Coronary Excimer Laser Angioplasty: Reduced Complications and Indium-111 Platelet Accumulation Compared With Thermal Laser Angioplasty

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The relative safety and thrombogenicity of pulsed excimer and thermal laser angioplasty systems were compared in 20 normal coronary artery segments in a total of seven pigs. Using similar over the wire catheter systems and laser delivery periods of 3 to 5 s, thermal laser angioplasty was achieved with a 1.3 mm metal probe heated with 10 W of continuous argon laser energy and excimer laser angioplasty was performed with a 4.5F excimer laser catheter consisting of 13 concentrically arranged 200 μm fiber optics delivering 35 to 40 mJ/mm² of xenon chloride (308 nm) excimer laser irradiation at a repetition rate of 25 to 30 Hz and a pulse duration of 120 ns.

On angiography, the incidence of vessel perforation (1 in 10 versus 3 in 10) and abrupt vessel closure (0 in 10 versus 2 in 10) was less with excimer compared with thermal laser angioplasty. Macroscopically, there was a greater incidence of mural and occlusive thrombus formation after thermal laser than after pulsed excimer laser angioplasty. Histologic examination confirmed that this thrombogenicity was associated with greater charring and coagulation necrosis of the media.

Quantitative indium-111-labeled platelet deposition was significantly increased after thermal laser angioplasty (median 87.2 x 10⁶/cm length) compared with excimer-treated (0.4 x 10⁶/cm length) or control (1.2 x 10⁶/cm length) segments (P < 0.001). Thus, excimer laser angioplasty was found to result in fewer complications and, as a consequence, less thrombosis and platelet accumulation than did thermal laser angioplasty.

(J Am Coll Cardiol 1990;16:502-6)

Although thermal laser angioplasty with an argon laser-heated metal probe has been a safe and effective adjunct to conventional balloon angioplasty in large straight peripheral arteries (1,2), initial attempts to perform percutaneous coronary thermal laser angioplasty were limited by difficulty in maneuvering the device in tortuous coronary arteries (3) and by a high incidence of thermally induced thrombosis (4). Pulsed excimer laser angioplasty has been proposed as an alternative to thermal laser angioplasty because of its ability to ablate calcified lesions with less thermal damage to surrounding tissue (5). However, there are conflicting in vitro reports (6,7) on the relative thrombogenicity of pulsed excimer versus continuous wave thermal laser irradiation. Because the latter two studies were performed in vitro rather than in vivo and platelet deposition was semiquantitative rather than quantitative, it is difficult to determine their clinical relevance. Therefore, in the present study, the relative safety and thrombogenicity of pulsed excimer and continuous wave thermal laser angioplasty systems were compared in vivo in normal swine coronary arteries using angiographic, histologic and quantitative indium-111-labeled platelet analysis.

Methods

Animal model. A total of seven normal Yorkshire albino pigs (42 ± 4 kg) were randomly treated with either excimer
or thermal laser angioplasty. All three coronary arteries were utilized for laser therapy. The procedures performed in the study were approved by the appropriate institutional review board and conformed to the Position of the American Heart Association on Research Animal Use.

Platelet labeling. Approximately 24 h before intervention, autologous platelets were labeled with indium-I I I tropolone as previously described (8). Briefly, indium-I I I tropolone was prepared from indium-I I I chloride by adding 25µg of tropolone dissolved in 25 µl of saline solution to an average of 640 µCi (range 500 to 900) of indium-I I I chloride. This solution was mixed with 0.5 ml of platelet-poor plasma. Platelets were harvested by two successive centrifugations. The isolated pellet of platelets was resuspended in 2 ml of platelet-poor plasma to obtain a platelet-rich plasma concentrate. The indium-tropolone complex was added to the platelet-rich plasma and the mixture incubated at 37°C for 20 min. Free indium-I I I was removed by washing with 4 ml of platelet-poor plasma. The final pellet of labeled platelets was resuspended in 4.5 ml of platelet-poor plasma and injected into the pig after low spin centrifugation to remove any microaggregates. The labeling procedure lasted for approximately 2 h. An average labeling efficiency of 38 ± 4% (mean ± SE) was obtained. The average injected activity was 364 ± 34 µCi (mean ± SE) in a total volume of 5 ml.

