In Vivo Assessment of Vascular Pathology Resulting From Laser Irradiation

Analysis of 23 Patients Studied by Directional Atherectomy Immediately After Laser Angioplasty

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Background. The pathological consequences of cardiovascular laser irradiation have been studied extensively in vitro. Previous in vivo studies of laser-induced injury have included analyses of acute and/or chronic findings in experimental animals. Little information, however, is available regarding the acute effects of laser irradiation of human vascular tissues in vivo.

Methods and Results. To determine the acute pathology resulting from laser irradiation of human vascular tissue in vivo, specimens retrieved from 23 patients by directional atherectomy immediately after laser angioplasty (19 peripheral and four coronary) were examined by light microscopy. Of the 23 patients, three (13.0%) were treated with a metal-capped ("hot-tip") fiber coupled to a continuous-wave neodymium:yttrium-aluminum-garnet (Nd:YAG) laser up to 18 W power and 18–305 seconds of cumulative exposure time; in all three patients (100%), thermal injury, including frank charring several cell layers thick, was seen along the luminal borders of the atherectomy specimen. In eight of the 23 patients (34.5%), laser angioplasty was performed using a 250-µsec holmium:YAG laser at fluences up to 2,300 mJ/mm², a repetition rate of 5 Hz, and 25–200 seconds of cumulative exposure; in seven of eight patients (85.5%), the atherectomy specimen showed signs of vascular injury consisting of central and satellite Alcian-blue-negative vacuoles. In two patients (25.0%), there was a "smudged" or "shredded" edge, whereas in one patient, frank signs of thermal injury were observed. Finally, in 12 of the 23 patients (52.2%), laser angioplasty was performed using a 120-µsec excimer laser at fluences up to 60 mJ/mm², a repetition rate of 25 Hz, and a cumulative exposure time of 21–315 seconds. Pathological findings among these 12 patients were limited to nine patients (75%) in whom a weakly basophilic, smudged, and/or shredded appearance approximately one cell layer thick was observed along the luminal border of the atherectomy specimen and two patients (16.7%) with small foci of vascular injury. None of the atherectomy specimens retrieved after excimer laser angioplasty disclosed signs of thermal injury.

Conclusions. These findings document that acute pathological alterations resulting from in vivo laser angioplasty are variable, depending on the laser source used, and are similar to that predicted by experimental studies performed previously in vitro. The prognostic implications of these varying pathological features remain to be clarified. (Circulation 1992;85:2185–2196)

Key Words: lasers • angioplasty • atherectomy • coronary artery disease • peripheral vascular disease

The pathological consequences of cardiovascular laser irradiation have been studied extensively in vitro. Previous in vivo studies of laser-induced injury have included analyses of acute and/or chronic findings in experimental animals. Little information, however, is available regarding the acute effects of laser irradiation of human vascular tissues in vivo.

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The biopsy capability of percutaneous directional atherectomy has been previously exploited for the analysis of primary and restenotic vascular lesions. Use of this technique to investigate tissue injury resulting from percutaneous laser irradiation has not been previously described. Accordingly, we investigated the acute pathological consequences of laser irradiation by histological examination of tissue specimens retrieved by percutaneous directional atherectomy immediately after laser angioplasty in 23 patients undergoing percutaneous peripheral or coronary revascularization.

Methods

Patients

Clinical findings in the 23 patients in the present study are summarized in Table 1. The 23 patients included 19 men and four women ages 46–87 years old.
(mean age, 67.6 years). Nineteen of the 23 patients had signs and/or symptoms (Rutherford class 3 or greater) of peripheral vascular disease. The remaining four patients had signs and/or symptoms of ischemic heart disease.

