a catheter inserted through the contralateral femoral artery. In total, 20 carotid arteries from 10 normal Yorkshire albino pigs (body weight, 24.3±1.3 kg) were treated by delivering the radiolabeled r-hirudin. In 2 arteries, electrical current was not applied at the time of delivery, so we could test passive diffusion of the drug through the system. In the remaining 18 arteries, a current density of 4 mA/cm² was used to deliver the drug during 5 minutes of balloon occlusion. Conventional balloon angioplasty was performed after delivery (lasting 5 minutes) in 8 arteries to assess the kinetics and distribution of the drug into injured vessel wall. To do so, we inflated an 8-mm-diameter balloon (balloon-to-vessel ratio, 1.5 to 2) to 8 to 9 atm during 30 seconds five times in the area previously treated by local delivery. Animals were euthanized with an overdose of sodium pentobarbital, and the carotid arteries were carefully dissected and removed. Experiments were planned to remove simultaneously both carotids from each animal. Two vessels were removed immediately after passive diffusion delivery, four immediately after iontophoresis, four immediately after iontophoresis followed by balloon angioplasty, three 1 hour after iontophoresis, four 1 hour after iontophoresis followed by balloon angioplasty, two 2 hours after iontophoresis, and one 3 hours after iontophoresis (Table). After we obtained weights, vessels were fixed in 4% paraformaldehyde.

So we could investigate iontophoresis-mediated vessel wall damage, both carotid arteries from an additional animal were similarly treated by delivering saline solution instead of radiolabeled r-hirudin. This animal was killed 48 hours after delivery. Evans blue (50 mL, 0.5%) was administered intravenously 15 minutes before death. The treated arteries were perfusion-fixed and processed for light and scanning electron microscopic examination.

Determination of Concentration and Distribution of r-Hirudin Within the Arterial Wall

The amount of r-hirudin delivered into the vessel wall was determined by counting 125I activity in the treated arterial seg-

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delivery followed by balloon angioplasty and 0.19±0.06 μg·g tissue⁻¹·mm⁻¹ at 1 hour (NS compared with matching values in noninjured vessels).

The concentration of r-hirudin, as measured by ELISA, in the extracted arterial segment was 2.24 μg·g tissue⁻¹·mm⁻¹ immediately after delivery and 0.18 μg·g tissue⁻¹·mm⁻¹ at 1 hour after delivery. The amount of r-hirudin calculated by iodine activity in the same segments was 1.92 and 0.09 μg·g tissue⁻¹·mm⁻¹, respectively. Local delivery of r-hirudin into the arterial wall had no systemic anticoagulant effect; activated partial thromboplastin time ratio was 2.85±0.29 before local delivery (100 IU·kg⁻¹·h⁻¹ of heparin were used for systemic anticoagulation) and 2.77±0.32 after local delivery (NS).

**Distribution of r-Hirudin Within the Vessel Wall**

Autoradiography of an artery excised immediately after r-hirudin delivery revealed many silver grains covering the entire arterial wall (Fig 2A), indicating that the drug was distributed throughout the intima, media, and adventitia. Although fewer autoradiographic grains were seen in the artery processed 1 hour after drug delivery (Fig 2B), the drug remained distributed throughout all vessel wall thicknesses. Balloon injury after local delivery did not change the distribution pattern of hirudin within the vessel wall, and the drug similarly was distributed through the entire vessel wall at the sites of arterial injury (Fig 2D and 2E).

**Iontophoresis-Mediated Vessel Wall Damage**

Evans blue stained less than 10% of the intimal surface where the iontophoretic delivery was performed. Scanning electron microscopy showed focal endothelial cell loss (less than 10% of intimal surface) at the site of iontophoretic delivery. Arterial cross sections taken from the treated arterial segments at 4-mm intervals revealed an intact internal elastic lamina, focal medial smooth muscle cell loss, an absence of inflammatory infiltrates, and a normal adventitia (Fig 3).

**Discussion**

This is the first demonstration of the in vivo use of the iontophoretic balloon delivery system to locally introduce r-hirudin into an arterial wall. The use of an electrical field enhanced the movement of r-hirudin into the arterial wall by 80-fold compared with passive diffusion delivery, i.e., when electrical current was not applied to the system. The fact that r-hirudin was detected by ELISA in the extracts from treated arteries indicates that iontophoresis changes neither the structure of the r-hirudin molecule nor, probably, its functional properties.

Retention of r-hirudin in the vessel wall was time dependent; by 1 hour after delivery, approximately 80% of the drug had left the wall, and by 3 hours later, the levels of r-hirudin in the artery were similar to those achieved by passive diffusion. Balloon angioplasty performed after iontophoretic delivery did not change hirudin kinetics into the arterial wall. Intravascular levels of r-hirudin, measured by iodine activity, were 0.65±0.44 μg·g tissue⁻¹·mm⁻¹ immediately after delivery followed by balloon angioplasty and 0.19±0.06 μg·g tissue⁻¹·mm⁻¹ at 1 hour (NS compared with matching values in noninjured vessels).

