Treatment of In-Stent Restenosis With Excimer Laser Coronary Angioplasty Versus Rotational Atherectomy
Comparative Mechanisms and Results

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Background—Atheroablation yields improved clinical results for balloon angioplasty (percutaneous transluminal coronary angioplasty, PTCA) in the treatment of diffuse in-stent restenosis (ISR).

Methods and Results—We compared the mechanisms and clinical results of excimer laser coronary angioplasty (ELCA) versus rotational atherectomy (RA), both followed by adjunct PTCA: 119 patients (158 ISR lesions) were treated with ELCA + PTCA and 130 patients (161 ISR lesions) were treated with RA + PTCA. Quantitative coronary angiographic and planar intravascular ultrasound (IVUS) measurements were performed routinely. In addition, volumetric IVUS analysis to compare the mechanisms of lumen enlargement was performed in 28 patients with 30 lesions (16 ELCA + PTCA, 14 RA + PTCA). There were no significant between-group differences in preintervention or final postintervention quantitative coronary angiographic or planar IVUS measurements of luminal dimensions. Angiographic success and major in-hospital complications with the 2 techniques were also similar. Volumetric IVUS analysis showed significantly greater reduction in intimal hyperplasia volume after RA than after ELCA (43 ± 14 versus 19 ± 10 mm³, P < 0.001) because of a significantly higher ablation efficiency (90 ± 10% versus 76 ± 12%, P = 0.004). However, both interventional strategies had similar long-term clinical outcome; 1-year target lesion revascularization rate was 26% with ELCA + PTCA versus 28% with RA + PTCA (P = NS).

Conclusions—Despite certain differences in the mechanisms of lumen enlargement, both ELCA + PTCA and RA + PTCA can be used to treat diffuse ISR with similar clinical results. (Circulation. 2000;101:2484-2489.)

Key Words: stent • restenosis • lasers • ablation • angioplasty • revascularization

Intracoronary stents reduce restenosis compared with balloon angioplasty (percutaneous transluminal coronary angioplasty, PTCA).1,2 However, in-stent restenosis (ISR) remains an important clinical problem. ISR is caused by intimal hyperplasia (IH).3,4 Intravascular ultrasound (IVUS) imaging has shown that the mechanism of lumen enlargement during PTCA of ISR is a combination of additional stent expansion and tissue extrusion outside the stent segment.5 Although ISR can be treated with PTCA, the recurrence rate, especially in diffuse ISR, is very high.5,6 In a comparative study of ISR therapy, we showed better long-term clinical outcome with excimer laser coronary angioplasty (ELCA) plus adjunct PTCA than with PTCA alone.7 The long-term outcome after rotational atherectomy (RA) has also been reported to be superior to historic controls of PTCA treatment of ISR.8 However, differences in ablation efficiency and clinical efficacy between these atheroablative techniques have not been studied.

In the present study, we compared the mechanism, atheroablative efficiency, and clinical results of ELCA versus RA (both followed by adjunct PTCA) for the treatment of diffuse ISR.

Methods
This study included 249 patients with diffuse (>10 mm in length) ISR in tubular slotted or multicellular stents. Interventional techniques were either ELCA + PTCA (n = 119 patients, n = 138 lesions) or RA + PTCA (n = 130 patients, n = 161 lesions). This represents a consecutive series of patients with diffuse ISR treated at our institution over a period of 3 years. The decision to perform atheroablation with ELCA versus RA was made by the operator. Exclusions were limited to patients participating in brachytherapy protocols (n = 273), focal ISR (n = 401), and saphenous vein graft ISR (n = 83).

Procedure
In lesions treated with ELCA Vitesse catheters (Spectranetics/Advanced Interventional Systems), the mean value of the largest
laser fiber catheter used was 1.81±0.18 mm in diameter; the maximum catheter size was 1.4 mm in 19 (12%), 1.7 mm in 59 (37%), and 2.0 mm in 80 (51%) cases. The laser catheter–to–artery ratio was 0.72±0.21. A single-pass technique was used in 52%. Energy densities were 35 to 55 ml/mm² (mean 45.7±5.5 ml/mm²). A “saline flush” technique was used in all cases. Adjunct PTCA was performed with nominal balloon size 3.6±0.6 mm, balloon-to-artery ratio 1.3±0.3, and maximum inflation pressure 17±3 atm. Additional stents were placed in 41 (25.6%) lesions.