All patients had previously undergone diagnostic angiography that documented the presence and extent of peripheral vascular or coronary arterial narrowing. Among the 19 patients with peripheral vascular disease, 19 (100%) had a subtotal (three) or total occlusion (16) involving variable lengths of the superficial femoral artery (SFA) and/or popliteal artery; in each of these 19 patients, laser angioplasty followed immediately by directional atherectomy was used to revascularize the SFA and/or popliteal artery. In one of these 19 patients (5.3%), conventional balloon angioplasty (performed after atherectomy) also was required to achieve a satisfactory angiographic result.

Among the four patients with ischemic heart disease, laser angioplasty/directional atherectomy was performed to revascularize the left anterior descending coronary artery (LAD) in three patients and the right coronary artery (RCA) in one patient. Adjunctive balloon angioplasty was applied to one of these patients after atherectomy.

**Laser Angioplasty**

Three different laser systems were used.

**Laser thermal probe.** In three of the 19 patients (15.8%) with peripheral vascular disease, laser angioplasty was performed using a continuous-wave neodymium:yttrium-aluminum-garnet (Nd: YAG) laser coupled to a metal-capped fiberoptic (“hot-tip” Laserprobe, Trimedyne, Santa Ana, Calif.) as described previously. In one of the three patients, a non–wire-guided device, 2.5 mm in diameter, was used to recenter a total occlusion; in the remaining two, a wire-guided 2.5-mm-tip catheter was used after the total occlusion had been successfully crossed with a 0.035-in. hydrophilic guide wire (Terumo, Piscataway, N.J.). The power and cumulative exposure time used in each of these three patients are indicated in Table 2.

**Holmium: YAG.** In four of the 19 patients (21.1%) with peripheral vascular disease and all four of the patients with ischemic heart disease, laser angioplasty was performed using a pulsed midinfrared holmium: YAG laser (Trimedyne) according to protocols approved by the Human Investigation Review Committees at St. Elizabeth’s Hospital and the Oschner Clinic. This laser operates at a wavelength of 2.1 μm and a pulse duration of 250 μsec. For two of four patients undergoing peripheral laser angioplasty, the laser was interfaced with a wire-guided, multifiber catheter containing 19 optical fibers, 250 μm in diameter; the catheter measured 3.0 mm in outer diameter and was advanced over a 0.035-in. guide wire. In two patients, the laser was interfaced with a wire-guided, multifiber catheter containing four optical fibers, 250 μm in diameter, with a window positioned 0.127 mm distal to the end of the optical fibers (“halo catheter”); this catheter also mea-

### TABLE 1. Clinical Findings Before and After Laser Atherectomy

<table>
<thead>
<tr>
<th>Patient</th>
<th>Sex</th>
<th>Age (years)</th>
<th>Ankle-brachial index Before</th>
<th>Ankle-brachial index After</th>
<th>Functional class* Before</th>
<th>Functional class* After</th>
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<tr>
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<td>0.65</td>
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<tr>
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<td>0.65</td>
<td>0.93</td>
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NA, not applicable; ND, not done.

*Per Rutherford et al. for patients with peripheral vascular disease; per Canadian Heart Association classification for patients with coronary artery disease.
Table 2. Procedural Details and Histological Findings