Experimental protocol. On the day of laser angioplasty, the pig was sedated with 500 mg of ketamine hydrochloride (Ketaset, Bristol Laboratories) given intramuscularly, and anesthesia was induced with 200 mg of intravenous pentobarbital with a booster of 130 mg every 45 min thereafter. The pig was then intubated and mechanically ventilated with room air with use of a Harvard respirator. Continuous electrocardiographic and intrarterial pressure monitoring was maintained throughout the experiment on a Tektronix 412 monitor. The right carotid artery was isolated by a surgical cutdown technique. Intravenous heparin was administered as a bolus injection of 100 U/kg and at a similar dose at 1 h intervals thereafter until the end of the experiment. To prevent arrhythmias, 250 mg of procainamide hydrochloride was given intramuscularly. An 8F catheter (RlI, Amplatz) was inserted through a carotid arteriotomy. Coronary arteriography was performed in two views (right and left anterior oblique) with a fluoroscopy unit (P150, Precise Optics) using Renografin-76 (meglumine diatrizoate) and recorded on 0.75 in. (1.91 cm) videotape (Umatic). Two hours after the catheterization and angioplasty procedure, the animals were killed by an overdose of pentobarbital.

Thermal laser angioplasty procedure. Thermal laser energy was delivered from a xenon chloride (308 nm) laser generator (CXV-300, Spectranetics) through a 4.5F central lumen catheter consisting of 13 concentrically arranged 200 µm fiber optics (Fig. 1). In an attempt to reproduce the operating technique used in the thermal laser procedure, the excimer laser catheter was inserted through the 8F guiding catheter and into all the coronary artery distributions over a 0.014 in. (0.36 mm) guide wire. Excimer laser energy was delivered for 3 to 5 s using an energy fluence of 35 to 40 mJ/mm² at a repetition rate of 25 to 30 Hz and a pulse duration of 120 ns as the excimer laser catheter was slowly advanced down the coronary artery. This technique is currently being used to evaluate the clinical efficacy of percutaneous coronary excimer laser angioplasty (10).

Control coronary segments. Under similar experimental conditions, 18 coronary segments selected from all three coronary arteries served as control segments in which angiography was performed and a 0.014 in. (0.36 mm) guide wire was passed to the distal coronary artery.

Tissue preparation. After removal of the heart, the left ventricle and coronary arteries were perfused for 15 min with 4% formaldehyde in 0.1 M sodium phosphate buffer (pH 6.9 to 7.1) at a controlled pressure of 100 mm Hg. After fixation, the arteries were dissected from the surrounding connective tissue and cut into 1 cm segments for counting in a gamma counter. The locations of the laser-treated or injured portion of the coronary arteries were identified by review of the recorded coronary arteriogram.

Platelet quantification. Platelets in tissue and blood were counted for 5 min in a Packard Auto-Gamma 5650 counter (United Technologies). Platelet deposition (×10⁶/cm of vessel length) was calculated from the blood platelet count and indium-I I I counts on the arterial wall and in the blood as
Table 1. Macroscopic Observations and Platelet Analysis After Laser Angioplasty in Seven Pigs

<table>
<thead>
<tr>
<th>Group</th>
<th>No.</th>
<th>Mural Thrombus</th>
<th>Occlusive Thrombus</th>
<th>Perforation</th>
<th>Platelet Accumulation ((10^2)cm length)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>18</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1.2 (0.2-7.0)</td>
</tr>
<tr>
<td>Excimer laser angioplasty</td>
<td>10</td>
<td>1</td>
<td>0</td>
<td>1</td>
<td>0.4 (0.1-5.1)</td>
</tr>
<tr>
<td>Thermal laser angioplasty</td>
<td>10</td>
<td>6</td>
<td>2</td>
<td>3</td>
<td>87.2 (19.2-318.1)</td>
</tr>
</tbody>
</table>

*Median and range; \(tp < 0.001\) versus control and excimer laser angioplasty. No. = number of coronary segments treated.

previously described (8). Statistical significance was determined by the Wilcoxon signed rank test and a p value <0.05 was accepted as significant.

**Histology.** After evaluation of indium-111 activity, the presence of mural or occlusive thrombus was assessed macroscopically. From each arterial segment, three cross sections were stained with hematoxylin-eosin, Masson's trichrome and Heidenhain-Weigert-Van Gieson's stains. Light microscopy was used to document thermal charring, coagulation necrosis, medial dissection or vessel perforation.

**Results**

**Angiographic results.** Immediate postlaser angioplasty arteriography revealed dye extravasation in 3 of 10 segments treated with thermal laser angioplasty compared with 1 of 10 segments treated with excimer laser angioplasty. The one excimer laser perforation occurred when the 4.5F catheter was advanced into a small distal left anterior descending coronary artery. In contrast, two thermal laser probe perforations occurred in the proximal left anterior descending coronary artery and one perforation occurred in the proximal right coronary artery. On one occasion, the laser probe was noted to adhere to the vessel wall despite vigorous attempts to keep the probe constantly moving during a 5 s laser pulse delivery. Abrupt vessel closure related to coronary vasospasm or thrombotic occlusion, or both, was noted angiographically in two thermal laser probe-treated segments, but in no segments treated with pulsed excimer laser angioplasty.