RA was performed with the use of a 1.50- to 2.15-mm diamond-coated metal burrs (Boston Scientific). The mean value of the largest burst used was 1.89±0.18 mm in diameter; maximum size was 1.5 mm in 15 (9.5%), 1.75 mm in 48 (30%), 2.0 mm in 86 (53%), and 2.15 mm in 12 (7.5%) of cases. The burst-to-artery ratio was 0.74±0.20. Adjunct PTCA was performed with nominal balloon size 3.2±0.4 mm, balloon-to-artery ratio was 1.4±0.4, and maximum inflation pressure was 14±5 atm. Additional stents were placed in 48 (26.2%) lesions.

**Angiographic Analysis**

Quantitative coronary angiographic analysis was performed by a core angiographic laboratory blinded to the results of the IVUS analysis and clinical follow-up. A previously validated system (ARTREK, Quantitative Cardiac Systems) was used with the contrast-filled catheter as the calibration standard. Minimal lumen diameter, reference diameter, and percent diameter stenosis were measured before atheroablation and after atheroablation plus adjunct PTCA (final) from multiple projections; the results from the single “worst” view were recorded. Ostial lesions begin at <3 mm of the major coronary artery ostium.

**IVUS Imaging Protocol**

Studies were performed with 1 of 2 commercially available systems. The first system (CVIS/Inter Therapy Inc) incorporated a single-element, 25-MHz transducer and an angled mirror mounted on the tip of a flexible shaft, which was rotated at 1800 rpm within a 3.9F short monorail polyethylene imaging sheath to form planar cross-sectional images in real time (used in 15 [4.7%] cases). The second system (Boston Scientific Corp/Cardiovacular Imaging Systems Inc) used a single-element, 30-MHz beveled transducer mounted on the end of flexible shaft and rotated at 1800 rpm within a 3.2F short monorail imaging sheath (used in 304 [95.3%] cases). With both systems, the transducer was withdrawn automatically at 0.5 mm/s to perform the imaging sequence.

IVUS imaging was performed after administration of 0.2 mg intracoronary nitroglycerin. The ultrasound catheter was advanced 10 mm beyond the target lesion, and an imaging run was performed at the aorto-ostial junction. Studies were recorded only during pullback onto half-inch, high-resolution s-VHS for off-line analysis. IVUS imaging was routinely performed before atheroablation and after atheroablation plus adjunct PTCA (final).

**Quantitative Planar IVUS Measurements**

Two-dimensional, cross-sectional area (CSA), and length measurements by IVUS have been validated. Area measurements were performed with the use of a commercially available program for computerized planimetry (TapeMeasure, Indec Systems Inc) at the image slice with the smallest lumen CSA and included stent, lumen, and IH (sten minus lumen) CSA. When the plaque encompassed the catheter, the lumen was assumed to be the physical size of the imaging catheter. The proximal and distal reference were defined as the most normal-looking cross section (largest lumen with the least plaque) within 10 mm proximal and distal to the ISR lesion but before side branches. ISR length was the axial length of the stent (mm) in which IH CSA was ≥75% stent CSA. If the ISR length continued into the contiguous reference segment, the ISR length included the length of the reference segment whose lumen CSA was ≤25% of the adjacent stent margin CSA. At a pullback speed of 0.5 mm/s, 2 seconds of the videotape playback is equal to 1 mm of axial stent length.

Energy densities were 35 to 55 ml/mm² (mean 45.7±5.5 ml/mm²). Ablation efficiency was normalized to the maximum ablation catheter size and was calculated as the ratio of the lumen volume after ablation divided by the theoretical cylinder with CSA equal to the area of the maximum ELCA catheter or RA burr used and with length equal to the ISR length with a preablation lumen area smaller than the ELCA catheter or RA burr (Figure).