<table>
<thead>
<tr>
<th>Patient</th>
<th>Artery</th>
<th>Laser</th>
<th>Catheter size (mm)</th>
<th>Exposure (seconds)</th>
<th>Output</th>
<th>RR (Hz)</th>
<th>% Diameter narrowing (%)</th>
<th>Histology</th>
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<td>90</td>
<td>11.5 W</td>
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<td>100</td>
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<td>LP</td>
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<td>18</td>
<td>13.0 W</td>
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<td>100</td>
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<td>305</td>
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<td>100</td>
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<td>100*</td>
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<td>LAD</td>
<td>Ho</td>
<td>1.6</td>
<td>59</td>
<td>2,300 mJ/mm²</td>
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<td>95</td>
<td>Pre-L: 40, Post-L: 0, Post-A: 0</td>
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<td>6</td>
<td>LAD</td>
<td>Ho</td>
<td>1.6</td>
<td>57</td>
<td>1,500 mJ/mm²</td>
<td>5</td>
<td>99</td>
<td>Pre-L: 20, Post-L: 0+</td>
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<tr>
<td>7</td>
<td>RCA</td>
<td>Ho</td>
<td>1.6</td>
<td>27</td>
<td>1,400 mJ/mm²</td>
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<td>99</td>
<td>Pre-L: 60, Post-L: 10, Post-A: 0</td>
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<td>Ho</td>
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<td>100</td>
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<td>Ho</td>
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<tr>
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<td>Ho</td>
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<td>100*</td>
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<tr>
<td>12</td>
<td>POP</td>
<td>Ex</td>
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<td>11</td>
<td>50 mJ/mm²</td>
<td>25</td>
<td>100*</td>
<td>Pre-L: 80, Post-L: 20, Post-A: 0</td>
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<tr>
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<td>50 mJ/mm²</td>
<td>25</td>
<td>100*</td>
<td>Pre-L: 70, Post-L: 20, Post-A: 0</td>
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<td>90</td>
<td>Pre-L: 75, Post-L: 20, Post-A: 0</td>
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<td>100*</td>
<td>Pre-L: 90, Post-L: 40, Post-A: 0</td>
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<tr>
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<td>50 mJ/mm²</td>
<td>25</td>
<td>100*</td>
<td>Pre-L: 70, Post-L: 25, Post-A: 0</td>
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<td>25</td>
<td>100*</td>
<td>Pre-L: 40, Post-L: 25, Post-A: 0</td>
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<tr>
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<td>60 mJ/mm²</td>
<td>25</td>
<td>100*</td>
<td>Pre-L: 90, Post-L: 15, Post-A: 0</td>
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<tr>
<td>20</td>
<td>F</td>
<td>Ex</td>
<td>2.2</td>
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<td>25</td>
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<td>315</td>
<td>40 mJ/mm²</td>
<td>25</td>
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<td>Pre-L: 60, Post-L: 30, Post-A: 0</td>
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<tr>
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<td>50</td>
<td>40 mJ/mm²</td>
<td>25</td>
<td>99</td>
<td>Pre-L: 40, Post-L: 20, Post-A: 0</td>
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</table>

A, atherectomy; CH, charring; ED, edge disruption; Ex, excimer; F, fistula; Ho, holmium; L, laser; LAD, left anterior descending coronary artery; LP, Laserprobe; POP, popliteal; RCA, right coronary artery; RR, repetition rate; SFA, superficial femoral artery; VI, vacuolar injury.

A, charring; ED, edge disruption; Ex, excimer; F, fistula; Ho, holmium; L, laser; LAD, left anterior descending coronary artery; LP, Laserprobe; POP, popliteal; RCA, right coronary artery; RR, repetition rate; SFA, superficial femoral artery; VI, vacuolar injury.

sured 3.0 mm in outer diameter and was advanced over a 0.035-in. guidewire.

For coronary laser angioplasty, the holmium:YAG laser was interfaced with either of two wire-guided, multifiber catheters containing 19 or 28 optical fibers, 100 μm in diameter; the catheters measured 1.6 mm and 2.0 mm, respectively, in outer diameter, and each was advanced over a 0.014- or 0.018-in. guidewire. In all cases, holmium laser angioplasty was used to treat a subtotal occlusion that had been previously crossed with a guidewire, including three peripheral lesions in which the guidewire was used to recalize the preexisting total occlusion. The pulse energy, repetition rate, and cumulative exposure used in each of these eight patients are listed in Table 2.

