Angiographic and histologic consequences of laser thermal angioplasty: comparison with balloon angioplasty

TIMOTHY A. SANBORN, M.D., CHRISTIAN C. HAUDENSCHILD, M.D., GARY R. GARBER, M.D., THOMAS J. RYAN, M.D., AND DAVID P. FAXON, M.D.

ABSTRACT The angiographic and histologic consequences of laser thermal angioplasty were examined and compared with those of conventional balloon angioplasty in an atherosclerotic rabbit iliac artery preparation immediately and 4 weeks after the procedure. Nineteen vessels in 13 rabbits underwent either laser thermal or balloon angioplasty in random order. Laser thermal angioplasty was performed in a total of nine vessels with either a 1.5 or 2.0 mm laser-heated metallic-capped fiber by delivery of 6 or 8 W, respectively, of argon laser energy for 5 sec duration during continuous advancement through the stenosis. Balloon angioplasty was performed in a total of 10 stenotic lesions with a 2.5 mm balloon catheter. The immediate enlargement of the angiographic luminal diameters was similar for both procedures; from 1.0 ± 0.2 to 1.9 ± 0.2 mm for laser thermal angioplasty vs 1.0 ± 0.1 to 2.0 ± 0.2 mm for balloon angioplasty. However, 4 weeks later the vessels treated with laser thermal angioplasty had less restenosis, defined as a 20% or greater reduction in luminal diameter (two of nine vessels [22%] vs 10 of 10 vessels [100%]; p < .001), and a significantly larger mean luminal diameter (1.6 ± 0.5 vs 1.0 ± 0.4 mm) than those treated with conventional balloon angioplasty (p < .02). Histologic examination 4 weeks after the procedure revealed less fibrocellular proliferation after laser thermal angioplasty, whereas those vessels treated with balloon angioplasty demonstrated evidence of prior fracture and dissection of the vessel wall with more of a fibrocellular proliferative response. Morphometric analysis of these histologic cross-sections confirmed a significantly larger lumen after laser thermal angioplasty compared with balloon angioplasty (1.24 ± 0.62 vs 0.64 ± 0.45 mm²; p < .05). In summary, in rabbit iliac artery stenoses, laser thermal angioplasty was associated with less restenosis and produced a significantly larger mean luminal diameter and mean luminal area than conventional balloon angioplasty. Differences in the pathophysiological mechanisms of angioplasty with these two techniques may be responsible for this observation and may have clinical relevance. Circulation 75, No. 6, 1281-1286, 1987.

LASER ANGIOPLASTY has the potential to serve as an adjunct or alternative to conventional balloon angioplasty, which has shown impressive clinical results but is limited by a lower success rate (54%) in totally occluded coronary vessels and is complicated by an early restenosis rate that approaches 30% to 40% . , . However, the cardiovascular use of lasers has been limited by a reported 20% to 66% incidence of vessel perforation in experimental and clinical studies and poor long-term patency in a preliminary clinical trial. If this technique is to achieve widespread clinical use, both the short- and long-term consequences of the procedure need to be assessed and compared with results of currently available balloon angioplasty to determine the precise role of this new therapy in relation to existing techniques.

In a prior study, improved safety and efficacy of laser thermal angioplasty was demonstrated in an atherosclerotic rabbit iliac artery preparation with a metallic-capped fiber (Trimedyne Inc., Santa Ana, CA) in which argon laser energy is converted to heat in the enclosed cap at the end of the fiberoptic fiber. In this previous study, a lower incidence of perforation and greater angiographic success were evident when

