Vascular Remodeling and the Local Delivery of Cytochalasin B After Coronary Angioplasty in Humans

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OBJECTIVES
This study sought to determine the safety, feasibility and outcome of local delivery of cytochalasin B at the site of coronary angioplasty.

BACKGROUND
Previous failures in the pharmacologic prevention of restenosis may have been related to inadequate dosing at the angioplasty site as a result of systemic drug administration. Alternatively, although previous experimental protocols have typically targeted control of excess tissue growth (intimal hyperplasia), it now appears that overall arterial constriction (vascular remodeling) is the major contributor to late lumen loss. Cytochalasin B inhibits the polymerization of actin and has proved to be a potent inhibitor of vascular remodeling in animal models.

METHODS
In this phase I, multicenter, randomized, controlled trial, cytochalasin B (or matching placebo) was administered to the site of a successful balloon angioplasty using a microporous local delivery infusion balloon.

RESULTS
The rate of drug delivery at a constant infusion pressure varied significantly from patient to patient (range 1.7 to 20.2 ml/min), perhaps related to a variable constricting effect of the atherosclerotic plaque on the infusion balloon. The minimal stenosis diameter after the procedure was slightly better in the active drug group (1.86 ± 0.44 vs. 1.49 ± 0.63 mm, p < 0.03), but this difference was not seen at four to six weeks. Although the study was not powered for clinical outcomes (n = 43), the combined end point (death, nonfatal infarction or repeat revascularization) was encountered in 20% of the patients receiving cytochalasin B and in 38% of the patients receiving placebo. Clinical restenosis occurred in 18% of the treatment group and 22% of the placebo group. There were no significant differences between groups in biochemical or electrocardiographic variables.

CONCLUSIONS
Cytochalasin B can be safely administered by local delivery after successful coronary angioplasty and warrants further study of its efficacy in reducing restenosis. (J Am Coll Cardiol 2000;35:583–91) © 2000 by the American College of Cardiology

Late luminal narrowing is the most common cause of recurrent angina pectoris in the first few months after a percutaneous coronary intervention. The pharmacologic prevention of this process has proved an elusive goal, with no unequivocally useful agent identified to date. Failure to achieve adequate drug concentrations has been implicated in the recurring pattern reported in the published data of favorable animal investigations followed by disappointing human trials (1). The local delivery of a drug directly to the site of intervention may be more therapeutic than systemic administration of the same agent. It theoretically should provide very high concentrations of the drug at the target site. In addition, local delivery may reduce the side effects of otherwise toxic agents. To date, the local delivery of a number of promising agents has been studied in animal models, including vascular endothelial growth factor (2), dexamethasone (3), a tyrosine kinase inhibitor (4), paclitaxel (5), urokinase (6), heparin (7), r-hirudin (8), thrombin inhibitor (9), colchicine (10) and c-myc antisense oligomers (11). These agents have generally targeted the reduction of tissue growth as a means of suppressing the intimal hyperplastic response. In contrast, the pharmacologic control of vascular remodeling (likely the more important contributor to late luminal narrowing) has received scant attention. Cy-
tochalasin B may be useful in inhibiting this detrimental remodeling process (12–14).

This report documents the results of the first Food and Drug Administration (FDA)-approved randomized trial involving local delivery of an experimental agent for the reduction of coronary restenosis. Cytochalasin B was administered by a microporous balloon infusion catheter to the target lesion immediately after successful balloon angioplasty. Biochemical and angiographic analyses were used to help assess the safety of the procedure.