**Excimer.** In 12 of the 19 patients (63.2%) with peripheral vascular disease, laser angioplasty was performed using a pulsed ultraviolet (excimer) laser (Spectranetics, Colorado Springs, Colo.) according to a protocol previously approved by the Human Investigation Review Committee at St. Elizabeth's Hospital. The laser operates at a wavelength of 308 nm and a pulse duration of 120 nsec. The laser was interfaced with one of three wire-guided, multifiber catheters containing 13 optical fibers 200 μm in diameter, 20 fibers 100 μm in diameter, or 45 fibers 100 μm in diameter. The catheters measured 1.7, 1.8, and 2.2 mm, respectively, in outer diameter and were advanced over a 0.018-in. stainless-steel guide wire (Flex-T, Peripheral Systems Group, Mountainview, Calif.). In 10 of 12 cases (83.3%), the excimer laser was used to treat a residual subtotal occlusion after successful guidewire recanalization of a preexisting total occlusion. The pulse energy, repetition rate, and cumulative exposure used in each of these 12 patients are listed in Table 2.

**Directional Atherectomy**

Percutaneous directional atherectomy was performed in each patient as previously described using a
commercially available atherectomy catheter approved by the US Food and Drug Administration for peripheral and coronary applications. In each case, directional atherectomy was performed immediately after laser angioplasty; in no case was this sequence interrupted by administration of lytic therapy or treatment with an alternative intervention. The peripheral atherectomy catheter (Simpson Atherocath, Devices for Vascular Intervention, Redwood City, Calif.) used was in all 19 cases a fixed-wire guided catheter, 8F or 9F in outer dimension, with a maximum working area (at full atherectomy balloon inflation) of 5.7 and 6.0 mm, respectively; in each case, the catheter was inserted through an 8F or a 9F introducer sheath (Angelion, Plymouth, Minn.) as required. The coronary catheter (Devices for Vascular Intervention) used was in all four cases a wire-guided catheter, 5F or 6F in outer dimension with a maximum working area of 3.0 and 3.5 mm, respectively. In each coronary case, the atherectomy catheter was advanced via a 9.5F or 11F guiding catheter (Devices for Vascular Intervention). For both the peripheral and coronary atherectomy procedures, upon fluoroscopic indication that the collecting chamber was nearly full, the catheter was removed and the specimen was immediately fixed in formalin in preparation for further tissue processing.

**Pathological Examination**

Each of the 23 specimens in the current investigation was prepared for light microscopic examination as previously described. Briefly, after 24–72 hours of formalin fixation, the specimen was cleared with xylene, impregnated with and embedded in paraffin, and cut at 4-μm intervals. Multiple sections from each specimen were stained with hematoxylin and eosin and Richardson's combination elastic-trichrome stain and then submitted for light microscopic examination. In selected cases in which vacuoles were observed, additional 4–μm sections were cut, stained with Alcian blue, and further examined by light microscopy. In the case of the four coronary specimens, blinded review was obviated by the fact that each of these specimens was substantially smaller than specimens obtained by directional atherectomy of peripheral vascular sites.

In addition to the specimens obtained from the 23 patients after laser angioplasty, an additional 30 specimens were obtained from consecutive patients undergoing either coronary (21) or peripheral (nine) directional atherectomy unassociated with laser angioplasty. These patients were studied as a portion of 96 patients comprising the on-going Atherectomy Biopsy Collaborative (ABC) Study. All 30 of these control specimens were processed and stained for light microscopic analysis in an identical fashion to specimens obtained after laser angioplasty.

**Results**

The histopathological findings identified among the 23 specimens examined in this series are summarized in Table 2. The histopathological features are described here as a function of the laser source used.

**Laser Thermal Probe**

A total of three patients underwent peripheral arterial revascularization using the Nd:YAG laser coupled to a metal-capped fiberoptic (hot tip). In all three patients (100%), light microscopic examination disclosed charring along the edges of the atherectomy specimen (Figure 1). The charring typically extended a thickness of 80–120 μm inward from the edge of the specimen. In one case, extensive calcific deposits (detected before atherectomy by fluoroscopy and intravascular ultrasound) were observed on the atherectomy specimen. No other distinctive histopathological features were observed in any of these three specimens.

