The Effects of Intracoronary Brachytherapy on the Natural History of Postangioplasty Dissections

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OBJECTIVES
The aim of this study was to determine the natural history of postangioplasty intravascular ultrasound (IVUS)-detected dissections and to assess the influence of intracoronary beta-radiation on dissection resolution.

BACKGROUND
Intracoronary radiotherapy is considered to impair exaggerated vessel healing. Conversely, excessive healing impairment may increase the risk of complications due to unhealed dissection. Alternatively, residual dissection may represent an innocent marker of adequate therapy.

METHODS
Immediate postangioplasty and six-month follow-up IVUS studies of 94 patients in the IVUS substudy of the MultiVitamins and Probucol (MVP) trial and 26 nonstented patients in the Beta Energy Restenosis Trial (BERT) were analyzed for the presence or absence of dissection.

RESULTS
Of the 28 patients with postangioplasty dissections in MVP, only one had evidence of residual dissection at six months (95% confidence interval [CI] for failure rate 0.2%; 20.2%). Conversely, 9 of 16 dissections had healed in BERT (95% CI for failure rate 30.6%; 79.2%) (p < 0.0002). Nevertheless, an index based on dissection arc and length demonstrated improvement in the irradiated patients. Irradiated patients with residual dissections showed significant increase in lumen area at six-months (5.10 ± 0.98 to 7.11 ± 2.61 mm², p < 0.02) not noted when there was resolution of the dissection (6.03 ± 2.38 to 6.36 ± 3.33 mm², p = NS). In both groups the external elastic membrane area was unchanged at follow-up.

CONCLUSIONS
Resolution appears to be the natural history of IVUS-detected dissections in most cases. Significant resolution of dissection occurs following intracoronary beta-radiation as reflected in reduced dissection index at six-months in these patients, although significant impairment of vessel wall healing was noted. (J Am Coll Cardiol 2000;36:59–64) © 2000 by the American College of Cardiology

Postangioplasty dissections have been associated with acute vessel closure and are a frequent cause for stent deployment in routine practice. Their association with long-term follow-up is less clear, although there appears to be no more restenosis in mild to moderate dissections (1).

The problem of restenosis appears to be due to an exaggerated healing response of the artery after balloon injury, with smooth muscle cell migration and multiplication causing luminal compromise when associated with a lack of compensatory vessel wall dilation (2–4). Intracoronary brachytherapy has recently been introduced to impair the vessel's healing ability in an attempt to limit this apparently exaggerated response (5,6). The degree of this impairment may correspondingly influence the vessel's ability to heal dissections. Intravascular ultrasound (IVUS) has been shown to be an extremely sensitive in vivo method for identifying coronary dissections (7–11).

The purpose of this analysis was to determine the natural history of postangioplasty dissections and to evaluate the effect of beta-radiation on the ability of these vessels to resolve dissections as a measure of healing.

METHODS
The study groups consisted of all the patients enrolled in the IVUS substudy of the MultiVitamins and Probucol (MVP) trial and the Canadian arm of the Beta Energy Restenosis Trial (BERT 1.5). Both trials were performed at the Montreal Heart Institute.

To determine the natural history of IVUS-detected postangioplasty dissections, the MVP patients were analyzed for the presence and degree of dissection immediately postangioplasty and at six-month follow-up. The MVP study design has been previously described, including inclusion and exclusion criteria (12). Briefly, patients referred for elective coronary angioplasty were evaluated at least 30 days prior to their scheduled procedure. Patients were eligible if they were scheduled to undergo standard balloon angioplasty on at least one native coronary artery and had at least one de novo target lesion with luminal narrowing of 50% or more by caliper measurements. In the MVP trial, patients were randomly assigned to treatment with probucol 500 mg twice daily, a multivitamin complex comprising vitamin E 700 IU, vitamin C 500 mg, and beta carotene 30,000 IU twice daily, both treatments or placebo. All medications

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Manuscript received July 30, 1999; revised manuscript received January 17, 2000, accepted March 2, 2000.
were commenced 30 days prior to scheduled angioplasty and continued until follow-up angiography was performed.

Of the 317 patients who were randomized to one of the MVP treatment arms, a total of 161 patients entered the trial prior to initiation of the IVUS substudy. In addition, 49 patients did not undergo baseline IVUS study for various reasons including target vessel too small, tortuous or diffusely diseased; and stent deployment and the presence of extensive dissection, thrombus, or recoil. Of the 107 patients who underwent IVUS after angioplasty, 11 were not studied at follow-up for various reasons, including total or subtotal occlusion, failure to cross the treated site, bypass surgery, death or withdrawal from the trial. In addition, two patients underwent both IVUS studies, but extensive calcification precluded quantitative analysis at the angioplasty site. Thus, 94 patients constituted this study population and were distributed into the groups as follows: 21 received probucol, 25 multivitamins, 20 the combined treatment, and 28 placebo.