METHODS

Patient group. Candidates were selected from patients scheduled to undergo nonemergent percutaneous transluminal coronary angioplasty (PTCA), with randomization occurring immediately after the successful completion of the angioplasty procedure. Inclusion criteria included: 1) age >21 and <80 years; 2) appropriate candidate for balloon angioplasty, as provided by the American College of Cardiology/American Heart Association (ACC/AHA) guidelines (15); 3) adequate renal and hepatic function; and 4) ability and willingness to provide written, informed consent. Patients were excluded if they had any of the following: 1) target lesion ≥12 mm in length or ACC/AHA type C morphology (16); 2) myocardial infarction or thrombolytic therapy within seven days; 3) unstable angina defined as rest pain or onset of unstable symptoms within 48 h; 4) previous target site coronary intervention; 5) target lesion located in a bypass graft; 6) insulin-dependent diabetes mellitus; 7) diastolic pressure >100 mm Hg; 8) ejection fraction <34%; 9) allergy to aspirin or contrast dye; 10) symptomatic carotid or renal artery stenosis; 11) severe arrhythmias; 12) stroke within six months; 13) coagulopathy; 14) pregnancy; 15) use of any other investigational agent within 30 days; 16) use of a fixed wire balloon catheter, a nonballoon interventional device or a “bailout” procedure during treatment of the target lesion; or 17) an angioplasty procedure that was unsuccessful or was complicated by a major dissection (class C through F according to the National Heart, Lung, and Blood Institute [NHLBI]) (17). The study received full approval from each center’s Institutional Review Board.

Coronary angioplasty and quantitative angiography. Balloon angioplasty was performed in accordance with standard practice (15) and included the use of periprocedural aspirin and heparin. The choice of additional medications, balloon catheters and inflation protocol was left to the discretion of the investigator. Angiographic images were obtained before angioplasty, after angioplasty and after local delivery of the study drug in at least two views after intracoronary injection of 100 to 200 μg of nitroglycerin. Follow-up angiography was performed four to six weeks after randomization in 17 patients, including all those in the highest dose treatment group. This period was selected to coincide with animal studies that demonstrated effective inhibition of remodeling four weeks after cytochalasin B administration (13,14). Consistent angiographic views were maintained throughout the procedure and during follow-up angiography.

All procedural and follow-up cineangiograms were forwarded to the Washington Hospital Center’s Angiographic Core Laboratory for analysis by observers who had no knowledge of treatment strategy. Standard morphologic criteria were used to characterize baseline lesion complexity (18) and to identify the occurrence of angiographic complications (19). Lesion length was determined by the “shoulder-to-shoulder” axial obstruction extent. Cine frames were selected from the two “sharpest and most severe” projections of the stenosis before and after the initial procedure and at late follow-up; sequential cine frames were matched for their position within the cardiac cycle. Quantitative angiographic analysis was performed using the CAAS algorithm (20). Using the contrast-filled injection catheter for image calibration, the minimal lumen diameter (MLD) and mean reference diameter (RD) were used to calculate the percent diameter stenosis [(1 – MLD/RD) × 100]. An MLD of 0.0 was imputed in the presence of a total occlusion at baseline or follow-up. Binary restenosis was defined as >50% follow-up diameter stenosis.

Local drug delivery. Immediately after balloon angioplasty, the dilating balloon catheter was exchanged for the drug delivery catheter. This balloon catheter (Microporous Infusion Catheter, Cordis, Miami, Florida) was constructed from a porous inner balloon with 64 pores of 25 μm in diameter, which provided most of the balloon’s strength. This was surrounded by a microporous membrane containing a high density of 0.8-μm pores that permitted controlled delivery of the study drug without jetting of fluid into the surrounding arterial wall (21). Each drug delivery balloon was 20 mm in length, and its diameter was individually selected to match the nominal diameter of the dilating balloon. The drug delivery balloon was centered in the dilated lesion and inflated between 4 and 5 atm for a total of 90 s. Patients unable to tolerate 90 continuous seconds of interrupted coronary blood flow (14% of patients overall) received two or more inflations for a total inflation time of 90 s. Based on in vitro and animal data, it was
anticipated that this inflation protocol would deliver between 9 and 24 ml of study drug (at a flow rate of 6 to 18 ml/min) to the treatment site. However, the actual total dose of the study drug delivered differed somewhat from patient to patient, as the drug was infused through the catheter at a constant infusion pressure, not infusion rate. No upper limit was set for the volume of drug infused.

