Intracoronary Thrombectomy With the X-Sizer Catheter System Improves Epicardial Flow and Accelerates ST-Segment Resolution in Patients With Acute Coronary Syndrome

A Prospective, Randomized, Controlled Study

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Background—In patients with acute coronary syndrome (ACS), percutaneous coronary intervention (PCI) may cause thrombus dislodgment followed by reduced flow and impaired microcirculatory function. We prospectively compared conventional PCI to a strategy of additional pretreatment using the X-sizer thrombectomy system.

Methods and Results—Sixty-six patients (51 [77%] men; 54.9 ± 9.9 years) with ACS (49 with ST-elevation infarction [STEMI]) and suspected intracoronary thrombus were randomized 1:1 to pretreatment with X-sizer and conventional PCI alone. Various aspects of epicardial flow and microvascular function were studied. Baseline data were similar in both groups. Postprocedural TIMI 3 flow was obtained in 90% of X-sizer–treated patients and in 84% of controls (NS); however, corrected TIMI frame count was lower in X-sizer–treated patients (18.3 ± 10.2 versus 24.7 ± 14.1; P < 0.05). No significant group differences were observed in final coronary flow reserve, myocardial blush grade, and myocardial dye intensity. In STEMI, the sum of ST elevation was significantly lower in X-sizer–treated patients immediately after (2.78 ± 3.05 versus 6.15 ± 6.32 mm; P < 0.03) and 6 hours after (2.17 ± 2.31 versus 4.14 ± 3.7 mm; P < 0.05) intervention. ST-segment resolution >50% was observed in 83% of X-sizer–treated patients and in 52% of controls (P < 0.03). Multivariate analysis identified X-sizer treatment as the single independent predictor of ST-segment resolution >50% (OR 4.35; 95% CI, 1.13 to 16.9; P < 0.04). Major adverse cardiac events after 30 days occurred in 2 patients in each group.

Conclusions—In ACS with suspected thrombus, pretreatment with the X-sizer catheter system improves epicardial flow and accelerates ST-segment resolution compared with conventional PCI alone. (Circulation. 2002;105:2355-2360.)

Key Words: reperfusion ■ embolism ■ infarction ■ microcirculation

Thrombus formation after plaque rupture accounts for vessel occlusion in acute myocardial infarction (AMI) and contributes to compromised flow in unstable angina. Percutaneous transluminal coronary angioplasty (PTCA) and stenting are important options for the treatment of patients with acute coronary syndrome (ACS) and are associated with higher reperfusion rates than pharmacological therapy. However, PTCA and stenting carry the risk of mobilizing thrombotic and thrombogenic material, causing distal embolization and microcirculatory impairment, which may limit myocardial salvage gained by these techniques.

The X-sizer is a novel thrombectomy device using an intracoronary helical cutter connected to an external passive vacuum source, allowing fragmentation and removal of intracoronary thrombotic material. It has been shown to be safe and efficacious in patients with thrombus-containing lesions. In the setting of ACS, this device may allow removal of soft material immediately before PTCA or stenting to avoid or minimize distal embolization. Initial thrombus removal also permits early identification of lesion characteristics and more site-specific treatment of the underlying culprit lesion, particularly in patients with total occlusion.

Therefore, this randomized study prospectively compared clinical outcome and various aspects of epicardial and microvascular function in patients with ACS undergoing either conventional PCI or a strategy of additional pretreatment using thrombectomy with the X-sizer catheter system.
Methods