The BERT study design has also been described (13), including inclusion and exclusion criteria. Patients were included if they had de novo lesions of <15 mm in length or diameter. In the BERT, patients were randomly assigned to intracoronary beta-radiation treatment with a prescribed dose of 12, 14, or 16 Gy at 2 mm from the source center, delivered immediately following successful angioplasty. Thirty patients were randomized and treated with intracoronary brachytherapy. Four patients underwent stenting within the first week postirradiation as has been previously reported. The remaining 26 patients comprised the irradiated, nonstented control population. In both these studies angiography and IVUS were performed immediately at the termination of the therapeutic procedure and again at six-month follow-up.

**IVUS examination and analysis.** The methodology for IVUS examination and analysis has been previously described for both studies (14,15). Briefly, IVUS examinations were always preceded by administration of intracoronary nitroglycerin (0.3 mg). The IVUS catheter was advanced to the treated site to an easily recognizable landmark and withdrawn up to the guiding catheter. An automatic pullback device was used at a speed of 0.5 mm/s in BERT, whereas slow manual pullbacks were performed by experienced operators in the MVP trial. The IVUS recordings were performed on high-resolution S-VHS tape for off-line analysis, with a detailed running audio commentary describing the location of the ongoing IVUS interrogation.

All the images were interpreted by experienced technic-ians supervised by a cardiologist blinded to treatment assignment within the specific trials. The postangioplasty and six-month follow-up IVUS studies were analyzed side by side. Great care was taken to ensure that the same and correct anatomic slice was used in both IVUS studies. Fluoroscopic and angiographic images and audio commentary were used to determine the axial location of the ultrasound transducer and of IVUS landmarks relative to the angioplasty site and to side branches. In both trials, IVUS landmarks (side-branches, veins, calciumication, and fibrotic deposits) were used to allow for matching of the anatomic slice in both studies using frame-by-frame review of the images. A known pullback speed facilitated matching of the cross-sectional image in BERT. Patients who underwent implantation of coronary stents were excluded from the analysis.

All the IVUS studies were prospectively analyzed for the presence of dissections at the angioplasty site. The recordings were also analyzed for arc and length of dissection, presence, position and arc of calciumication, vessel area as represented by that circumscribed by the external elastic membrane and lumen area. The arcs (in degrees) of dissections and calciumication were graded in the IVUS slice showing the most extensive dissection/calcification according to a previously described system (8). In this classification a grade of 1 was assigned to an arc of dissection or calciumication of 1° to 90°, grade 2 for 91° to 180°, grade 3 for 181° to 270° and grade 4 for an arc >270°. The length of dissection in BERT was determined based on the speed of the automatic pullback and the number of frames in which it could be identified. A semi-quantitative assessment of dissection length was made in MVP based on several recorded elements including IVUS landmarks, recorded fluoroscopy of catheter position and detailed audio comments. This assessment consisted of a three-point scale with the length of the dissection reported as short 1), medium 2), and long 3) corresponding to estimations of <6 mm, 6 to 10 mm and >10 mm in length. Dissection length was also defined using the same scale in BERT to allow correlation between both trials. A dissection index of length (0 to 3) multiplied by arc (0 to 4) was also calculated in an attempt to classify the size of the dissection based on a combination of these parameters.

To determine the natural history and the effect of effective antirestenotic treatments on dissection resolution, patients in the MVP trial with postangioplasty dissections were analyzed for the presence and extent of dissection at six-month follow-up. The same analysis was performed for the patients in BERT to determine the effect of intracor-o-nary brachytherapy on the resolution of dissections.

**Statistical analysis.** Characteristics of patients with post-angioplasty dissections were summarized using mean ± SD or frequency tables (n and %) depending on the nature of
the variable. The Student unpaired t test was performed to test for mean differences among groups (BERT versus MVP and residual versus resolved dissection). To compare proportions, either the chi-square test or, when appropriate, the Fischer exact test was used. Two-way (time-group) repeated-measure analysis of covariance controlling for baseline values (16) was used to test differences between groups for the evolution across time of continuous variables (lumen area and index). When time × treatment interaction was significant at a significance level of 25% (p < 0.25), slice effect (also known as simple effect [17]) analyses were performed. All tests were done with an overall significance level of 5%—that is, a p value < 0.05 was considered statistically significant. SAS release 6.12 software was used to perform all statistical analyses.