Dosing regimen. This phase I study was designed using a randomized, double-blind, placebo-controlled, dose-escalating protocol. The first 10 patients received cytochalasin B (Biostent, NeoRx Corporation, Seattle, Washington) at a concentration of 0.1 \( \mu g/ml \) (vs. placebo in a 4:1 ratio of active drug to placebo); the second 10 patients received a concentration of 0.5 \( \mu g/ml \) (4:1 active drug to placebo); the third 10 patients received a concentration of 1.5 \( \mu g/ml \) (4:1 active drug to placebo); and the final group of 13 patients received a concentration of 8.0 \( \mu g/ml \) (1:1 active drug to placebo). The dose of 8.0 \( \mu g/ml \) represents the maximal solubility of the study drug in aqueous solution.

Assessment of safety. Blood and urine tests were obtained at baseline and at 24 h, seven days and 24 weeks after study drug administration and included measures of renal and hepatic function, electrolytes, lipid metabolism, hematologic variables and markers of myocardial injury. Electrocardiograms and vital signs were also obtained at these same intervals. Clinical safety assessments were performed in person or by telephone at 24 h, seven days and four-week intervals thereafter until completion of the study at six months.

Data analyses. Although this trial was designed as a phase I study, the sample size provided adequate statistical power (alpha = 0.05 and beta = 0.10) to detect a clinically important difference (0.5 mm) in net gain in MLD between the two treatment groups. Continuous and categoric data were analyzed using paired and the unpaired t test and the Fischer exact test. The change in MLD was analyzed using analysis of covariance, with the immediate post-PTCA MLD taken as a covariate. The transition in aneurysm, dissection or Thrombolysis in Myocardial Infarction trial (TIMI) status from pre-PTCA to post drug infusion and to four- to six-week follow-up was computed by the Stuart Maxwell test for each treatment group. Multiple linear regression analysis was used to study variables that potentially influenced the drug delivery rate.

RESULTS

Patient demographic data. A total of 43 patients were enrolled in this study, and each received the study drug (or placebo) by local catheter delivery as described earlier. These 43 patients were divided into two groups, based on whether they received cytochalasin B (n = 30) or placebo (n = 13). The drug-treated group was further stratified into four subgroups, based on the concentration of cytochalasin B received—0.1 \( \mu g/ml \) (n = 8), 0.5 \( \mu g/ml \) (n = 8), 1.5 \( \mu g/ml \) (n = 8) and 8.0 \( \mu g/ml \) (n = 6). Table 1 provides baseline demographic and clinical data for each main group. Importantly, there were no statistically significant differences between the drug group and the placebo group.

Drug delivery rate. Figure 1 demonstrates the wide variability from patient to patient in flow rates provided by the drug delivery catheter, despite a consistent fluid-driving pressure of 4 to 5 atm. This is in contrast to the relatively low variability encountered using the same catheter in vitro or in a nondiseased intact porcine coronary model. One
explanation for this disparity involves a variable-constricting effect of the human atherosclerotic plaque on the inflated balloon, thereby impeding the delivery of fluid across the porous membrane. The role of factors that might potentially contribute to this wide variability was explored using both simple and multiple linear regression analysis (Table 2). We studied the relation of the diameter of the inflated drug delivery balloon to five measurements of coronary size: 1) the lumen diameter of the adjacent coronary artery free of obvious disease (RD); 2) the smallest lumen diameter of the lesion before intervention (MLD before PTCA); 3) the smallest lumen diameter of the lesion after completion of PTCA but before insertion of the drug delivery catheter (MLD after PTCA); 4) the nominal diameter of the PTCA balloon used (nominal balloon); and 5) the predicted maximal diameter of the PTCA balloon based on the maximal inflation pressure used and the manufacturer’s balloon compliance data (predicted balloon).

