Intracoronary Fibrin-Specific Thrombolytic Infusion Facilitates Percutaneous Recanalization of Chronic Total Occlusion

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OBJECTIVES
We sought to investigate the benefit, predictors of procedural success, and safety of pre-procedural intra-coronary fibrin-specific lytic infusion (ICL) in patients with failed prior percutaneous coronary intervention (PCI) for chronic total occlusions (CTO).

BACKGROUND
Percutaneous coronary intervention for CTO remains a challenge with a high incidence of procedural failure secondary to inability to cross the occlusion with the guidewire.

METHODS
Eighty-five patients who underwent unsuccessful PCI procedures of CTO (more than three months’ duration) had a repeat attempt of recanalization with the use of pre-procedural ICL. Patients received a weight-adjusted dose of either alteplase (tPA) (2 to 5 mg/h) or tenecteplase (TNK) (0.5 mg/h) for a total of 8 h. The total dose of ICL therapy was infused split between the guiding catheter and an intracoronary infusion catheter. A step-down multivariate logistic regression analysis was completed to determine the best predictors of procedural success. In-hospital major adverse cardiac events (MACE) including myocardial infarction, acute reocclusion, stroke, and death, as well as bleeding complications, were also examined.

RESULTS
The procedure was successful in 46 of 85 cases (54%). Four of 85 (5%) contained dissections that did not result in perforations, tamponade, or MACE. The incidence of groin complications was 7 of 85 (8%) and of bleeding complications requiring transfusions was 3 of 85 (3.5%). On multivariate analysis, predictors of success were tapering morphology (odds ratio, 15.5; 95% confidence interval, 3.73 to 63; p = 0.0002) and lack of bridging collaterals (odds ratio, 5.08; 95% confidence interval, 1.53 to 17; p = 0.008).

CONCLUSIONS
Intracoronary infusion of fibrin-specific thrombolytic therapy may provide a valuable and safe option for facilitating percutaneous revascularization of CTO.

Despite the introduction of novel technologies, newer guidewires, and the tremendous advancement of technical skills, percutaneous coronary intervention (PCI) for chronic total occlusion (CTO) remains a challenge in interventional cardiology and is unsuccessful in 30% to 40% of patients (1–5). The mechanism of failure is usually secondary to the inability to cross the occlusion with a guidewire in the majority of cases, whereas the inability to advance or inflate a balloon catheter accounts for only a few cases (6). On the other hand, successful recanalization is associated with improved clinical outcome, lower need of coronary bypass surgery, and a lower cumulative rate of cardiac death and infarction (6). Thus, novel approaches to assist in recanalization of CTO have been proposed in recent years.

Histologically, an atherosclerotic plaque is invariably present in CTO and multiple layers of clot occur on top of episodes of plaque fissuring, accounting for the complete occlusion (7). Pre-procedural fibrin-specific intracoronary lytic infusion (ICL) may lyse the most recent clot component of CTO, allowing passage of the guidewire and facilitating recanalization. We sought to examine the feasibility, predictors of procedural success, and safety of fibrin-specific ICL before repeat PCI for CTO.

METHODS

Study population. The study protocol was approved by the Human Investigation Committee, and all patients provided written informed consent. Between September 1999 and May 2004, 85 patients with CTO in whom the initial attempt at recanalization was unsuccessful were treated with ICL before repeat PCI. Patients with recent coronary occlusion (CTO within the previous three months), an acute myocardial infarction (MI) within the previous three months, and contraindication for lytic therapy were excluded.