**Holmium:YAG**

Atherectomy specimens were obtained immediately after holmium laser angioplasty in eight patients; four involved peripheral arterial revascularization, and four involved coronary revascularization. The most distinctive feature of these eight specimens (four of four coronary specimens; three of four peripheral specimens) was the finding of irregular-shaped vacuoles, typically arranged as one or two large central vacuoles surrounded by multiple satellite vacuoles (Figure 2). This finding was usually associated with a mild intensification of hue at the perimeter of the zone of vacuolar injury. In two cases, these findings also were associated with edge disruption typical of that observed after excimer laser irradiation (see below). In one patient, foci of charring qualitatively similar to that observed with the continuous-wave Nd:YAG laser also were observed (Figure 3).

**Excimer**

Atherectomy specimens were obtained from 12 patients immediately after excimer laser peripheral angioplasty. In nine of 12 (75%), a distinctive pattern of fine edge disruption approximately one or less cell layer thick was observed along the perimeter of the specimen. In all cases, the hue of the disrupted edge was intensified relative to the underlying plaque (Figure 4). In most such cases, the involved cells had a “smudged” or “ground glass” appearance (Figure 4), whereas in others the histoarchitecture of the involved cells appeared finely shredded (Figure 5). In two cases, several foci of vacuoles were observed with (one) or without (one) associated edge disruption. In none of the 12 cases were there foci of charring.

**Clinical Results**

Clinical results are summarized in Table 1. A satisfactory angiographic result was achieved in 17 of 17 patients (100%) with peripheral vascular disease. In 18 of the 19 patients (94.7%), this was confirmed by intravascular ultrasound examination, as described previously. A satisfactory angiographic result also was achieved in all four patients undergoing coronary revascularization.

**Controls**

The 21 specimens obtained by directional coronary atherectomy and the nine specimens obtained by directional atherectomy of peripheral arterial sites were reviewed for each of the pathological findings described
above. Findings of thermal injury similar to those illustrated in Figure 1 were not observed in any specimen. Pathological alterations corresponding to vacuolar injury also were not observed in any patients. Finally, edge disruption similar to that illustrated in Figure 5 was observed in one patient (3.3%); edge disruption in this single non–laser-treated patient, however, was distinguished from that observed in the laser-treated patients by the absence of any tinctorial changes accompanying the shredded or smudged appearance resulting from pulsed laser angioplasty.

Complications

In one of 19 patients (5.3%) undergoing peripheral revascularization, an arteriovenous fistula was documented by angiography and intravascular ultrasound. This was unassociated with any acute or chronic sequellae. Serial noninvasive testing has subsequently disclosed improved noninvasive indices up to the time of most recent follow-up examination, 10 months after revascularization (ankle-brachial index, 0.99 versus 0.78 immediately before procedure).

Discussion

Previous studies have documented the usefulness of directional atherectomy as a unique biopsy instrument for the study of vascular pathology. These studies initially involved light microscopic analyses of peripheral[17-19,23] and coronary[20–22] atherosclerotic lesions. More recently, the versatility of this instrument has been
Figure 2. Vacuolar ('vesicular') injury resulting from holmium laser angioplasty. Top left panel: Series of vacuoles (V) seen in light microscope (×50) section of atherectomy specimen excised from superficial femoral artery of patient 9. Bottom left panel: Higher-power (×100) photomicrograph of above section. Top right panel: Series of vacuoles in superficial (presumably abraded) aspect of plaque excised from superficial femoral artery of patient 10. Bottom right panel: Extensive focus of vacuoles in atherectomy specimen excised from right coronary artery of patient 7 (all hematoxylin and eosin; top and bottom right, ×100).
FIGURE 3. Thermal injury accompanying vacuolar injury in atherectomy specimen excised from superficial femoral artery immediately after holmium laser angioplasty. Low-power (×50, top panel) and higher power (×100, bottom panel) photomicrographs showing extensive focus of charring (CH), which interdigitates with several large and multiple small vacuoles (V) (elastic tissue/trichrome stain).

demonstrated in studies of messenger RNA expression in restenotic lesions as well as growth characteristics of smooth muscle cells obtained from primary and restenotic stenoses. The present study was designed to further exploit the biopsy capability of directional atherectomy by determining the nature and extent of acute pathological injury associated with laser angioplasty performed in vivo.

