Fluorescence-Guided Laser-Assisted Balloon Angioplasty in Patients With Femoropopliteal Occlusions

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In 12 patients (aged 64±10 years) with femoropopliteal occlusions (1–27 cm; average, 8.4 cm length) that could not be recanalized by standard guidewire-balloon angioplasty techniques, percutaneous laser-assisted balloon angioplasty was performed by use of a new fluorescence-guided dual-laser system. Plaque detection by 325-nm laser-excited fluorescence spectroscopy provided real-time feedback control to a 480-nm pulsed dye laser (2-μsec pulses) for atheroma ablation. By means of a common 200-μm optical fiber, after diagnostic fluorescence sensing, computer algorithms directed a fire or no-fire signal (5 Hz) to the treatment laser for selective plaque removal. Laser recanalization (15–50 mJ/pulse) was successful in 10 of 12 patients; this procedure was followed by definitive balloon angioplasty in seven of 12 patients with increased ankle/arm indexes (from 0.60±0.12 at baseline to 0.84±0.11 after treatment, p=0.0043). In laser and balloon angioplasty failures, all femoropopliteal occlusions were heavily calcified, and there were two mechanical guidewire perforations without clinical sequelae. Ablation of calcified lesions required higher pulse energies and greater total energy per centimeter of recanalized tissue (1,837±1,251 mJ/cm vs. 90±39 mJ/cm, p=0.0036). Fluorescence spectroscopy (n=219 sites) was helpful in flush occlusions and correctly identified plaque, underlying media, and thrombus by changes in fluorescence intensity, shape, and peak position. Thus, when fluorescence-guided laser angioplasty was used in a subgroup of patients refractory to standard angioplasty techniques, primary recanalization and subsequent balloon angioplasty of femoropopliteal occlusions was successful in 83% and 58% of the patients, respectively. Importantly, treatment of heavily calcified lesions accounted for all of the failures and will require modified delivery systems to create larger primary channels and to increase catheter-tip control, which should improve clinical results in the future. (Circulation 1990;81:143–155)

The success of laser angioplasty in patients with peripheral vascular disease has been limited by an unacceptable frequency of vessel wall perforations1–3 and limited recanalization efficacy, especially in situations of chronic total occlusions.4 Creative solutions to these problems have largely focused on the use of more sophisticated pulsed laser systems, such as excimer and erbium:YAG lasers, which can more efficiently ablate variable composition atheroma (including calcified material) without eliciting thermal damage to surrounding normal tissue.5–8 However, precise tissue ablation with newer pulsed lasers still does not prevent transmural perforation at vessel endpoints and cannot accurately direct the course of plaque recanalization within an eccentric stenosis or a total occlusion.9 Therefore, an integrated laser catheter delivery system that is capable of reliable in vivo plaque recognition may be necessary for safe and effective laser angioplasty, especially in the small, tortuous conduits of the coronary and distal peripheral arterial circulations.

Recently, in our laboratories, we have demonstrated that laser-excited fluorescence spectroscopy is a highly sensitive and specific technique for atheroma detection in patients during open heart surgery and cardiac catheterizations.10 Moreover, we have

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also shown that real-time fluorescence spectroscopic plaque recognition can be combined with 480-nm pulsed dye laser ablation to improve target site specificity; thus, vessel wall perforation can be prevented in vitro.11

The present report describes the clinical application of an integrated dual laser system that makes use of laser-excited fluorescence guidance to control pulsed laser ablation of plaque. In these preliminary studies, after standard angioplasty techniques were unsuccessful, the laser system was used to create a small primary channel; this procedure was followed immediately by balloon angioplasty to achieve definitive recanalization of chronic total femoropopliteal obstructions.

**Methods**

**Study Inclusion Criteria**

Patients with the following conditions were considered protocol candidates: 1) symptomatic peripheral vascular disease for more than 3 months, including effort-induced claudication, rest pain, or both, 2) total superficial femoral artery or popliteal artery occlusions or both with a discernible superficial femoral artery entry point beyond the profunda bifurcation, 3) angiographic distal reconstitution of the parent vessel beyond the lesion with at least two-vessel infrapopliteal runoff, and 4) absent ipsilateral inflow disease of the iliac or common femoral arteries or both. Subtotal obstructions of the ipsilateral superficial femoral artery proximal to the total occlusion were treated with balloon angioplasty after recanalization and dilatation of the target lesion.

Before laser angioplasty, all lesions were vigorously probed with standard vascular guidewires (0.035 in. o.d.). Straight or curved solid-shaft guidewires (as anatomically indicated) encased in polyurethane and coated with a frictionless hydrophilic polymer (Terumo Corporation, Tokyo, Japan) were initially used in an attempt to penetrate the occluded segment. In addition, other metallic Teflon-coated guidewires (straight, curved torque, or 1-mm J-tip shapes) were used to test mechanical resistance of the lesion. In all cases, at least 15 minutes were spent and at least three guidewire configurations were used to traverse the total occlusion after vascular access was achieved. Only lesions that could not be successfully crossed with guidewires were treated with laser angioplasty.

**Patient Population**

Eighteen lesions in 17 patients were treated in the Interventional Radiology Department of the Clinical Center, National Institutes of Health, Bethesda, Maryland. Successful guidewire penetration and balloon angioplasty was accomplished in six total occlusions (33%) in five patients. In two of these lesions, chronic infusions (24–48 hours) of intra-arterial thrombolytic agents (urokinase, streptokinase, or both) were required to achieve definitive lysis of residual thrombus.