Patient Population
The ethics committee of the University of Vienna approved the study protocol. All patients with ACS admitted to the General Hospital of Vienna between November 2000 and October 2001 undergoing primary or rescue PCI were screened. Patients with native vessel occlusion or with an intraluminal filling defect were eligible. Sixty-six patients were entered into the study. After having given informed consent, patients were randomized 1:1 to X-sizer treatment followed by PTCA or stenting or to PTCA or stenting alone. Diagnosis of ST-segment elevation AMI (STEMI) was based on chest pain for >30 minutes and ST-segment elevation ≥1 mm in 2 or more contiguous leads on the 12-lead ECG. Rescue PTCA was defined as PTCA within 12 hours after failed systemic thrombolysis. Ischemic time was determined as the time interval from symptom onset to first balloon inflation. Patients with unstable angina were included if they presented with recurrent chest pain at rest associated with ischemic ST-segment or T-wave changes. Most of these patients also had elevated serum values of CK-MB and troponin T. Before intervention, patients with STEMI received unfractionated heparin, acetylsalicylic acid (ASA), -blockers, and analgesics unless contraindicated. Patients with unstable angina were pretreated with low-molecular-weight heparin, ASA, and nitroglycerin. Administration of glycoprotein (GP) IIb/IIIa inhibitors was at the treating physician's discretion. During intervention, unfractionated heparin was administered to maintain the activated clotting time >300 seconds. Immediately after stent implantation, 300 mg clopidogrel was given followed by 75 mg/d for 30 days. All patients were treated with ASA 100 mg/d. Patients were followed for a period of 30 days, and major adverse cardiac events (MACE), including death, reinfection, and target lesion revascularization, were monitored.

X-Sizer Catheter System
The X-sizer catheter system (EndiCOR Medical Inc) consists of a dual-lumen catheter shaft connected to a handheld control module. Two catheter sizes, 1.5 mm (7F compatible) and 2-mm (8F compatible), were used (Figure 1). The X-sizer catheter was inserted over a 0.014-inch guidewire and was gently advanced to the culprit lesion. The inner lumen contains a helical cutter rotated at ~2.100 rpm. Activation of the system leads to fragmentation of the thrombus, which is consecutively removed by vacuum through the outer lumen.

Angiographic Measurements
All measurements were performed by 2 experienced observers who were blinded to randomization. Disagreements were resolved by consensus. Quantitative measurements were performed using a computer-assisted quantitative coronary arteriographic (QCA) edge-detection algorithm (ACOMPC, Version 2.1 on Windows NT, Siemens). All QCA measurements were made in end-diastolic frames and were analyzed in 2 different views. Percent diameter stenosis was calculated from the minimal lumen diameter (MLD) and a computer-estimated reference diameter (RD). All measurements are given as mean values of the 2 projections.

Figure 1. a, Acute occlusion of the mid RCA. b, Thrombectomy with X-sizer 1.5 mm (arrow). c, Result after thrombectomy. d, Final result after stent implantation.

Angiographic TIMI flow grade was visually estimated, as previously described. The corrected TIMI frame count (cTFC) was measured with a frame counter on a digital film viewer (ACOMPC) analyzing the number of cine frames required for contrast to first reach a standardized distal coronary landmark. Recorded cine film speed was 25 frames/s. In case of an occluded vessel, cTFC was set to a value of 100.

For evaluation of myocardial blush and myocardial dye intensity, an extended angiographic film sequence of up to 16 seconds was acquired. The grading system introduced by van’t Hof et al was used. For more quantitative analysis, a region of interest (ROI) (mean size, 2150±650 pixels in a 512×512-pixel matrix; 8-bit grayscale with 256 shades of gray in the distal coronary bed of the target artery was defined. Using commercially available software (Osiris 4.0; University of Geneva), myocardial dye intensity was calculated from end-diastolic frames as average intensity within the defined ROI. Frames before contrast injection and frames showing maximum contrast intensity were chosen to calculate the difference in gray pixel units.

Coronary Flow Measurements
Measurements of coronary flow velocity and coronary flow reserve (CFR) were performed after completion of coronary intervention...
using a 0.014-inch Doppler guidewire (FloWire and FloMap, Cardio-metrics Inc). Doppler measurements were obtained distal to the treated lesion at baseline and after injection of 18 and 12 μg adenosine into the left and right coronary artery, respectively. CFR was calculated as the ratio of maximum hyperemic to baseline resting average peak flow velocity.10

**Electrocardiographic Analysis**

All ECG recordings were analyzed by 2 observers (S.D. and B.S.) blinded to study randomization and angiographic findings. A 12-lead ECG was acquired at time of presentation, immediately after intervention, and 6, 12, 18, and 24 hours after intervention. Mean time interval between the preintervention and postintervention ECG was 190±45 minutes in control patients and 203±66 minutes in X-sizer–treated patients (P=0.52). In STEMI, the magnitude of ST-segment elevation was measured 40 ms after the end of the QRS complex. ST-segment score was calculated as the sum of ST-segment elevation >0.1 mV for leads V1 though V6 and I, II, and aVL in anterior infarction and for leads II, III, aVF, V5, and V6 in inferior infarction. In case of true posterior infarction, reciprocal ST-segment depressions in V1 and V2 >0.1 mV were also included. Persistent ST-segment elevation >50% in the postintervention ECG was considered to represent impaired reperfusion.11,12