The pathological features of laser irradiation have been previously studied using cadaveric tissues irradiated in vitro and a variety of animal models irradiated in vivo. The earliest of these studies involved continuous-wave laser irradiation of cadaveric human vascular tissues and identified two distinctive light microscopic findings at the perimeter of the ablation site: a superficial, predominant zone of charring, and a subjacent, more diminutive zone of polymorphous lacunae, or vacuoles. These findings have come to be recognized as the histological hallmarks of thermal injury. The appropriateness of this designation was confirmed by the fact that identical histological and ultrastructural findings resulted from straightforward thermal angioplasty achieved with the laser thermal probe (Laserprobe or hot tip). Correlative thermographic and histological analyses of tissue irradiated with the laser thermal probe demonstrated that vacuoles and charring typically occurred at temperatures exceeding 120°C.

In selected cases, these pathological consequences of thermal ablation have been confirmed in studies of human vascular tissues irradiated in vivo. Geschwind et
FIGURE 4. Atherectomy specimen excised from superficial femoral artery of patient 19 immediately after excimer laser angioplasty. Top panel: Low-power (×40) photomicrograph shows disruption along luminal borders of excised plaque (arrowheads). Higher-power photomicrographs (middle panel, ×100; bottom panel, ×200) show intensified hue and smudged or ground glass appearance.
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FIGURE 5. Atherectomy specimen excised from superficial femoral artery of patient 14 immediately after excimer laser angioplasty. Top and middle panels show alternative pattern of edge disruption, more subtle than that seen in patient 19 (Figure 4). In this case, there is focal "shredding" (arrows) along border of specimen. In addition, there is intensification of hue along border of specimen, seen best in bottom panel (all hematoxylin and eosin, ×100).
al demonstrated superficial charring and a subjacent zone of vacuoles at the neoluminal perimeter of residual plaque obtained from the popliteal artery 14 days after percutaneous continuous-wave Nd:YAG laser angioplasty using conventional fiberoptics. Rosenthal et al documented charring and vacuolization at the site of attempted Laserprobe ablation of a high-grade stenosis of the LAD in a patient who died and was studied at necropsy 2 weeks after the procedure. Lee et al and Diethrich et al used percutaneous angiography to study the acute effects of Laserprobe ablation in human peripheral arteries; each observed macroscopic evidence of charring. Although Lee et al also performed percutaneous atherectomy after use of the Laserprobe, description of the atherectomy specimen did not include comments regarding the result of light microscopic examination.

In contrast to the histopathology of thermal angioplasty, in which charring typically predominates over vascular injury, holmium:YAG laser irradiation characteristically results in mild-to-severe vascular injury, with a less conspicuous zone of thermal injury. This appears to be the case regardless of whether the laser is operated in the so-called "Q-switched" mode (pulse duration in the nanosecond regimen) or the more commonly used (present report included) "free running" mode (pulse duration in the microsecond regimen).

In vitro studies from our own laboratory, for example, using the free running mode demonstrated no signs of pathologic tissue injury at low fluences (<250 mJ/mm²); at higher fluences, macroscopic charring was typically absent, histological foci of charring were typically minimal, but histological foci of vascular injury ranged from moderate to extensive. Haase et al, using a 100-μsec holmium:YAG laser to irradiate atherosclerotic aorta in vitro, observed a small zone of light microscopic charring in all specimens, whereas the extent of vacuole formation related directly to applied pulse energy. These findings were associated with palpable pressure waves during advancement of a 200-μm fiber at energy densities >65 J/cm²; at >150 J/cm² in air, saline, and blood, the pressure wave was accompanied by an intense plasma light.