RESULTS

In the MVP IVUS substudy, 28 of the 94 patients were found to have IVUS evidence of dissection at the completion of the angioplasty procedure. No significant differences were noted between the different treatment arms with regard to proportions of patients with dissections. In the BERT study, 16 of the 26 nonstented patients had IVUS evidence of dissection immediately following percutaneous transluminal coronary angioplasty (PTCA) and irradiation (Table 1). The baseline characteristics of the patients and vessels are presented in Table 2, while the features of dissections immediately postangioplasty and at six-month follow-up are shown in Table 3. There was a significantly higher number of men with dissections in the MVP trial (24 men:4 women) (p < 0.001) not present in the BERT (8 men:8 women).

In the 28 patients with postangioplasty dissections from the MVP trial, complete resolution occurred with only a single dissection not entirely resolved at six months (95% confidence [CI] for failure rate 0.2%; 20.2%) (p = 0.0001, baseline to follow-up). That patient was treated in the combined probucol and multivitamin arm of the trial. In contrast, 7 of the 16 dissections identified immediately postangioplasty in BERT were still present at six-month follow-up (Fig. 1) with 9 having resolved (95% CI for failure rate 30.6%; 79.2%) (p < 0.0002, vs. MVP) (Fig. 2). Irrespective of the treatment, no postprocedural IVUS-detected dissection went on to vessel occlusion at six months. Comparison of patients from both trials revealed no significant differences between baseline characteristics except for a smaller proportion of women in the MVP as stated above. Due to the very low proportion of women in the cohort of patients with dissections from the MVP, male gender was also found to be significantly more frequent in the patients with resolution of dissection (p < 0.02). Within the BERT study, no significant differences in baseline characteristics between patients with and without dissection resolution were found. When compared directly with MVP, a significant impairment of dissection resolution occurred at six months in the cohort from the BERT study (p < 0.002).

Postprocedure lumen size, calcification and size of dissection were not correlated with dissection resolution. When specifically assessing the irradiated patients, a significant reduction of dissection index from postprocedure to follow-up was noted (p = 0.0001) (Table 3). When assessing only the irradiated patients with residual dissections there was a tendency for improvement in dissection index that did not reach statistical significance owing to the small numbers. Of these seven patients, three had a reduction in index at follow up, while four were unchanged (p = 0.25 based on the exact McNemar test). No patient had an increased index at follow-up. There was no correlation with prescribed radiation dose. Three of six vessels (50%) prescribed 16 Gy had residual dissections, whereas two of seven (29%) and two of three vessels (67%) had been prescribed 14 and 12 Gy, respectively. Of the four patients undergoing

Table 1. Treatment Subgroups in the BERT and MVP Studies

<table>
<thead>
<tr>
<th></th>
<th>Beta-Radiation</th>
<th>Probucol</th>
<th>Multivitamins</th>
<th>Both</th>
<th>Placebo</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients</td>
<td>26</td>
<td>21</td>
<td>25</td>
<td>20</td>
<td>28</td>
<td>94</td>
</tr>
<tr>
<td>Dissection acute</td>
<td>16</td>
<td>6</td>
<td>9</td>
<td>6</td>
<td>7</td>
<td>28</td>
</tr>
<tr>
<td>Dissection follow-up</td>
<td>7*</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>1</td>
</tr>
</tbody>
</table>

*p < 0.02 beta-radiation versus total MVP.

Table 2. Baseline IVUS Characteristics of Patients With Dissections

<table>
<thead>
<tr>
<th></th>
<th>BERT</th>
<th>MVP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients with dissections</td>
<td>16</td>
<td>28</td>
</tr>
<tr>
<td>Gender (male/female)</td>
<td>8/8</td>
<td>24/4*</td>
</tr>
<tr>
<td>Age (yrs)</td>
<td>58.6 ± 11.7</td>
<td>57.5 ± 10.0</td>
</tr>
<tr>
<td>Target vessel (LAD/Cx/RCA)</td>
<td>6/6/4</td>
<td>12/8/8</td>
</tr>
<tr>
<td>Calcification (grade)</td>
<td>1.63 ± 1.27</td>
<td>1.24 ± 1.10</td>
</tr>
<tr>
<td>Calcification (superficial/deep)</td>
<td>10/6 (62.5/37.5%)</td>
<td>12/9 (42.9/32.1%)</td>
</tr>
<tr>
<td>Post-PTCA lumen area (mm²)</td>
<td>4.58 ± 2.91</td>
<td>4.87 ± 2.18</td>
</tr>
<tr>
<td>Post-PTCA EEM area (mm²)</td>
<td>13.95 ± 5.71</td>
<td>13.48 ± 4.01</td>
</tr>
</tbody>
</table>

*p < 0.001 men to women. Cx = circumflex artery; LAD = left anterior descending artery; RCA = right coronary artery.
target lesion revascularization (TLR) within one year of the index procedure in the BERT, none had IVUS evidence of residual dissection at six months. None of the seven patients with residual dissections at six months fulfilled angiographic criteria of restenosis or underwent TLR. A single patient with a residual dissection underwent target vessel revascularization for a lesion proximal to the treated site, unrelated to the dissection. Therefore, no correlation between residual dissections and restenosis or poorer outcomes was found.