From the Evans Memorial Department of Clinical Research and the Department of Medicine, University Hospital, Boston University Medical Center and Mallory Institute of Pathology, Boston.
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Address for correspondence: Timothy A. Sanborn, M.D., Department of Cardiology, University Hospital, 75 Newton St., Boston, MA 02118.
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the laser-heated probe was compared with direct argon laser vaporization with a bare fiberoptic positioned inside a No. 4F angiographic catheter (USCI). In the last 2 years, the clinical safety and efficacy of laser thermal angioplasty was demonstrated when the technique was used as an adjunct to balloon angioplasty in patients with peripheral vascular lesions that were considered difficult or impossible to treat by conventional means.\textsuperscript{10, 11} More recently, the feasibility of percutaneous coronary laser thermal angioplasty has also been demonstrated.\textsuperscript{12, 13} Whether laser thermal angioplasty is associated with less restenosis than balloon angioplasty is not known. Therefore the present study was designed to analyze the angiographic and histologic consequences of laser thermal angioplasty and to compare the results with those of conventional balloon angioplasty in an experimental preparation.

Methods

**Experimental animals.** Atherosclerosis was induced in the aorta and iliac arteries (left and right) of 13 male New Zealand white rabbits (weight 3 kg) by balloon deendothelialization and a 2% cholesterol diet as previously described.\textsuperscript{14} All animals were treated and anesthetized to conform to the guiding principles of The American Physiological Society.

**Experimental design.** After 6 weeks on the atherogenic diet, the animals were anesthetized with thiopental and a No. 4F Swan-Ganz balloon catheter was advanced through a right carotid arteriotomy to the aortic bifurcation for cineangiography. Previous studies have found this 6 week frame to be adequate for the development of significant left or right iliac lesions.\textsuperscript{14-16} With a proximal iliac segment used as a relative nondiseased control vessel (2 to 3 mm), when a stenosis of 50% to 95% (0.6 to 1.5 mm luminal diameter) was found in either the left or right iliac artery, the animals were randomized to treatment with either laser thermal angioplasty or balloon angioplasty. An ipsilateral femoral arteriotomy was performed for retrograde advancement of either a 2.5 mm intraoperative balloon catheter or a 1.5 to 2.0 mm laser heated probe attached to a flexible 300 mm diameter quartz core fiberoptic fiber. The goal was to obtain similar postangioplasty luminal diameters for comparative purposes. Heparin was placed in all flush solutions (2000 U/liter); however, systemic heparinization was not administered in order to maximize the chance of restenosis.

**Balloon angioplasty procedure.** Balloon angioplasty was performed by inflating the balloon three times to 5 atm for 30 sec as previously described.\textsuperscript{14, 16} The balloon catheter was then removed and repeat angiography was performed. Successful angioplasty was defined as a reduction of the stenosis by greater than 20% and to less than 50% residual stenosis relative to a proximal nondiseased control segment.

**Laser thermal angioplasty procedure.** In studies with the laser-heated probe, a 1.5 mm metallic probe (figure 1) was first advanced through the lesion without laser pulse delivery, and repeat cineangiography was performed as a control for any mechanical dilation of the stenosis with the 1.5 mm device. After the second cineangiogram, the 1.5 mm probe was advanced through the lesion with a steady continuous motion over approximately 2 cm while delivering a single pulse of 6 W of argon laser energy for 5 sec. This amount of laser energy is capable of developing a temperature of over 400°C at the metallic tip.\textsuperscript{9} Immediately after laser pulse delivery, repeat cineangiography was performed to document the angiographic change. To be consistent with the balloon angioplasty procedure, a reduction of the stenosis by greater than 20% and to less than 50% residual stenosis was considered a successful angioplasty. In four procedures, it was felt that an adequate reduction of the stenosis to less than 50% residual stenosis was not obtained with the 1.5 mm device on repeat angiography and a larger 2.0 mm laser-heated probe (figure 1) was advanced through the lesion, using the same technique while delivering a second pulse of 8 W of argon laser energy for 5 sec.

In both laser and balloon angioplasty studies, care was taken to maintain similar height on the image intensifier for all cineangiograms. After the angioplasty procedure, the catheter was removed and the carotid and femoral arteriotomies were closed by ligation.