Pre-procedural lytic therapy. Patients underwent coronary angiography, and a guide catheter with pre-manufactured side holes was placed in the target vessel. Over a guidewire, a 3-F intracoronary infusion catheter (Ultrafuse-X catheter, SciMed, Maple Grove, Minnesota) was positioned at the face of the CTO. Patients received a weight-adjusted infusion of either alteplase (tPA, Genentech, San Francisco, California; 0.025 to 0.05 mg/kg/h; 2 mg/h for weight ≤60 kg, 3 mg/h for weight 61 to ≤80 kg, 4 mg/h for weight 81 to ≤105 kg, and 5 mg/h for weight ≥105 kg) or a standard dose of tenecteplase (TNK) (Ge-
nentech; 0.5 mg/h) for 8 h before PCI, with the total dose divided between the infusion catheter and the guide catheter (Fig. 1). The dose was divided between the guide catheter and the infusion catheter to prevent clot formation in the guide catheter. Intravenous heparin was administered during ICL to achieve activated clotting time levels between 200 and 250 s. The doses of lytic agents were derived from previous studies using tPA and TNK in the peripheral circulation, whereas the duration of infusion and the dose of heparin were derived from previous studies using heparin with urokinase infusion before revascularization of coronary and peripheral occlusions. The femoral sheath, guiding catheter, and ultrafuse catheter were securely sutured to the skin to ensure stability and were covered with a sterile dressing. Patient immobility during the infusion was ensured to minimize bleeding and groin complications, and adequate analgesia and sedation was administered to optimize patient comfort. Patients were observed in the coronary care unit during ICL infusion and were brought back to the laboratory for attempted recanulation using standard equipment, and in select cases the Frontrunner (LuMend, Stanford, California) device was used. On their second visit, the sheath and catheters were exchanged and empiric antibiotics were given (1 g cefazolin IV; if allergic to cephalosporins, 1 g vancomycin).

Angiographic analysis. Angiographic analysis of the target vessel was performed independently by two experienced interventional cardiologists. In cases of disagreement, a third reviewer adjudicated the findings. The following angiographic variables were examined: morphology of the stump, absolute or functional occlusion, age and length of occlusion, vessel diameter, vessel and segment of the occlusion, number of diseased vessels, presence of in-stent restenosis, presence of moderate or severe calcification, proximal vessel tortuosity, presence of bridging and contralateral collaterals, and side branch at the site of occlusion. Procedural variables examined were the French size, guiding catheter, guidewire used (hydrophilic vs. non-hydrophilic), and mechanism of failure (inability to pass guidewire, inability to pass balloon catheter, and inability to inflate balloon). In-hospital major adverse cardiac events (MACE), bleeding complications, and the need for transfusion were also examined.

Definitions. The CTO was defined as obstruction of a native coronary artery with no luminal continuity and with Thrombolysis In Myocardial Infarction (TIMI) flow grade 0. The duration of the occlusion had to be >3 months, estimated from clinical events such as MI, or proven by previous angiography. Procedural success was defined as restoration of TIMI flow grade 3 with a residual stenosis of <50%; MACE was defined as acute reocclusion, Q-wave and non–Q-wave MI, urgent coronary artery bypass graft or repeat PCI, stroke, or death. The diagnosis of Q-wave MI was documented by the presence of new pathologic Q waves on the electrocardiogram. Non–Q-wave MI was defined as three-fold increase of total creatine kinase with increase of MB fraction, without new abnormal Q waves. Bleeding complications included groin hematoma (of any size), gastrointestinal, genitourinary, retroperitoneal, or intracranial bleeding, as well as the need for transfusion.

Statistics. Statistical analysis was performed using SAS software (version 6.18, SAS Institute Inc., Cary, North Carolina). Categorical variables were examined using a Pearson chi-square test in all cases, except as noted when a Fisher two-sided exact test was used. Continuous variables were examined using the Student t test. A p value of <0.05 was considered statistically significant. A step-down multivariate logistic regression analysis was performed to determine the best predictors of procedural success. Included in the first step were variables with p < 0.1 in the univariate analysis, and included bridging collaterals, presence of single-vessel disease, and tapering morphology of the occlusion.

Figure 1. An angiogram (left) showing a guiding catheter situated in the right coronary artery. A guidewire is advanced in the vessel and a 3-F Ultrafuse-X catheter is advanced to the site of occlusion. The guiding catheter and Ultrafuse-X catheter (right) are sutured to the skin and covered in a sterile fashion.
RESULTS

Clinical characteristics. Baseline clinical characteristics of the patients are shown in Table 1. The majority of patients had a history of hypertension, 63 of 85 (74%); hyperlipidemia, 75 of 85 (88%); multivessel disease, 72 of 85 (85%); ejection fraction (EF) >50%, 31 of 54 (57%); and presented with progressive symptoms of angina (angina class ≥2), 70 of 85 (82%).