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**Fig 1.** Bar graph of mean tissue concentrations of r-hirudin (μg·g tissue⁻¹·mm⁻¹) after passive diffusion; immediately after active iontophoresis; and at 60, 120, and 180 minutes after active iontophoresis in noninjured carotid arteries. Bars indicate SEM. Drug concentrations were 80-fold greater with iontophoretic than with passive delivery, but by 3 hours later, most of the drug had left the vessel wall.

**Statistical Analysis**

All values are mean±SEM unless otherwise stated. Comparisons were performed by using the Mann-Whitney U test. Two-tailed P<0.05 was considered statistically significant.

**Results**

**Determination of r-Hirudin Penetration Into the Vessel Wall**

Intravascular levels of r-hirudin into noninjured carotid arteries, measured by iodine activity after iontophoresis with 4 mA/cm² continuous current for 5 minutes, were 80-fold greater than those achieved by passive diffusion (without electricity) (0.78±0.38 versus 0.01±0 μg·g tissue⁻¹·mm⁻¹, respectively). The arterial tissue levels of r-hirudin declined over time, reaching 0.14±0.04 μg·g tissue⁻¹·mm⁻¹ at 1 hour, 0.08±0.01 μg·g tissue⁻¹·mm⁻¹ at 2 hours, and 0.02±0 μg·g tissue⁻¹·mm⁻¹ at 3 hours after delivery (Fig 1). Balloon angioplasty performed after iontophoretic delivery did not change hirudin kinetics into the arterial wall. Intravascular levels of r-hirudin, measured by iodine activity, were 0.65±0.44 μg·g tissue⁻¹·mm⁻¹ immediately after delivery followed by balloon angioplasty and 0.19±0.06 μg·g tissue⁻¹·mm⁻¹ at 1 hour (NS compared with matching values in noninjured vessels).

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Fig 2. Autoradiographs performed in a carotid artery after iontophoretic delivery followed by balloon angioplasty. A, Immediately after iontophoresis in a noninjured segment. Many silver grains are seen covering the entire arterial wall, indicating that the drug is distributed throughout the intima, media, and adventitia. B, One hour after iontophoresis in a noninjured segment. Although many fewer grains are seen, the drug remains distributed throughout the entire wall thickness. C, Control autoradiograph from a section of renal artery not treated by local delivery. Only background grains are seen over the media. D, Immediately after iontophoresis at the angioplasty injury site. The drug is similarly distributed across the vessel wall. E, One hour after iontophoresis at the angioplasty injury site (dark-field micrographs; original magnification, ×200).

Eventually, retention of small molecules, such as r-hirudin, might be improved by binding to larger biomolecules. For example, it has been reported that dextran-bound hirudin distributed in plasma exhibited a prolonged half-life of 7 hours.9 The kinetics of r-hirudin in an atherosclerotic vessel wall remains unknown.

A common problem in the investigation of local drug delivery systems is arterial damage caused by the deliv-
ery systems themselves. Such injury may result in significant neointimal proliferation.\textsuperscript{10,11} The degree of acute vessel wall damage associated with the use of the iontophoretic balloon system, assessed 48 hours after delivery, was minimal (less than 10% endothelial denudation and only focal smooth muscle cell damage) and less than that observed with either perforated balloon systems\textsuperscript{12,13} or polymer-coated stents.\textsuperscript{14} In addition, with iontophoresis, r-hirudin was distributed throughout the entire circumference of the artery and penetrated the intima, media, and adventitia.

The need for a relatively long duration of vessel occlusion to achieve high local concentrations of a drug within the vessel wall makes it desirable to use a reperfusion lumen catheter to avoid distal ischemia during delivery. However, shorter delivery times achieved by the use of multiple inflations and drug-delivering periods (ie, two or three inflations lasting 1 to 2 minutes each) might be investigated to allow percutaneous delivery within a clinically suitable duration of occlusion time to approach coronary atherosclerotic lesions.

This technology may have clinical relevance for the local treatment of arteries undergoing catheter-based interventions, such as angioplasty, atherectomy, rotablation, or stenting. We have chosen for this initial study r-hirudin because of its potent antithrombin activity and because thrombin is believed to play a key role in the pathogenesis of acute thrombosis after vascular injury. The effect of locally delivered r-hirudin and the strategy for preventing thrombus formation and intimal hyperplasia after vessel wall injury have not been addressed in this initial study and should be investigated in future studies. Moreover, other therapeutic agents or strategies (ie, antiproliferative agents or gene transfer therapy) also might be promising when approached by the iontophoretic balloon system.

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