**Follow-up studies.** All animals were maintained on a 2% cholesterol diet without any medication for 4 weeks, at which time they were reanesthetized and underwent repeat angiography as described above. The high cholesterol diet and omission of antplatelet therapy were chosen to maximize the likelihood of potential restenosis. The 4 week time frame was chosen based on previous experience that showed it to be a convenient time to examine restenosis angiographically as well as thrombosis and fibrocellular proliferation histologically after balloon angioplasty.\textsuperscript{15, 16} After angiography, the animals were killed with an overdose of thiopental, and the iliac arteries were perfused with formalin at 80 mm Hg for histologic analysis.\textsuperscript{14, 16} Restenosis at 4 weeks was defined as a reduction of the luminal diameter by greater than 20% from the postangioplasty luminal diameter.

**Angiographic and histologic analysis.** Cineangiograms taken immediately and 4 weeks after balloon or laser thermal angioplasty were viewed on a Vanguard projector and compared. Luminal diameters were measured with hand-held calipers by determining the most stenotic portion of the vessel before, immediately after, and 4 weeks after the balloon or laser procedure. In this manner, a resolution of 0.2 mm could be made as previously reported.\textsuperscript{14, 16} All angiograms were read independently at different times in random sequence by two angiographers who were blinded to the type of angioplasty performed. Intraobserver and interobserver discrepancies were 0.2 mm or
less; these discrepancies were resolved by subsequent simultaneous measurements. Comparison of the incidence of restenosis between groups was made by Fisher's exact test (two-tailed). The luminal diameters after laser or balloon angioplasty were compared by a nonpaired t test.

The cineangiograms were subsequently used by the angiographer for identification of the exact anatomic locations of laser pulse delivery or balloon angioplasty. For histologic examination, sections were stained with hematoxylin-eosin, modified trichrome, and Verhoeff-Van Gieson elastin stains and were evaluated by at least two investigators with respect to luminal size, fibrocellular proliferation, and presence and amount of thrombosis.

Morphometric analysis of stained histologic cross-sections was performed as previously described. Briefly, stained histologic cross-sections were projected on a Zeiss MOP II digital image analyzer (Carl Zeiss, New York) to allow calculation of the cross-sectional areas of the iliac arterial lumen and arterial wall (neointima plus media as demarcated by the external elastic lamina). The total cross-sectional area was calculated by addition of the arterial wall and the lumen areas. Student's t test (nonpaired) was used to determine statistical significance, and a p value of less than .05 was accepted as significant.

Results

Angiography. Angiographic results were analyzed immediately and 4 weeks after balloon angioplasty in a total of 10 vessels from five animals and after laser thermal angioplasty in nine vessels from eight animals (figure 2). The luminal diameters (mean ± SD) before balloon and laser procedures were similar in each group (1.0 ± 0.1 and 1.0 ± 0.2 mm, respectively). In studies with the laser-heated probe, advancement of the 1.5 mm probe without laser pulse delivery did not result in a significant increase in mean luminal diameter (1.1 ± 0.1 mm). Thus mechanical dilation did not represent a significant mechanism of action of this device. The mean luminal diameter increased similarly to 2.0 ± 0.2 mm after balloon angioplasty and 1.9 ± 0.2 mm after laser thermal angioplasty. No vessel perforation, intraluminal thrombosis, or distal embolization occurred with either procedure. An angiographic example of successful laser thermal angioplasty with a 1.5 mm laser-heated probe is shown in figure 3. Angiographic results of successful balloon angioplasty in this experimental preparation were similar to those shown in previous reports from this laboratory and by Block et al.

On repeat angiography 4 weeks later, restenosis defined as a decrease in the luminal diameter by greater than 20% was noted in all 10 vessels (100%) treated by balloon angioplasty as compared with only two of nine vessels (22%) treated with laser thermal angioplasty (p < .001) (figure 2). One of the vessels treated with balloon angioplasty developed a total occlusion; none of the successful laser thermal angioplasty procedures developed a total occlusion.

In terms of the actual angiographic results 4 weeks after each procedure, the vessels treated with laser thermal angioplasty had a significantly larger mean luminal diameter of 1.6 ± 0.5 mm compared with 1.0 ± 0.4 mm for vessels treated with balloon angioplasty (p < .02). Whether bilateral or unilateral angioplasty was performed made no difference in the 4 week result.