The 32-point Selvester QRS score was used to estimate the maximum area at risk and the infarcted area after a median of 7 (5 to 10) days. This score uses width and amplitude of Q, R, and S waves in the 12-lead ECG, as previously described. The amount of infarcted myocardium was calculated as the percentage of score points at follow-up in relation to the maximum obtainable score within the initial area at risk.13

**Statistical Analysis**

The primary end point of the total study population was the cTFC. Assuming a pooled SD for cTFC in both groups of 30%, a sample size of 30 patients in each group allows demonstration of a 25% reduction in cTFC by X-sizer in a 2-sided test (α=0.05) with a power close to 0.9. Considering a potential dropout rate of 10%, 66 patients were planned for study inclusion.

Data are presented as mean±SD, median (interquartile range), or number (%) of patients. SPSS V10.0 statistical software system (SPSS Inc) was used for calculations. Differences in normally distributed continuous variables were tested by an unpaired Student’s t test. The Mann-Whitney U test was used to compare abnormally distributed continuous variables. Categorical data were compared with a χ2 test and Fisher’s exact test for expected count <5. Multivariate stepwise logistic regression analysis was performed to identify independent predictors of ST resolution after intervention of >50%. This model included age, vessel size, infarct location, ischemic time, cTFC after intervention, use of GP IIB/IIIa inhibitors, and X-sizer treatment. ORs and associated 95% CIs are provided. A 2-sided P value ≤0.05 was considered statistically significant.

**Results**

**Patient Population**

A total of 66 patients (51 [77%] men; 54.9±9.9 years of age) entered the study. Five patients, 3 randomized to X-sizer treatment and 2 control patients, were excluded from additional analysis for the following reasons. The lesion could not be crossed with the X-sizer catheter in 2 patients, 1 of whom developed type C dissection with vessel occlusion. Another patient with right coronary artery (RCA) occlusion developed sustained ventricular fibrillation after guidewire insertion before X-sizer application and required prolonged resuscitation. In 1 control patient, the lesion could not be crossed with the guidewire, and in another control patient, the thrombus situated at the RCA ostium was dislodged by aspiration through the guiding catheter. Baseline characteristics of the remaining 61 patients are presented in Table 1. There were no significant differences between the 2 treatment groups.

**Procedural Results and Clinical Outcome**

Mean time to balloon time was 291±177 minutes in X-sizer–treated patients and 279±185 minutes in controls (P=0.81). X-sizer catheter sizes of 1.5 and 2.0 mm were applied in 28 and 5 patients, respectively. Intracoronary activation time of the X-sizer was 102±52 seconds (range, 30 to 248). Stent implantation without balloon predilation was performed in 14 patients treated with X-sizer and in 2 patients in the control group (P<0.001). The number of balloons used per patient was lower in X-sizer–treated patients (0.60±0.62 versus 1.45±0.72; P<0.001). Stent length (X-sizer, 17.4±8.6 versus control, 17.7±9.1 mm; P=0.87) and number of implanted stents per patient (X-sizer, 1.17±0.53 versus control, 1.03±0.48; P=0.3) were comparable in both groups. MACE after 30 days, as assessed on an intention-to-treat basis, occurred in 2 of 33 (6.1%) patients randomized to X-sizer and in 2 of 33 (6.1%) control patients. MACE included 3 deaths in patients with cardiogenic shock (2 X-sizer–treated patients) and 1 target vessel revascularization because of stent thrombosis in a control patient. In X-sizer–treated patients, the peak CK-MB of 142±137 U/L was reached after 9.1±6.0 hours, and in control patients, the peak CK-MB of 171±128 U/L was reached after 8.5±5.9 hours (P=0.42).