Angiographic characteristics. The angiographic features of most CTO were unfavorable, and in 3 of 85 (4%) cases, the lesion length could not be estimated. All CTO were >3 months in duration; 16 were 3 to 6 months old, 16 were 6 to 12 months old, and the remainder (53 CTO) were more than 12 months old. The majority of occlusions were in the right coronary artery (RCA), 53 of 85 (62%); >15 mm in length, 62 of 82 (73%); abrupt morphology, 64 of 85 (75%); and with a side branch at the area of occlusion, 51 of 85 (60%). There were 14 occlusions with small side branches (<1 mm), 16 occlusions with moderate-sized size branches (1 to 2 mm), and 21 occlusions with large side branches (≥2 mm). The majority were in the proximal and mid vessel (60 of 85, 76%), but there were no ostial CTOs in this series.

Initial versus repeat PCI: technical factors. Institution, operators, and procedural duration. The initial PCI attempt was made at our institution in 60 of 85 procedures. In these cases, the repeat PCI was performed by the same operator in all but three procedures. There were eight different operators involved in the study. Data on the initial procedure was available in only these 60 procedures performed at our institution. The initial and repeat procedural durations and fluoroscopy times are shown in Table 2. The procedural duration of the repeat PCI attempt in the 60 patients whose initial procedure was performed at our institution was a mean of 64 ± 28 min and a median of 61 min, and the fluoroscopy time was 23 ± 12 min with a median of 21 min. The initial and repeat failed procedures were aborted if the procedural duration was ≥55 to 60 min, and/or the fluoroscopy time was ≥15 to 20 min, and/or four different guidewires were used, and/or complications occurred.

Table 1. Baseline Clinical Characteristics of All Patients Receiving ICL (n = 85)

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>ICL (n = 85)</th>
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<tbody>
<tr>
<td>Age (mean ± SD)</td>
<td>62 ± 11</td>
</tr>
<tr>
<td>Female</td>
<td>15 (18%)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>63 (74%)</td>
</tr>
<tr>
<td>Diabetes</td>
<td>19 (22%)</td>
</tr>
<tr>
<td>Hyperlipidemia</td>
<td>75 (89%)</td>
</tr>
<tr>
<td>Current smoker</td>
<td>12 (14%)</td>
</tr>
<tr>
<td>Previous MI</td>
<td>37 (44%)</td>
</tr>
<tr>
<td>Previous CABG</td>
<td>24 (28%)</td>
</tr>
<tr>
<td>Multivessel disease</td>
<td>72 (85%)</td>
</tr>
<tr>
<td>Ejection fraction &gt;50%</td>
<td>31/54 (57%)</td>
</tr>
<tr>
<td>Angina class ≥2</td>
<td>70 (82%)</td>
</tr>
</tbody>
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CABG = coronary artery bypass grafting; ICL = intracoronary lytic therapy; MI = myocardial infarction.

Percutaneous coronary intervention. Initial PCI. The wires used in the initial procedure were similar to those used in the repeat attempt and are shown in Table 2. None of the novel Japanese guidewires were used, and the Frontrunner was attempted in four cases. All failures were caused by the inability to cross the CTO with the guidewire.

Repeat PCI. The repeat PCI was performed within six months in 86% of patients, the remainder was performed two years and beyond. The procedure was successful in 46 of 85 cases (54%). There was no difference in the procedural success in the first 42 procedures performed between September 1999 and February 2003 and the last 43 patients performed between February 2003 and May 2004 (23 of 42, 55%; vs. 23 of 53, 53%, respectively; p = 0.91). Of the 85 patients studied, 61 patients received tPA and 24 received TNK. A 7-F guide catheter with side holes was used in 59 of 85 (70%) cases, whereas an 8-F system was used in the remaining cases. Simultaneous contralateral injections were used in five cases (two failures and three successes), where a 6-F diagnostic catheter was used to engage the non-target PCI vessel for visualization of contralateral collaterals and the distal target vessel. There were six cases of in-stent restenosis (four failures and two successes). The same wires were used in the repeat attempt except for the use of the novel Japanese guidewires (Asahi and Miracle Bros.) in two cases. The wires successful in crossing the CTO included the Soft Reflex (Cordis, Johnson & Johnson, Miami Lakes, Florida) (16 cases), Whisper (Guidant, Santa Clara, California) (11 cases), Cross IT (Guidant) (7 cases), Gold Glide (Boston Scientific, SciMed, Natick, Massachusetts) (3 cases), Standard Reflex (Cordis, Johnson & Johnson) (2 cases), and the Miracle Bros. (Abbot Vascular, Santa Fe Springs, California) (1 case). Successful recanalization occurred after the use of one to four of this group of guidewires. The Frontrunner (LuMend, Stanford, California) was optionally used at the operator’s discretion in 15 of 85 cases (18%) after the use of at least two different wires and 15 min of fluoroscopy. It was successful in crossing the CTO in 4 of 15 (27%) cases. The time until crossing the CTO was (mean 34 ± 17 min, median 32 min). Among the failed procedures, inability to cross the occlusion with a guidewire was the primary cause of failure in 38 of 39 (97%).