Histology. At 4 weeks, histologic results after laser thermal angioplasty were characterized by a large residual lumen with a variable endothelial and pseudothelial lining (figure 4, A). A thin, circumferential, condensed fibrous cap overlying a cellular intima was noted with minimal evidence of thrombosis or fibrocellular proliferation. There was no evidence of disruption of the internal elastic membrane (figure 5). Adjacent areas of iliac arteries did not show any evidence of thermal damage. In contrast, histologic results 4 weeks after balloon angioplasty revealed evidence of the original fibrous cap that was split by the balloon procedure as well as considerable loose fibrocellular material that filled in the dissection planes and
FIGURE 3. Angiographic example of laser probe results demonstrating (A) diffuse right iliac disease and more discrete higher-grade left iliac lesion which were both successfully treated with good angiographic improvement (B).

FIGURE 4. A, Cross-section of a patent rabbit iliac vessel 4 weeks after laser thermal angioplasty, demonstrating minimal fibrocellular proliferative response and a thin, condensed fibrous cap. B, Histologic section 4 weeks after balloon angioplasty, revealing moderate fibrocellular proliferation caused by the dilation, which partially fills the lumen and obliterates the prior dissection planes between the neointimal flaps and the media. (Verhoff–Van Gieson elastin stains; original magnification ×26.)

the lumen to result in a smaller residual arterial lumen (figure 4, B). This gave the impression of a layered effect similar to that previously reported after balloon angioplasty.\textsuperscript{15, 16} Histologic findings after laser thermal angioplasty did not reveal this layered appearance suggestive of recent fibrocellular proliferation. In the two vessels that did demonstrate restenosis after laser thermal angioplasty, the histologic results showed evidence of neointimal dissection and organizing thrombus formation.

Morphometric analysis of these histologic cross-sections confirmed the angiographic results, with a significantly larger mean luminal area of 1.24 ± 0.62 mm\textsuperscript{2} after laser thermal angioplasty as compared with 0.64 ± 0.45 mm\textsuperscript{2} after balloon angioplasty (p < .05). There was no significant difference in the arterial wall or total vessel cross-sectional area (table 1).

Discussion

In this experimental study comparing laser thermal angioplasty with conventional balloon angioplasty, the laser procedure resulted in significantly less restenosis (22% vs 100%; p < .001) and a significantly larger luminal diameter at 4 weeks than balloon dilation (1.6 ± 0.5 vs 1.0 ± 0.4 mm; p < .02). These angiographic results with balloon angioplasty are similar to those previously reported in two other studies of restenosis in this experimental preparation.\textsuperscript{15, 16}

The histologic and morphometric results in the present study confirm the angiographic results of a larger lumen in the laser thermal angioplasty group (1.24 ± 0.62 vs 0.64 ± 0.45 mm\textsuperscript{2}; p < .05). The histologic results suggest that less neointimal dissection and fi-
brocellular proliferation occurred after laser thermal angioplasty compared with balloon angioplasty. These qualitative observations of less neointima in the laser thermal angioplasty group could not be confirmed quantitatively in the morphometric analysis because disruption of the internal elastic lamina after balloon angioplasty prevented clear separation of the intima from the media. Thus the intimal and medial areas had to be analyzed together as vessel wall area.