**Clinical Data and Follow-Up**

Patient charts were reviewed, and clinical, demographic, and laboratory data were entered prospectively into the database by a dedicated Data Coordinating Center. Clinical follow-up was performed with telephone contacts or office visits at 1, 3, 6, and 12 months. Major late clinical events were source documented and adjudicated, including death, Q-wave myocardial infarction, and ischemia-driven target lesion site revascularization (TLR; percutaneous or surgical).

**Statistical Analysis**

Statistical analysis was performed with the use of StatView 4.02 (Abacus Concepts) or SAS (Statistical Analysis Systems, SAS Institute Inc). Categorical data were presented as frequencies and compared with paired and unpaired Student’s t tests. We conducted multivariate logistic regression analysis to investigate a potential difference in TLR between the 2 groups, controlling for baseline variables with significant between-group differences. A value of P<0.05 was considered significant; probability values >0.10 are reported as not significant.

**Results**

Baseline characteristics are shown in Table 1. More left anterior descending lesions were treated with ELCA+PTCA than with RA+PTCA (38% versus 23%, P=0.01). The groups had similar percentages of lesions >20 mm in length (60% in both groups) and of total occlusions (7% in the ELCA+PTCA versus 5% in the RA+PTCA group, P=NS). Each group included 58 (36%) lesions with recurrent ISR.
Procedural Results
We observed no perforations, 1 (0.6%) abrupt closure in the ELCA+PTCA group, and 2 (1.1%) no-reflow cases in the RA+PTCA group (P=NS for angiographic complications). Major in-hospital complications were also similar in the 2 groups: 1 (0.7%) death in each group and 4 bypass surgery operations in the ELCA+PTCA group (3.3% versus 0%, P=NS). There were no Q-wave myocardial infarctions in either group. We documented postprocedure elevation of creatine kinase-MB >5× normal in 11% (n=14) with ELCA+PTCA versus 8% (n=11) with RA+PTCA (P=NS); creatine kinase-MB >2× normal occurred 28% and 23%, respectively (P=NS).

There were no differences with respect to preprocedure and final luminal dimensions by quantitative angiography (Table 2). The acute gain was 1.50±0.38 mm with ELCA+PTCA and 1.53±0.41 mm with RA+PTCA (P=NS).

Both groups had similar preatheroablation and final dimensions by quantitative planar IVUS analysis as well (Table 3). There was a trend toward a smaller reduction in IH CSA than with RA+PTCA (2.92±1.08 mm² versus 3.38±1.08 mm², P=0.09). The contribution of stent expansion to the final luminal gain was 15% in the ELCA+PTCA group versus 13% in the RA+PTCA group (P=NS).

Volumetric IVUS Analysis
This analysis included only those patients with routine preatheroablation, postatheroablation, and final IVUS imaging. After both ELCA and RA, lumen gain was entirely due to atheroablation/extrusion; we observed no additional stent expansion. In the ELCA subgroup, 72% of the overall luminal gain (final-atheroablation) was due to ELCA, and 73% was due to adjunct PTCA (54% additional stent expansion and 46% tissue extrusion). In the RA subgroup, 46% of the luminal gain (final-atheroablation) was due to RA and 54% was due to adjunct PTCA (52% additional stent expansion and 48% tissue extrusion). Ablation efficiency was higher with RA compared with ELCA: 90±10% versus 77±12% (P=0.004) (Table 4).