The MLD after PTCA showed the strongest univariate correlation to the drug delivery rate, although the correlation coefficient was small ($r = 0.068$) and the relation was not statistically significant ($p = 0.67$). In an attempt to improve the predictive power, a multivariate model was created (Table 2). No important improvement was realized, however, because the model was only able to account for 1% of the wide variance in delivery rate observed during the study ($r^2 = 0.0103$). Figure 2 details the relation between the drug delivery rate and the single best predictor—MLD after PTCA. The slight downward slope of the multivariate regression line suggests that the rate is lower for drug delivery balloons that are “oversized” relative to the dimensions of the residual stenosis, but this effect is overshadowed by the wide scatter of data points and the marked disparity between observed and predicted values shown on the graph.

Quantitative coronary angiographic measurements. Blinded quantitative angiographic measurements are shown in Table 3. Baseline values of MLD, RD and percent diameter stenosis were similar between the groups. However, immediately after balloon angioplasty and local drug delivery, the stenosis lumen was larger in patients treated with cytochalasin B than in those given placebo (mean MLD $1.86 \pm 0.44$ vs. $1.49 \pm 0.63$ mm), a difference of borderline statistical significance ($p = 0.03$). Both groups showed a modest reduction in MLD from immediately before to immediately after drug infusion ($-0.16 \pm 0.29$ vs. $-0.24 \pm 0.76$ mm, $p = $ NS).

### Table 2. Predictors of Drug Infusion Rate

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<th>Univariate Analysis</th>
<th>Multivariate Analysis</th>
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<tr>
<td></td>
<td>r</td>
<td>p Value</td>
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<tr>
<td>MLD after PTCA</td>
<td>0.068</td>
<td>0.67</td>
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<tr>
<td>Reference diameter</td>
<td>0.053</td>
<td>0.74</td>
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<tr>
<td>Nominal PTCA balloon diameter</td>
<td>0.044</td>
<td>0.78</td>
</tr>
<tr>
<td>Predicted PTCA balloon diameter</td>
<td>0.015</td>
<td>0.92</td>
</tr>
<tr>
<td>MLD before PTCA</td>
<td>0.013</td>
<td>0.93</td>
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MLD = minimal lumen diameter; nominal PTCA balloon diameter = diameter at nominal inflation pressure as provided by each manufacturer; predicted PTCA balloon diameter = diameter at the maximal inflation pressure used in each patient based on balloon compliance data provided by each manufacturer; PTCA = percutaneous transluminal coronary angioplasty.
or worsened dissection versus 11.3 ml/min for those without a dissection, with a mean rate of 9.6 ml/min for patients with a new dissection. The frequency of worsening of an established dissection and one showing the creation of a new dissection, four demonstrating worsening of an established dissection, four demonstrating worsening of an established dissection and one showing resolution of an established dissection. The frequency of angiographic dissection after local drug delivery was statistically similar (45% vs. 54%) between patients who received cytochalasin B infusion at any dose (drug group) and those who received placebo infusion (placebo group). Analysis of the 17 patients (40% of enrollees) with routine follow-up angiograms obtained at four to six weeks demonstrated spontaneous healing and resolution of dissections in all but one patient.

The presence of a new or worsened dissection after drug delivery could not be predicted by the drug/placebo infusion rate, with a mean rate of 9.6 ml/min for patients with a new or worsened dissection versus 11.3 ml/min for those without a dissection (p = 0.28). Similarly, the relative size of the drug delivery balloon could not be shown, statistically, to influence the likelihood of developing a dissection. The mean ratio of drug delivery balloon to post-PTCA stenosis lumen diameter (MLD) was 1.95 for patients with a new or worsened dissection and 1.75 for patients without a dissection (p = 0.35), and the mean ratio of balloon to reference segment diameter was 1.07 for patients with a new or worsened dissection and 1.02 for patients without a dissection (p = 0.25).

On routine four- to six-week angiography, 3 (18%) of 17 patients showed the appearance of a small (mean diameter 2.6 mm) aneurysmal outpouching near the site of the initial target stenosis that was not observed before balloon angioplasty, after balloon angioplasty or after drug delivery (Fig. 4). Two of these patients had received cytochalasin B and one placebo. Intravascular ultrasound evaluation of one of these diverticula revealed that it was confined to the atherosclerotic plaque and adjacent intima, excluding a true anatomic arterial aneurysm.