**Angiographic Results**

Angiographic data before and after intervention are presented in Table 2. TIMI flow grading before and after intervention is shown in Figure 2. Postprocedural TIMI 3 flow was achieved in 27 of 30 (90%) patients pretreated with X-sizer and in 26 of 31 (84%) control patients (NS). However, final cTFC (18.3±10.2 versus 24.7±14.1; P<0.05) and cTFC/MLD (7.5±4.2 versus 10.2±6.0; P<0.05) were lower in X-sizer–treated patients (Table 2).

In patients treated with X-sizer, myocardial blush grade (MBG) improved from 0.3±0.6 before intervention to 1.6±0.9 after thrombectomy and additionally improved to 1.8±1.0 at the end of intervention. In control patients, initial

<table>
<thead>
<tr>
<th>TABLE 1. Baseline and Clinical Data</th>
<th>X-Sizer (%) (n=30)</th>
<th>Control (%) (n=31)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>55.9±9.9</td>
<td>53.9±10.0</td>
<td>0.44</td>
</tr>
<tr>
<td>Male sex</td>
<td>22 (73)</td>
<td>24 (77)</td>
<td>0.71</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>5 (17)</td>
<td>4 (13)</td>
<td>0.68</td>
</tr>
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<td>Present smoker</td>
<td>17 (57)</td>
<td>17 (55)</td>
<td>0.89</td>
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<tr>
<td>Hypercholesterolemia</td>
<td>18 (60)</td>
<td>18 (58)</td>
<td>0.88</td>
</tr>
<tr>
<td>Hypertension</td>
<td>16 (53)</td>
<td>11 (36)</td>
<td>0.16</td>
</tr>
<tr>
<td>Cardiogenic shock</td>
<td>4 (13)</td>
<td>2 (7)</td>
<td>0.21</td>
</tr>
<tr>
<td>Rescue PTCA</td>
<td>7 (23)</td>
<td>3 (10)</td>
<td>0.15</td>
</tr>
<tr>
<td>Previous infarction</td>
<td>3 (10)</td>
<td>3 (10)</td>
<td>0.97</td>
</tr>
<tr>
<td>Multivessel disease</td>
<td>13 (43)</td>
<td>15 (48)</td>
<td>0.69</td>
</tr>
<tr>
<td>ST-elevation MI</td>
<td>23 (77)</td>
<td>23 (74)</td>
<td>0.83</td>
</tr>
<tr>
<td>GP IIB/IIIa inhibitor</td>
<td>22 (73)</td>
<td>21 (68)</td>
<td>0.63</td>
</tr>
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</table>
MBG was 0.4±0.5 and improved to 1.6±1.1 after the intervention. No significant differences in final MBG were observed between both groups. Quantitative dye intensity measurements also failed to show significant differences between both treatment groups (Table 2). However, in patients presenting with initial TIMI flow grade 0/1 (n=47), myocardial dye intensity showed significantly greater improvement after intervention in X-sizer–treated patients (7.3±4.5 versus 4.7±3.3 gray scales; P<0.04).

Coronary Flow Reserve
CFR after intervention was similarly reduced in both groups (Table 2). Regardless of treatment randomization, CFR was significantly lower in patients with initial TIMI flow grade 0/1 than in patients with initial TIMI flow grade 2/3 (1.4±0.32 versus 2.0±0.81; P<0.03).

### Discussion
The present prospective randomized study was designed to assess feasibility and potential benefits of treatment with the X-sizer catheter system in patients with ACS. We demonstrated that thrombectomy with the X-sizer before PTCA or...
Stent implantation improves epicardial flow and coronary microcirculatory function.

In patients with AMI, rapid restoration of epicardial flow has been recognized as an important predictor of clinical and angiographic outcome. Compared with pharmacological approaches, mechanical reperfusion techniques permit almost immediate restoration of epicardial flow with achievement of TIMI 3 flow in up to 85% of cases. In our study, final TIMI 3 flow was obtained in 90% of patients pretreated with X-sizer compared with 84% of patients in the control group. However, more quantitative evaluation using cTFC measurements revealed achievement of significantly faster epicardial flow in patients after X-sizer treatment. Transforming our data to frame rates of 30 per second, final mean cTFC was 22.0 in patients treated with X-sizer compared with 29.6 in control patients. A cTFC value of 20 has allowed stratification of patients into high- and low-risk groups. Moreover, in patients with TIMI 3 flow achieved after primary PTCA, a cutoff value for cTFC of 23 was shown to be highly predictive for clinical and functional outcome.