Kopchok et al demonstrated that the extent, if not the nature, of the pathological injury was a reflection of the pulse duration used. The extent of lateral tissue injury resulting from a 250-μsec (free-running) pulse duration (at 390 mJ/mm²) approached a maximum of 225 μm; in contrast, use of the Q-switched mode reduced the zone of histopathological injury (at 300–450 mJ/mm²) to <20 μm.

The histopathological findings resulting from excimer laser irradiation were first described in synthetic organic polymers, human hair, cartilage, and corneal tissue by Srinivasan and Mayne-Boynton; their findings indicated that the excimer laser could be used to inscribe exceptionally clean and precisely etched cuts devoid of thermal injury characteristic of previous generations of biomedical lasers. Subsequent studies demonstrated that identical histological results could be achieved in cardiovascular tissues; specifically, these studies have consistently disclosed no light microscopic signs of charring or vascular injury. Occasionally, detailed light microscopic and ultrastructural analyses have identified subtle morphological and tinctorial alterations of those cells at the perimeter of the laser crater. On light microscopic examination, the cytoplasm has the appearance of ground glass and/or a fine shredding along the edge of the lumen, frequently associated with an intensified hue. Similar light microscopic findings have been alluded to in studies involving noncardiovascular tissues. Scanning electron photomicrographs have disclosed that a blisterlike deformity constitutes the ultrastructural correlate of this light microscopic finding.

The experimental conditions of these previous experimental studies have, by the in vitro nature of their design, involved certain variables that may have decisively influenced the pathological outcomes. These variables include the nature of the tissue (normal versus atherosclerotic, fresh or live versus preserved), the ablation medium (air versus saline versus blood), delivery vehicle (native laser beam versus static or moving optical fiber), and the conditions of irradiation (subablation versus supra-ablation threshold). In contrast, analysis of the 21 atherectomy specimens in current study reflects pathological alterations resulting from fiber-mediated, laser ablation of live human atherosclerotic plaque in a pulsatile blood field.

Histological examination of atherectomy specimens obtained immediately after Laserprobe angioplasty in the current series was noteworthy for two reasons. First, light microscopic findings in all three patients provided detailed confirmation of the acute histopathological consequences of thermal angioplasty described previously. Second, the fact that all three atherectomy specimens disclosed these well-documented histopathological features of thermal injury validates the usefulness of directional atherectomy for in vivo identification of pathological alterations resulting from alternative forms of laser irradiation.

It should be noted that "thermal artifact" has been described in specimens obtained by directional atherectomy from four of 73 patients reported by Garratt et al. There are two reasons, however, that the findings interpreted as thermal injury in the present study are unlikely to represent such artifact. First, the hue of classic laser-induced thermal injury as seen on hematoxylin and eosin–stained sections differs from the "muddy, dark blue-gray coagulated appearance" observed as the result of atherectomy alone. Second, thermal injury of the type shown in Figure 1 of the present study was observed in each of the three patients treated with the Laserprobe versus none of the control specimens.