Within the group of patients having undergone intracoronary radiotherapy, there was a significant increase in lumen size in those patients with residual dissections from 5.10 ± 0.98 mm² postprocedure to 7.11 ± 2.61 mm² at six months (p < 0.02). This contrasted with the irradiated patients with healed dissections where lumen area was unchanged at follow-up (6.03 ± 2.38 versus 6.36 ± 3.33 mm², p = NS). The external elastic membrane (EEM) area remained constant in both groups of irradiated patients (Table 4).

**DISCUSSION**

Studies have been performed to determine the effect of immediate postangioplasty dissection on outcome, and, in particular, on restenosis (1,10,18). There is, however, a paucity of reported information on the natural history of these dissections with regard to resolution and vessel repair. The IVUS represents the most sensitive imaging modality for determining the presence and characteristics of intracoronary dissections in current clinical use. It was therefore used for this assessment.

Ionizing radiation produces significant effects on wound healing (19). Progressive loss of vessels, fibrous tissue replacement and reduction of neovascularization may occur (20). Fibroblasts can be permanently altered by radiation, being unable to produce sufficient collagen to keep up with wound demands. Alternatively, the collagen that is produced may not mature quickly enough to meet the demands of the acute phases of wound healing (19,21–23). Radiation...
therapy has been employed in treatment of keloid formation to limit the exaggerated healing response in that condition (24, 25). Intracoronary brachytherapy has been recently introduced as a method to combat postangioplasty restenosis. This is based on the rationale that restenosis represents an exaggerated healing response to balloon damage. The resolution of IVUS-detected intimal dissections is a manifestation of the vessel’s ability to heal the tear. To impair the healing process that results in restenosis, intracoronary radiation may also effectively impair or slow the vessel’s ability to resolve dissections.

The cohort from the MVP trial demonstrates that nearly all dissections in nonirradiated coronary vessels have resolved by six months after standard balloon angioplasty. The uniform resolution of IVUS-detected dissections in this study, irrespective of the treatment group, the vessel size, or any other IVUS criteria, excludes the role of any of these features as risk factors for lack of dissection resolution. The relatively large cohort from the BERT that was seen to have residual dissections at six months implicates intracoronary brachytherapy as the cause of a reduced ability of the vessel to heal dissections. The residual dissections, however, had no correlation with a worse outcome. This is in distinction to some degree with the recent publication of late acute occlusion in two nonstented vessels with major dissections following angioplasty and radiation (26). It should be noted, however, that these dissections were more severe than in our cohort.

Despite residual dissections being manifest in a relatively large group of patients, the reduction in arc and length over six months indicates that the healing process has been only partially impaired. In the presence of an increased lumen area in patients with residual dissections, the beginning of aneurysm formation cannot be excluded; however, in the presence of a maintained EEM area, this finding may represent a desirable result due to adequate radiation dosage. Two-year IVUS follow-up will be enlightening with regard to ongoing healing and related vascular remodeling.

Study limitations. This is a comparison of two different studies, with different although similar inclusion and exclusion criteria. The angioplasty in the BERT was more aggressive, with 16 of 26 (62%) nonstented patients having dissections as opposed to 28 of 94 (30%) patients in the MVP study. Despite this, the starting populations of patients and lesions with dissections were similar. All four arms of the MVP trial were included even though an effect of the active treatment arms on healing cannot be excluded. The only nonresolved dissection from the MVP came from the combined probucol and multivitamin group and would have been excluded had only the control group been used.

The IVUS studies in the MVP trial were performed using a manual pullback technique and therefore a precise measurement of dissection length could not be determined. Rather, a semi-quantitative estimate was relied upon in that study. Finally, the relatively small numbers may limit the ability to determine significant risk factors for lack of dissection resolution.

Conclusions. The natural history of IVUS-detected postangioplasty dissections appears to be resolution by six-month follow-up in the majority cases. Intracoronary brachytherapy to prevent restenosis impairs the ability of vessels to resolve these dissections. The presence of residual dissections appears not to be correlated with a poor outcome and, in fact, is associated with an increased lumen area. Nevertheless, the majority of dissections have completely resolved by six months after intracoronary radiation, with the remaining vessels demonstrating evidence of partial healing.

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REFERENCES

4. Post MJ, Borst C, Kuntz RE. The relative importance of arterial...