Table 3. Quantitative Coronary Angiographic Measurements

<table>
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<tr>
<th>Drug Group</th>
<th>Placebo Group</th>
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<tr>
<td>MLD at baseline (mm)</td>
<td>1.05 ± 0.31</td>
</tr>
<tr>
<td>Reference diameter (mm)</td>
<td>2.91 ± 0.40</td>
</tr>
<tr>
<td>Percent diameter stenosis</td>
<td>64 ± 11</td>
</tr>
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* p = 0.03. Data are presented as the mean value ± SD.

FIGURE 3. The frequency and severity of angiographic dissections observed immediately after balloon angioplasty and immediately after local drug delivery. The letters A through F denote progressive grades of severity, with the corresponding boxes representing the number of patients with dissections in each grade. The width of each interconnecting line is proportional to the number of patients involved. One patient was excluded from this blinded analysis because his cineangiographic film was not available.

Angiographic morphology. Blinded analysis of the coronary angiograms by the core laboratory revealed luminal irregularities classified as dissections in 36% of patients immediately after balloon angioplasty. As shown in Figure 3, this proportion increased to 48% immediately after local drug/placebo delivery (p = NS), with six angiograms revealing the creation of a new dissection, four demonstrating worsening of an established dissection and one showing resolution of an established dissection. The frequency of angiographic dissection after local drug delivery was statistically similar (45% vs. 54%) between patients who received cytochalasin B infusion at any dose (drug group) and those who received placebo infusion (placebo group). Analysis of the 17 patients (40% of enrollees) with routine follow-up angiograms obtained at four to six weeks demonstrated spontaneous healing and resolution of dissections in all but one patient.

Clinical outcomes. The combined study end point (death, nonfatal myocardial infarction and/or repeat coronary revascularization) was encountered in 11 patients over the six-month follow-up period (Table 4), occurring in 38% of the placebo group and 20% of the drug group (p = NS). Two patients died. One patient in the placebo group experienced threatened abrupt closure in the laboratory, which was
successfully treated with further PTCA therapy. Eight hours later, the patient had fatal ventricular fibrillation. The other fatality occurred in a patient in the 0.5-μg/ml cytochalasin B drug group. An intracoronary stent was placed after local drug delivery owing to a suboptimal angiographic result. Ten days later, angiographically documented subacute stent thrombosis occurred in the setting of binge drinking and noncompliance with all prescribed medications. The patient died six days later from complications arising from this myocardial infarction.

One patient experienced symptomatic restenosis at four to six weeks, as documented on the study-mandated coronary angiogram. In addition, late (>6 weeks) angiography was performed for clinical indications in eight patients who had recurrent chest pain. Restenosis (diameter stenosis >50%) was observed in six patients, all of whom went on to receive repeat target lesion revascularization by either operation or percutaneous intervention. For the purpose of computing the restenosis rate, patients were included if they had restenosis or if they received a full six months of clinical follow-up without angiographic restenosis. The one patient who received emergent coronary artery bypass graft surgery for failed PTCA during his initial procedure was excluded, as restenosis of the target lesion, if it occurred, would likely be clinically unapparent. When patients were grouped according to assigned treatment, the angiographically confirmed restenosis rate was 18% for the treatment group and 22% for the placebo group.

DISCUSSION

Vascular remodeling and cytochalasin B. Renarrowing of the coronary lumen after balloon angioplasty can result from a combination of encroachment by new tissue growth (neointimal hyperplasia) or constriction of the entire cross section of the artery (vascular remodeling) (22). Because 67% to 83% of late loss in the initial gain afforded by balloon angioplasty is due to this remodeling process (23–25), previous pharmacologic efforts designed to blunt the hyperplastic component of restenosis might fail to eliminate clinically important renarrowing, even if they were successful. A strategy that includes targeting the cellular mechanisms involved in remodeling may ultimately be required for a meaningful clinical response.