In the case of the holmium laser, findings in the present study indicate that vascular injury constitutes the predominant tissue effect associated with this laser in vivo. This observation is consistent with previous suggestions regarding the proposed mechanism of holmium: YAG laser ablation. Because the photon energy associated with a wavelength of 2.1 μm is insufficient to break molecular bonds, holmium laser irradiation has been inferred to cause tissue ablation principally by vaporizing water. The efficiency of this mechanism is optimized by proximity of this wavelength to a water absorption peak at 1.93 μm; as a result, the energy absorption in water of the holmium laser wavelength is 100-fold that of the Nd:YAG laser wavelength.
Elegant time-resolved flash photographic analyses performed in vitro by van Leeuwen et al. have documented that fiber-mediated holmium-induced vaporization of water results in the development of a vapor cavity around the fiber tip. The cavity reached a maximum dimension of 4.7 mm at \( \approx 300 \mu \text{sec} \) after the laser pulse and then imploded at \( \approx 450 \mu \text{sec} \); additional cavities were then formed, and these too, imploded, at \( \approx 750 \mu \text{sec} \). Although the most intense acoustic signals recorded by hydrophone were recorded upon the collapse of the vapor cavity, studies by Chen and Israelechvili suggest that tissue damage resulting from such vapor cavities is likely to occur during formation of such cavities. Further studies of pulsed infrared laser ablation by Fujiyama et al. have indicated that shock waves may propagate at supersonic velocities from the site of such cavity formation, producing tissue damage, including additional cytoplasmic vacuolization.

Analysis of in vivo consequences of excimer laser angioplasty disclosed findings similar to those previously recognized in vitro. Histological evidence of charring was consistently absent. Subtle alteration of those cells at the edge of the tissue specimen (presumed to represent the most superficial portion of the luminal border of the atherectomy specimen) was the only consistent histological alteration. These observations thus confirm previous in vivo42 and in vivo histopathological analyses indicating that the results of fiber-mediated application of excimer laser irradiation in a blood field are similar to those observed after excimer laser irradiation performed in air or saline.

It must be acknowledged that the clinical nature of this study dictated certain aspects of the experimental design concerning the laser parameters used. For example, because clinical laser angioplasty systems are designed such that the manufactured laser catheter can only be coupled to that manufacturer's laser, irradiation from each laser described in this study was delivered by a unique laser/fiberoptic catheter. Thus, we cannot exclude the possibility that the histopathological observations were in some way a function of the manner in which the fiberoptics were configured for a particular laser and catheter. Likewise, as indicated above, the energy and/or powers required for ablation of atherosclerotic plaque in vitro ("ablation threshold") vary as a function of laser wavelength and energy profile. Consequently, it is not feasible to perform a comparative study of several lasers using identical laser output parameters. In the present study, we chose instead to compare the histopathological consequences associated with the common end point of clinically (angiographically) apparent plaque ablation.

These findings imply that potentially important differences may exist among these three lasers with regard to operative mechanisms responsible for in vivo ablation of human plaque. Although photoablative decomposition, or tissue molecular bond-breaking, has been alleged to represent the mechanism responsible for excimer ablation,32,34 there is evidence that excimer irradiation also may have thermal5,7 and photoacoustic43 effects. Histological examination of the post–laser atherectomy specimens suggests that such potential thermal effects are mitigated by combined use of relatively low pulse energy repetition rate and cumulative exposure. Histological evidence of photoacoustic phenomena is apparently obviated by use of a wavelength with a lower coefficient of water absorption as well as a pulse duration in the nanosecond versus microsecond regime.

Specific implications that these anatomic findings might have for chronic consequences of laser irradiation remain to be clarified. From the standpoint of acute tissue effects, evidence of thermal injury in the atherectomy specimens retrieved after laser thermal angioplasty is consistent with previous reports of spasm,44 with or without acute thrombus formation, believed to result from the vasoconstrictor effects of heat in patients treated with the laser probe. Conversely, the absence of thermal injury after excimer ablation is consistent with the marked reduction in clinically apparent spasm in patients treated with excimer laser angioplasty.46,47 Although experimental studies have suggested that photoacoustic effects may be responsible for occasional cases of spasm and/or dissection resulting from pulsed laser angioplasty, this issue, too, awaits further clarification.

Finally, although the efficacy of combined laser/atherectomy remains to be established, the clinical experience reported here suggests that this approach is at least safe. Only one complication, an arteriovenous fistula that ultimately closed spontaneously, was noted. Although this must be attributed to the combination of instruments used, vessel wall perforation has been reported after atherectomy without laser angioplasty.48

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