**Macroscopic and histologic results.** Gross macroscopic examination of the coronary artery segments revealed two occlusive and six nonocclusive mural thrombi in the 10 segments treated with thermal laser angioplasty, but only one nonocclusive mural thrombus was noted after excimer laser angioplasty (Table 1). The perforations noted angiographically were confirmed by macroscopic examination. Histologically, the surface of the vessels treated with thermal laser angioplasty was characterized by significant charring and coagulation necrosis deep into the media (Fig. 2). On occasion, vessels treated with thermal laser angioplasty demonstrated intimal and medial separation from the external elastic lamina as if the portion of the vessel wall had been pulled off as a result of the sticking encountered with this thermal device (Fig. 3). This type of separation between...
media and adventitia far exceeds that occasionally seen as a sectioning artifact. In contrast, the majority of vessels treated with excimer laser angioplasty demonstrated endothelial and intimal denudation without significant charring, coagulation or cell necrosis. On only one occasion was there evidence of removal of the internal elastic lamina and a portion of the media; however, there was no coagulation or significant necrosis of the media (Fig. 4).

Platelet deposition. The findings of indium-111–labeled platelet quantitative analysis revealed striking differences after excimer versus thermal laser angioplasty procedures (Table 1). Although the median value and range of platelet deposition with excimer laser angioplasty (0.4 × 10^6/cm length [range 0.1 to 5.1]) was not significantly different from that in control segments (1.2 × 10^6/cm length [range 0.2 to 7.0]), there was a significant increase in platelet deposition after thermal laser angioplasty (87.2 × 10^6/cm length [range 19.2 to 318]) compared with both control and excimer laser angioplasty treatment of coronary artery segments (p < 0.001).

Discussion

Laser catheter safety and handling. This study demonstrates that there are fewer complications (perforation, adherence, occlusion) with pulsed excimer laser delivery compared with continuous wave thermal energy in normal swine coronary arteries when similar over the wire angioplasty techniques and equal duration of laser energy delivery (3 to 5 s) are used. The complications of perforation and occlusion were related to “sticking” and difficulty in keeping the heated metal tip moving constantly back and forth in the vessel. Historically, in peripheral arteries, this constant motion technique was necessary to prevent complications.
However, clinical application in peripheral arteries was easier because the vessels were straight and of larger diameter. Furthermore, the distance between the operator and the lesion was minimal (10 to 30 cm). In this experimental design, which mimics the clinical coronary artery situation, both laser catheters were inserted through 100 cm guiding catheters into smaller, more tortuous coronary arteries. The requirement of keeping the metal tip moving during laser delivery and the cooling down period was difficult to accomplish in these coronary arteries and complications resulted. The pulsed excimer system in the coronary artery was superior in terms of ease of handling because it could be slowly advanced in the coronary artery.

Relative thrombogenicity. In what may be of significant clinical relevance, pulsed excimer laser irradiation did not cause any increase in platelet deposition relative to that in control segments. In contrast, however, laser angioplasty with a thermal probe induced significantly more thrombosis than was observed in either control or pulsed excimer-treated coronary artery segments.

From previous in vivo studies, it is known that platelet accumulation is substantially greater on type I collagen fibers (11) and deep medial structures (12). In addition, it has been shown (13) that platelet deposition depends on the local flow characteristics of the area. Interestingly, two reports (14,15) of experimental balloon angioplasty noted a correlation between greater platelet accumulation with medial tears and the extent of angioplasty-induced dissection. Therefore, the difference in thrombogenicity with the two laser systems evaluated in this study is most likely related to different degrees of medial dissection or thermal necrosis of the media, or both, that occurs with the different angioplasty techniques. Although these studies were performed in normal arteries, it is expected that similar results would be obtained in atherosclerotic vessels. Indeed, comparable results have recently been observed in atherosclerotic rabbit iliac arteries (Marmur JD, unpublished observations).

These in vivo results confirm one previous report (6) of an in vitro system in which no difference in adherent platelets and platelet thrombi was noted in excimer-treated or control segments. However, in contrast to that in vitro report (6), we found the thermal angioplasty system to cause significantly more thrombosis and platelet deposition than either the excimer-treated or control (guide wire-passed) segments. The latter difference is probably related to the difficulty of maneuvering these thermal devices from a distance in small tortuous vessels. Because platelet deposition after angioplasty appears to be one of the contributing factors for restenosis, the fact that excimer laser angioplasty can be performed without significant platelet accumulation may be important in terms of restenosis.

Conclusions. A pulsed excimer laser angioplasty system was found to result in fewer complications, less histologic damage and, as a consequence, less thrombosis and platelet accumulation than did a thermal laser angioplasty system with a similar over the wire catheter design. Initial clinical evaluation (10) of this device confirms these experimental results.

We thank Rene Hill, BS and Efim Mogilevsky, DVM for their technical expertise. The assistance of Marcy Leoncini in the preparation of the manuscript is greatly appreciated.

References