One-Year Clinical Outcome
Long-term results are shown in Table 5. No significant difference was documented between the 2 groups; TLR rates were almost identical (26.2% with ELCA+PTCA versus 27.9% with RA+PTCA, P=NS). TLR was also similar in both groups when patients with additional stent implantation were excluded: 29.8% ELCA+PTCA versus 26.3% RA+PTCA (P=NS). By multivariate analysis, controlling for baseline between-group differences (lesion location), the selection of interventional technique (ELCA+PTCA versus RA+PTCA) still was not predictive of TLR.
TABLE 4. Volumetric IVUS Results

<table>
<thead>
<tr>
<th></th>
<th>ELCA+PTCA</th>
<th>RA+PTCA</th>
<th>P</th>
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<tbody>
<tr>
<td>No. of lesions</td>
<td>16</td>
<td>14</td>
<td></td>
</tr>
<tr>
<td>Before intervention</td>
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<td></td>
<td></td>
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<tr>
<td>IH length, mm</td>
<td>17.1±10.4</td>
<td>19.5±11.9</td>
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<tr>
<td>Stent volume, mm³</td>
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<td>NS</td>
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<td>Lumen volume, mm³</td>
<td>44±18</td>
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<td>NS</td>
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<tr>
<td>IH volume, mm³</td>
<td>96±23</td>
<td>123±33</td>
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<tr>
<td>After atheroablation</td>
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<tr>
<td>Stent volume, mm³</td>
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</tr>
<tr>
<td>Lumen volume, mm³</td>
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<td>72±13*</td>
<td>NS</td>
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<td>Ablation efficiency, %</td>
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<td>After adjunct PTCA</td>
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<td>Stent volume, mm³</td>
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<td>Lumen volume, mm³</td>
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<tr>
<td>IH volume, mm³</td>
<td>55±11†</td>
<td>52±9†</td>
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<tr>
<td>Changes final—post</td>
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<tr>
<td>Change in stent volume, mm³</td>
<td>28±11</td>
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<td>Change in IH volume, mm³</td>
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Variables are mean±SD.
*P<0.03 compared with before intervention; †P<0.03 compared with both after atheroablation and before intervention.

Discussion

Atheroablative techniques have been advocated for the treatment of diffuse ISR in response to the poor long-term results achieved with PTCA alone (restenosis rates 54% to 85%).27–29 The superior results reported after atheroablation plus adjunct PTCA have been attributed to the greater reduction of in-stent neointimal tissue. If atheroablation per se was a strong determinant of clinical outcome, then differences between atheroablative devices with respect to ablation efficiency and the amount of IH removed should translate into improved long-term clinical benefit. In the present study of diffuse ISR, both ELCA+PTCA and RA+PTCA improved lumen dimensions by a combination of tissue ablation, tissue extrusion, and additional stent expansion. Although RA achieved greater IH ablation, this was not accompanied by improved 1-year clinical outcome.

Mechanistic Comparison of ELCA+PTCA Versus RA+PTCA

In vitro and in vivo animal models originally suggested that excimer lasers precisely cut through atheroma, including calcium, without harmful thermal injury.19–24 Conversely, IVUS has indicated that the mechanism of lumen enlargement after ELCA of nonstented lesions was a combination of tissue ablation (76% of lumen enlargement) and vessel expansion (24% of lumen enlargement) with no evidence of calcium ablation.24 In the present study, volumetric IVUS analysis showed that all of the lumen enlargement during ELCA treatment of ISR was the result of tissue ablation. This was probably related to the absence of calcium in ISR lesions and to the scaffolding effects of endovascular stents that may limit laser-induced vessel expansion. As with ELCA, we found luminal enlargement after RA to be exclusively due to tissue ablation. This was similar to a previous volumetric IVUS study assessing tissue ablation after RA of nonfibrocalcific plaque.25

We found 77% ablation efficiency for ELCA, which is similar to the theoretical ablation capacity of the 2.0 Vitesse ELCA catheter and to previous in vitro data with the same catheter.26 Similar ablation efficiency has also been reported for the 1.7 Vitesse ELCA catheter.26 Newer-generation “optimally spaced” ELCA catheters have been shown in vitro to increase ablation efficiency by 20% compared with the currently approved concentric catheters, with a potential to equalize the difference that we observed in ablation efficiency between ELCA and RA. These catheters were not available at the time of the present study.