Procedural outcome and in-hospital complications. There were 4 of 85 (5%) contained dissections that did not result in perforations or tamponade. There were no major adverse cardiac events. The incidence of groin hematoma was 7 of 85 (8%), and incidence of bleeding complications requiring blood transfusions was 3 of 85 (3.5%). Only four patients (5%) had elevations in the total creatine kinase with increase of MB fraction, which were all less than a threefold increase from baseline.

CTO angiographic characteristics and procedural success. Univariate analysis of angiographic and procedural variables in the successful group and the failure group is shown in Table 3. On multivariate analysis, predictors of successful
repeat PCI after ICL were tapering morphology (odds ratio, 15.5; 95% confidence interval, 3.73 to 63; \( p = 0.0002 \)), and lack of bridging collaterals (odds ratio, 5.08; 95% confidence interval, 1.53 to 17; \( p = 0.008 \)) (Fig. 2). Images before and after PCI for CTO of the RCA are shown in Figure 3.

**DISCUSSION**

Recanalization of CTO is associated with a lower incidence of cardiac deaths or MI, reduced need for bypass surgery, and improved anginal class in the majority of patients (6). Predictors of successful revascularization have been described in multiple studies based on single-center experience (1–5,8–13). More recently, a multicenter randomized trial conducted in Europe concluded that occlusion length and duration, the presence of moderate to severe calcifications, and multivessel disease predicted procedural failure (6). Given the favorable outcomes, novel mechanisms that enhance the success of revascularization may have far-reaching clinical benefits. This study examines the safety and feasibility of ICL in patients with previously unsuccessful attempts of recanalization of CTO. Infusion of intracoronary lytic agents before a repeat attempt at recanalization was associated with success in >50% of cases. Because initial PCI for CTO is only successful in 60% to 70% of cases (1–5) and the majority of patients in this study had angiographically unfavorable morphology, this additional success is extremely promising. In addition, the incidence of MACE, bleeding complications, and need for transfusion was minimal. The multivariate angiographic predictors of procedural success in this group of patients were tapering morphology and lack of bridging collaterals.

**Comparison with previous CTO studies.** Previous studies have shown various predictors of successful recanalization of CTO. These have included tapering morphology, shorter occlusion length and duration, single-vessel disease, left anterior descending artery CTO, absence of side branches and bridging collaterals, proximal vessel tortuosity, and moderate to severe calcifications (1–6). However, the definition of CTO varies widely among these studies, and subsequently the predictors of successful PCI. Our study included CTO with many of the unfavorable angiographic characteristics reported in these studies. There are no studies that have reported the predictors of successful reattempt at revascularization of CTO after initial failure. Thus, we believe that our study reaffirms the importance of tapering morphology and lack of bridging collaterals as predictors of procedural success for PCI of CTO, even in repeat attempts after an initial failed procedure and with the use of ICL.

**Comparison with previous studies of lytic infusion.** Previous studies have examined the use of urokinase infusion of chronic occlusions of recanalization of peripheral arteries (14), saphenous vein bypass grafts (15), and native coronary arteries (16,17). The infusion of fibrin-specific thrombolytic therapy in peripheral arterial occlusions for clot lysis has been reported at doses and durations similar to those used in

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**Table 3. Univariate Analysis of the Angiographic Characteristics of All Patients Receiving ICL**