The mechanism of restenosis after angioplasty is not entirely known. Experimental studies15, 16 and several human case reports18, 19 suggest that restenosis is caused by a fibrocellular proliferation of smooth muscle cells. Thrombus formation may also play a role.15 Experimental studies have found increased indium-111 and chromium-51 labeled platelet accumulation at the site of angioplasty, which was related to neointimal dissection or medial tears seen on histologic examination.20, 21 It can only be speculated that this increased platelet accumulation leads to the release of a greater amount of growth factors, which in turn stimulate smooth muscle cell proliferation. It is hypothesized that by removing obstructing atherosclerotic lesions in a circumferential manner, laser thermal angioplasty leaves behind a smoother arterial surface that is less likely to develop smooth muscle cell proliferation and subsequent restenosis. Balloon angioplasty, on the other hand, is known to stretch and fracture obstructing lesions and leave behind intimal flaps and dissection planes14 that may serve as a nidus for platelet and fibrous deposition.20, 21 By causing a secondary zone of thermal injury,5 laser thermal angioplasty may also alter the response of the remaining smooth muscle cells to the stimulating effects of various growth factors. The present study provides angiographic and histologic evidence to support these hypotheses. Whether this finding can be reproduced in advanced human atherosclerotic lesions remains to be determined. Initial clinical results are too limited to draw any conclusions.10-13

Antiplatelet agents and systemic heparinization were not administered in the present study in order to maximize the restenosis effect. Although restenosis after balloon angioplasty could have been partially prevented by the administration of antiplatelet agents as previously reported,16 these agents are not 100% effective. Clinically, restenosis occurs in approximately 30% to 40% of coronary angioplasty procedures despite pretreatment with systemic heparin, antiplatelet agents, calcium-channel blockers, coumadin, and low-molecular weight dextran; therefore, consideration of improvements in the technique of angioplasty is warranted. Our results suggest that a smooth arterial surface after angioplasty may play a very important role.

In this study, no angiographic or histologic evidence of aneurysm formation was noted in any of the nine vessels studied 4 weeks after laser thermal angioplasty. This result is in contrast to that reported by Lee

TABLE 1
Morphometric analysis 4 weeks after angioplasty (mean ± SD)

<table>
<thead>
<tr>
<th>Group</th>
<th>Area (mm²)</th>
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<th></th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Lumen</td>
<td>Intima + media</td>
<td>Total</td>
</tr>
<tr>
<td>Laser thermal angioplasty</td>
<td>1.24 ± 0.62</td>
<td>2.15 ± 0.55</td>
<td>3.35 ± 0.36</td>
</tr>
<tr>
<td>Balloon angioplasty</td>
<td>0.64 ± 0.45*</td>
<td>2.44 ± 0.95</td>
<td>3.08 ± 0.68</td>
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*p < .05 vs laser thermal angioplasty.
et al., in which aortic aneurysms were noted at 14 days in two of four rabbits treated with direct argon laser radiation distributed in a narrow coaxially directed beam. Circumferential removal of neointima by the laser-heated probe in an evenly distributed manner without damage to the media or the internal and external elastic lamina may have contributed to the absence of aneurysm formation as well as to the lack of vessel perforation with the device. Whether similar results can be accomplished with electrical rather than laser energy remains to be determined.

This study represents the first detailed angiographic report of follow-up results of laser angioplasty of significant stenotic lesions. Ginsberg et al. published a case report of successful percutaneous laser angioplasty in a human subject in which 6 month clinical status and noninvasive measurements were unchanged from the initial results. Choy et al., however, found no long-term angiographic patency in five patients after intraoperative coronary laser recanalization. The latter result may have been influenced by competitive flow from concurrent bypass surgery, poor distal runoff, and small laser channels. Indeed, from prior preliminary unpublished results (Sanborn et al.), channels smaller than 1.5 mm in the rabbit iliac artery had a lower patency rate 4 weeks after the procedure.

In conclusion, in this experimental preparation, laser thermal angioplasty was associated with less restenosis and produced a significantly larger mean luminal diameter and luminal area than conventional balloon angioplasty at follow-up 4 weeks after the procedure. Our histologic findings suggest that less fibrocellular proliferation is responsible for these results and that the smooth arterial surface seen immediately after laser thermal angioplasty may be responsible for this reduced fibrocellular proliferation. In preliminary clinical trials in superficial femoral and popliteal arteries, laser thermal angioplasty has also proved safe and effective as an adjunct to balloon angioplasty in lesions that were difficult or impossible to treat by conventional means. If clinical studies confirm these findings of less restenosis after laser thermal angioplasty, then the procedure may be a useful adjunct or alternative to balloon angioplasty.

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