Cytochalasin B is a member of a family of fungal metabolites first identified in 1967 and grouped according to their ability to cause polyploidy in dividing cells (26). This property arises from the disruption of cytoskeletal function, an effect that also leads to inhibition of platelet aggregation, clot retraction, migration and phagocytosis. Specifically, cytochalasin B inhibits the polymerization of actin into microfilaments by blocking the terminal addition of new actin monomers (27). During balloon angioplasty, vascular smooth muscle cells undergo microfilament depolymerization as a consequence of direct trauma. As a result, these cells undergo a phenotypic change from a contractile to a secretory/migratory phenotype. Cytochalasin B delivered to the arterial wall near the time of PTCA-induced depolymerization leads to capping of actin filaments, thereby preventing the normal process of repolymerization that occurs over the ensuing weeks. Preclinical data suggest that delaying this natural repolymerization results in matrix secretion while the artery is in its maximally dilated state, thereby increasing arterial wall stiffness and reducing remodeling. The ability to decrease restenosis with cytochalasin B through sustained dilation as opposed to inhibition of neointimal thickening has been shown in porcine femoral and coronary balloon injury models (13,14).

Local drug delivery procedure. The drug/placebo solution was delivered successfully in every patient, with the target infusion rate of 6 to 16 ml/min obtained in 79% of the study group. Nevertheless, Figure 1 reveals a wide variability in the drug delivery rate, well in excess of the narrow range of flow rates recorded when the same delivery system was studied in vitro or in a nonatherosclerotic animal artery. In

![Figure 4. Example of an asymptomatic angiographic “aneurysm” observed on the four- to six-week follow-up (f/u) study that was not present either before balloon angioplasty (pre) or immediately after local drug/placebo delivery (post). The thin arrows denote the site of the stenosis; the thick arrow indicates the aneurysm.](image-url)
this trial, the nominal diameter of the drug delivery balloon was selected to match the nominal diameter of the PTCA balloon. However, it is possible that this method of balloon sizing for ideal “fit” and drug delivery is suboptimal, given the complex morphology, variable radial compliance and unpredictable elastic recoil present in human atherosclerotic lesions. Attempts to explain this variability were not particularly fruitful, but did raise the possibility that selection of the ideal drug delivery balloon diameter might be improved by relating it to the MLD of the stenosis after PTCA, a measurement now rapidly available in many catheterization laboratories through in-laboratory quantitative coronary angiography.

The wide variability in flow rates encountered is not necessarily deleterious. Drug penetration into the lesion is most directly related to maintenance of a steady head of driving pressure, and is therefore more pressure-dependent than flow-dependent. Numerous drug investigations into the techniques of local drug delivery have verified that only a small fraction of infused agent (<2.5%) is actually deposited within the arterial wall, with the remainder either dispersed in the periadventitial space or myocardium or washed downstream into the systemic circulation (28).

**Angiographic analyses.** Quantitative coronary angiography was performed at four time points—before PTCA, after PTCA but before drug delivery, after drug delivery and (in selected patients) at four to six weeks after the procedure. One unexpected finding in this trial was an apparent improvement in early results (greater MLD) in patients treated with higher doses of cytochalasin B (p = 0.03). The postulated mechanism for restenosis reduction by the study drug implies a more delayed effect. However, cytochalasins possess additional biologic activities, such as interference with platelet function (29), that might contribute to this early phenomenon.

Both drug and placebo groups experienced a modest decrease in MLD after the local infusion. Whether this was related to the local delivery procedure per se or to the well-described phenomenon of transient luminal constriction immediately after PTCA (30) cannot be ascertained from this trial. By four to six weeks, the MLD had improved in both groups, consistent with recent data describing the typical time course of lumen diameter changes after balloon angioplasty (31). A nonsignificant trend toward a less marked change in mean MLD was found with the cytochalasin B–treated group. This would be consistent with the hypothesis of drug-induced inhibition of remodeling, perhaps blocking short-term favorable as well as long-term unfavorable changes in MLD.