Although epicardial flow has been identified as an important predictor of clinical outcome, it is well known that patency of the epicardial vessel does not necessarily indicate adequate reperfusion at the level of coronary microcirculation. Impairment of microvascular function may occur particularly with mechanical reperfusion techniques, which may lead to dislodgment of thrombi, causing distal macroembolization and microembolization. Distal embolization and slow or no reflow have been reported in up to 30% of patients treated with primary PTCA. Evaluation of myocardial blush, coronary Doppler flow studies, and analysis of ST-segment resolution have been validated as surrogate markers for restoration of microvascular function and were also analyzed in the present study.

Recently, it has been demonstrated that improvement of myocardial blush after PTCA correlates with long-term mortality. Nevertheless, visual assessment of myocardial blush remains subjective, and more quantitative approaches are presently being developed. We quantified enhancement of dye intensity after contrast injection in predefined dependent myocardial regions and observed significantly greater enhancement of dye intensity after X-sizer treatment in patients with initial TIMI flow grade 0/1. Destro et al used a similar method to measure myocardial blush and demonstrated that increased dye intensity was associated with improved recovery of regional myocardial function.

Measurement of CFR is an accepted method to evaluate microvascular function. As reported in patients after primary PTCA, CFR values were markedly reduced in both of our treatment groups. Higher CFR values in patients with initial TIMI grade 2/3 flow suggest a significant role of early vessel patency for preserving microcirculatory function in patients with ACS.

In patients with STEMI, early ST-segment resolution after coronary intervention has been shown to be associated with greater myocardial salvage and improved clinical outcome. In the present study, early ST-segment resolution was observed in significantly more patients treated with X-sizer than in control patients (82.6% versus 52.2%; P<0.03). Reduction of ST-segment elevation was more pronounced up to 6 hours after intervention in X-sizer–treated patients and only later tended to equalize in both groups. Notably, X-sizer treatment was found to be particularly
effective in patients with a reference vessel diameter >3 mm, which presumably reflects the higher thrombus burden present in larger vessels.4 However, multivariate analysis, including vessel size, infarct location,23 and other parameters with potential influence on microcirculatory function, identified pretreatment with X-sizer as the single predictive parameter for immediate ST-segment resolution after intervention.

Recently, other intracoronary thrombectomy devices using ultrasound energy24 or rheolytic thrombectomy,25 have been applied in thrombus-containing lesions of native and bypass vessels. Some of these studies reported promising results, with achievement of final TIMI grade 3 flow in up to 88% of patients. Most studies were not randomized, and parameters of coronary microcirculatory function were not investigated. At present, only preliminary data evaluating safety and efficacy of X-sizer treatment in patients with AMI are available.4,26 Technical success was reported in ≈90% of patients, and final TIMI flow grades were comparable with those achieved in our study. Neither of these registries used a control group, and data on CTFC and CFR were not reported.

Our study was not powered to demonstrate benefits in clinical outcome. Instead, it used surrogate markers known to be associated with improved ventricular function and mortality. The group of patients with non-STEMI was also too small to evaluate the effects of X-sizer treatment in this particular setting. ECG analysis was performed at predetermined time points before and after intervention, and mean time intervals between ECG tracings obtained before and after intervention were similar in both groups. Continuous ECG recordings could have provided more accurate information but are difficult to apply during cardiac interventions in acutely ill patients. Thrombectomy with X-sizer might increase procedural costs. We analyzed balloon and stent usage in both groups and found similar numbers of implanted stents but a 3-fold higher balloon use in conventionally treated patients.

In conclusion, our data demonstrate that thrombectomy with the X-sizer before PTCA or stent implantation has the potential to minimize thrombus dislodgment and distal embolization, leading to improvements of coronary epicardial flow and microvascular function. On the basis of our results, X-sizer treatment should be particularly considered in patients presenting with STEMI with occluded vessels >3 mm. Larger trials are required to investigate if X-sizer treatment will also result in improvements of ventricular function and clinical outcome.

References

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