The 90% ablation efficiency we found for RA was similar to previous reports in non-ISR lesions.27–29 The marginal differences may reflect different elastic properties of lesions within a stent as compared with the previous reports on RA in de novo lesions.29 In the present volumetric IVUS analysis, only 2.0-mm burrs were studied. Ablation efficiency has not been shown to differ among different burr sizes in experimental conditions (D. Dillard, Boston Scientific Engineering Department, Seattle, Wash; personal communication).

The mechanism of adjunct PTCA was similar in both groups, through an almost equal magnitude of tissue extrusion and stent expansion. The magnitude of additional stent expansion during adjunct PTCA (15% and 19% in the 2 groups) was similar to stand-alone PTCA in previous volumetric IVUS studies as reported by us and others.5,7

Short-Term Clinical Results

Despite these mechanistic observations, both ELCA+PTCA and RA+PTCA achieved similar final lumen dimensions by angiography and planar IVUS analysis. Thus, the greater ablation efficiency of RA was
balanced by a relatively smaller contribution of adjunct PTCA to the final lumen dimensions. However, the current study also showed the limitations of these techniques. First, the mean final angiographic residual diameter stenosis measured 18% to 22%. Second, despite ablation with both ELCA and RA, there was still significant residual neointimal tissue within the stent (27% after ELCA + PTCA and 29% after RA + PTCA).

Long-Term Clinical Results
In a previous study comparing ELCA + PTCA versus PTCA alone, we reported superior long-term results with ELCA + PTCA, but the use of ELCA per se was not an independent predictor of TLR.7 The independent determinant of late outcome was the final procedural luminal gain, whether by ablation, by tissue extrusion, or by additional stent expansion.7 In the present study, the similar final lumen dimensions after ELCA + PTCA and RA + PTCA were accompanied by similar long-term results (Table 5). Atheroablation per se may not offer a specific long-term advantage over tissue extrusion or stent expansion as long as final lumen dimensions were maximized. One possible explanation is that diffuse ISR may, in some patients, represent a biologically aggressive response that cannot be counteracted by the simple approach of atheroablation regardless of the efficiency. On the other hand, we cannot exclude the possibility that catheters with greater ablation efficacy might have yielded greater reduction in IH hyperplasia and possibly incur an additional clinical benefit.

The 2 interventional techniques had a 26% to 28% TLR rate. This “relatively” low TLR may be explained by 2 factors. (1) The 1-year mortality rate was 5% to 8%; these patients might otherwise have presented with recurrence. (2) A significant number of patients were excluded from this analysis because of participation in vascular brachytherapy protocols; these patients may have represented a higher-risk group. The placebo arm of the Washington Radiation In-Stent Restenosis Trial had a clinical recurrence rate of 60%, whereas the active treatment arm (103) had a markedly lower recurrence rate.30

Study Limitations
This study was a retrospective analysis of lesions treated with ELCA + PTCA or RA + PTCA; lesions were not randomized to the 2 treatment strategies. The operators were not blinded to any of the IVUS imaging runs. The volumetric IVUS methods used to separate IH tissue ablation from extrusion was available only in the subset of patients with IVUS imaging after atheroablation (before PTCA). Since final IVUS imaging was routinely performed immediately after completion the intervention, this study was unable to investigate the recently reported time-dependent effect of tissue reintrusion within the treated segment.31 Although the type and length of the initially restenosed stents were unavailable, we have previously documented that the length of IH (measured by IVUS) rather than the stent length is a predictor of recurrent ISR.32 We do not believe that stent recoil contributed significantly to the results because tubular-slotted and multicellular stents do not recoil.33,34 It is possible that with more aggressive tissue ablation, the final procedural result might have been improved in both groups. However, the anticipated (but not yet proven) clinical benefit from even more aggressive atheroablation should be carefully evaluated against the risk of procedural complications, which were very small with the present approach.

Conclusions
Despite the higher ablation efficiency of RA compared with ELCA, ELCA + PTCA and RA + PTCA yield similar long-term clinical results in the treatment of diffuse ISR in native coronary arteries.

References


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