Minor angiographic dissections are commonly seen after successful balloon angioplasty. Indeed, pathologic studies have shown that intimal flaps are a regular feature of balloon dilation (32), with some investigators reporting a lower restenosis rate in treated lesions showing angiographic evidence of a local dissection (33). In contrast, severe dissections may lead to abrupt vessel closure and a poor clinical result. In this study, careful analysis at the core angiography laboratory revealed a dissection frequency after PTCA of 38%, a value consistent with other core laboratory readings (34,35). The apparent further increase in the frequency and severity of dissections after local infusion is worthy of note. All but four of the dissections observed after infusion were classified as none severe (grades A through C); all of the more severe dissections were present before drug infusion; and all but one dissection resolved spontaneously in four to six weeks in patients receiving follow-up angiography. Whether the local drug delivery process itself can produce arterial injury has been previously explored in animal models, with conflicting results reported to date. Some investigators have demonstrated significant arterial injury after infusion into atherosclerotic and nonatherosclerotic arteries, with an injury pattern suggestive of jet-related dissections (36,37). In contrast, other investigators have found no increased injury (38,39). It is possible that the delivery of solute into the arterial wall results in an increase of fluid in the extracellular space and uncoupling of cells, resulting in propagation of dissection. Given this uncertainty, a careful evaluation of this phenomenon in future local drug delivery trials is warranted. Additional planned clinical studies of cytochalasin B will use a different style of drug delivery catheter; this may help determine whether it is the design of the drug delivery system per se or the infusion process itself that produces these altered angiographic findings (38).

Angiographic “aneurysms” are uncommon after balloon angioplasty (40). The presence of three such aneurysms in this small cohort raises the possibility that they were related to the local drug delivery procedure. Alternatively, the true prevalence of angiographic aneurysms after routine PTCA could be underappreciated, as routine follow-up angiography is rarely performed in this four- to six-week time frame. Anecdotal intravascular ultrasound data from this study suggest that the observed diverticula are not true arterial aneurysms (pseudoaneurysms), as their extent of involvement appeared to be limited to the atherosclerotic plaque and nearby intima. Except for one instance of early restenosis, all three patients experienced a benign course during six months of follow-up.

**Clinical outcomes and future directions.** This study was neither designed nor powered to reliably detect differences in clinical outcomes. The 47% reduction in the primary end point and the 19% reduction in clinical restenosis observed with cytochalasin B should not be interpreted as evidence of drug efficacy, given the wide confidence limits afforded by the small patient group. Nevertheless, the results obtained are useful in establishing the safety of the technique. They also provide the framework for future clinical trials with active local drug delivery, in general, and with therapy using cytochalasin B, in particular. A large-scale
study will be required in the future to accurately assess the efficacy.

**APPENDIX**

**Sites, Principal Investigators and Study Coordinators**

**Indiana University, Indianapolis, Indiana:** Robert Wilensky, MD, James Dillon, MD, and Laura Perkins, RN; **Veterans Affairs Puget Sound Health Care System, Seattle, Washington:** Kenneth G. Lehmann, MD, Miriam S. Platt and Samantha Heath–Lange; **Providence Heart Group, Seattle, Washington:** Jeffrey A. Werner, MD, and Rhonda Staton, RN, CCRN; **University of Washington, Seattle, Washington:** Joseph W. Chambers, MD, and Rene DeVine, RTR; **Community Hospital East, Indianapolis, Indiana:** Edward Harlamert, MD, and Rhonda Sprague, RN, BSN; **William Beaumont Hospital, Royal Oak, Michigan:** Cindy Grines, MD, and Rose Golias; and **Cleveland Clinic Foundation, Cleveland, Ohio:** A. Michael Lincoff, MD, and Susan Hejl, RN.

**Angiography Core Laboratory**

Washington Hospital Center, Washington, DC: Jeffrey J. Popma, MD, and Alexandra J. Lansky, MD.

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**REFERENCES**