<table>
<thead>
<tr>
<th>Failure (n = 39)</th>
<th>Success (n = 46)</th>
<th>( p ) Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vessel</td>
<td></td>
<td></td>
</tr>
<tr>
<td>RCA</td>
<td>25 (64%)</td>
<td>28 (61%)</td>
</tr>
<tr>
<td>LAD</td>
<td>7 (18%)</td>
<td>10 (22%)</td>
</tr>
<tr>
<td>LCX</td>
<td>4 (10%)</td>
<td>4 (9%)</td>
</tr>
<tr>
<td>Lesion length &gt;15 mm</td>
<td>33/37 (89%)</td>
<td>38/45 (84%)</td>
</tr>
<tr>
<td>Lesion diameter &gt;3 mm</td>
<td>35 (90%)</td>
<td>42 (91%)</td>
</tr>
<tr>
<td>Tapering morphology</td>
<td>4 (10.3%)</td>
<td>22 (47.8%)</td>
</tr>
<tr>
<td>Bridging collaterals</td>
<td>19 (49%)</td>
<td>14 (30%)</td>
</tr>
<tr>
<td>Contralateral collaterals</td>
<td>18 (46%)</td>
<td>26 (57%)</td>
</tr>
<tr>
<td>Side branch at site of occlusion</td>
<td>25 (64%)</td>
<td>26 (57%)</td>
</tr>
<tr>
<td>Moderate or severe calcification</td>
<td>8 (21%)</td>
<td>16 (35%)</td>
</tr>
<tr>
<td>Proximal vessel tortuosity</td>
<td>11 (28%)</td>
<td>7 (15%)</td>
</tr>
<tr>
<td>Distal location</td>
<td>8 (21%)</td>
<td>12 (26%)</td>
</tr>
</tbody>
</table>

ICL = intracoronary lytic therapy; LAD = left anterior descending artery; LCX = left circumflex; RCA = right coronary artery.

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**Figure 2.** Multivariate predictors of successful recanalization of chronic total occlusion with intracoronary lytic therapy infusion in patients with previous failed attempts. CI = confidence interval.
The positioning of the intracoronary ultrafuse catheter at help "soften" the plaque, allowing passage of the guidewire. In addition, absence of bridging collaterals prevents dilution of the dose of administered lytic therapy at the desired site. The majority of our cases were performed in the proximal and mid RCA CTO. We believe that the RCA is more patulous and has fewer branching points proximally, and thus may contain a higher clot burden in the CTO, which would be more responsive to lytic therapy than in left coronary occlusions. Moreover, because of a separate ostium and fewer side branches proximally, a higher lytic dose may be delivered through the guide catheter. However, the type of vessel was not a predictor of procedural success in our study and further studies may be required to validate this hypothesis.

Study limitations. Data on the initial procedure were present in only 60 of 85 patients. This affects our knowledge of technical factors involved in this procedure. These data are difficult to obtain because some of these procedures were performed more than five years ago. However, the majority of patients underwent failed prior attempts as designated by high-volume experienced operators at our institution. Moreover, neither the procedural and fluoroscopy time, nor the number and types of wires used were different between failure in the first and second attempts, reflecting the lack of major technical differences between the initial and failed attempts in the majority of the procedures.

The results of the study may have been influenced by selection criteria and operator experience. Therefore, they may not be fully reproducible under different conditions. By definition, only patients who had failed previous PCI were enrolled, and thus ICL was not compared with placebo. In theory, attempts to recanalize the vessel may have been more aggressive on the second attempt, after ICL administration, and may account for the additional success rate. Moreover, the administration of heparin may have contributed to recanalization.

The optimal time for using this technique after a failed attempt, especially that causing a significant dissection, is unknown. However, we propose a period of four to six
weeks after the initial PCI to help heal the dissection. Further studies randomizing ICL to standard PCI in initial revascularization attempts may be necessary.

The sample size of 85 patients was small, and larger studies are required. However, the procedural success and relative safety of this technique makes it a valuable option in patients with continued symptoms in whom the primary attempt fails. A multicenter randomized study is planned in the upcoming two years to further study this technique. The results of this study will help provide answers to many of the hypotheses suggested in our study.

Conclusions. This study reports the largest series of ICL to facilitate recanalization of CTO in patients with progressive symptoms in whom prior attempts failed. A high success rate with a low incidence of complications was observed with the use of fibrin-specific lytic agents as compared with previous studies of urokinase. Delivery of an adequate dose of ICL is essential and is enhanced by a tapering morphology of the occlusion and the lack of bridging collaterals; ICL should be considered a valuable tool in the management of CTO.

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REFERENCES