In the remaining 12 lesions in 12 patients, after unsuccessful attempts at standard balloon angioplasty, laser recanalization of the total occlusion was attempted. This patient cohort (Table 1) consisted of 10 men and two women, from 41 to 78 years old (mean age, 64 years), all of whom had claudication (two also had rest pain). There were two patients with diabetes, three with coexistent coronary artery disease, nine cigarette smokers, one with hypercholesterolemia (>250 mg/dl), and seven with systemic hypertension requiring pharmacologic management. In 11 patients, the treatment vessel was the superficial femoral artery, and in the twelfth, the lesion was confined to the popliteal artery. Based on direct measurements on cut-film angiograms calibrated with a Bell-Thompson ruler, total occlusion length averaged 8.4 cm (range, 1.0–27.0 cm). Five of the lesions contained focal or diffuse areas of dense calcification.

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**Table 1. Laser-Assisted Balloon Angioplasty: Patient Characteristics and Treatment Factors**

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age/sex</th>
<th>Lesion length (cm)</th>
<th>Calcification</th>
<th>Angle/brachial index</th>
<th>Pulse energy range (mJ)</th>
<th>Total energy (mJ)</th>
<th>Number of pulses</th>
<th>Energy/cm tissue</th>
<th>Success</th>
<th>Balloon angioplasty success</th>
<th>Complications</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>76/F</td>
<td>10.0</td>
<td>+</td>
<td>0.42</td>
<td>15–20</td>
<td>3,532</td>
<td>190</td>
<td>1,177</td>
<td>–</td>
<td>–</td>
<td>Mechanical perforation</td>
</tr>
<tr>
<td>2</td>
<td>78/M</td>
<td>7.2</td>
<td>–</td>
<td>0.50</td>
<td>15</td>
<td>481</td>
<td>31</td>
<td>67</td>
<td>+</td>
<td>+</td>
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</tr>
<tr>
<td>3</td>
<td>68/M</td>
<td>14.5</td>
<td>+</td>
<td>0.73</td>
<td>15–40</td>
<td>26,824</td>
<td>863</td>
<td>1,850</td>
<td>+</td>
<td>+</td>
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</tr>
<tr>
<td>4</td>
<td>41/M</td>
<td>1.0</td>
<td>–</td>
<td>0.71</td>
<td>35</td>
<td>141</td>
<td>4</td>
<td>141</td>
<td>+</td>
<td>+</td>
<td>Mechanical perforation</td>
</tr>
<tr>
<td>5</td>
<td>59/M</td>
<td>13.0</td>
<td>–</td>
<td>0.70</td>
<td>35</td>
<td>694</td>
<td>20</td>
<td>53</td>
<td>+</td>
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</tr>
<tr>
<td>6</td>
<td>62/M</td>
<td>3.7</td>
<td>+</td>
<td>0.54</td>
<td>35–45</td>
<td>14,773</td>
<td>361</td>
<td>3,992</td>
<td>+</td>
<td>+</td>
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<tr>
<td>7</td>
<td>67/M</td>
<td>4.2</td>
<td>+</td>
<td>0.58</td>
<td>35–45</td>
<td>5,087</td>
<td>129</td>
<td>1,211</td>
<td>+</td>
<td>+</td>
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<tr>
<td>8</td>
<td>76/F</td>
<td>2.1</td>
<td>–</td>
<td>0.58</td>
<td>35</td>
<td>490</td>
<td>14</td>
<td>70</td>
<td>+</td>
<td>+</td>
<td>Mechanical perforation</td>
</tr>
<tr>
<td>9</td>
<td>62/M</td>
<td>4.5</td>
<td>+</td>
<td>0.72</td>
<td>35–50</td>
<td>4,301</td>
<td>96</td>
<td>956</td>
<td>–</td>
<td>–</td>
<td>Mechanical perforation</td>
</tr>
<tr>
<td>10</td>
<td>51/M</td>
<td>8.5</td>
<td>–</td>
<td>0.60</td>
<td>35–45</td>
<td>1,361</td>
<td>36</td>
<td>160</td>
<td>–</td>
<td>–</td>
<td>Mechanical perforation</td>
</tr>
<tr>
<td>11</td>
<td>66/M</td>
<td>27.0</td>
<td>–</td>
<td>0.73</td>
<td>35</td>
<td>140</td>
<td>4</td>
<td>70</td>
<td>–</td>
<td>–</td>
<td>Mechanical perforation</td>
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<td>64/M</td>
<td>5.5</td>
<td>–</td>
<td>0.38</td>
<td>35</td>
<td>140</td>
<td>4</td>
<td>70</td>
<td>+</td>
<td>+</td>
<td>Mechanical perforation</td>
</tr>
</tbody>
</table>

SFA, superficial femoral artery.
within the treatment vessel, defined as radiopacity of the vessel wall occupying at least one third of the occluded segment length on plane-film x-rays. In two patients, previous balloon angioplasty attempts had been unsuccessful, and in a third, previous surgical endarterectomy was performed with subsequent reocclusion of the treated segment.

Laser Angioplasty System

A dual laser system (MCM Laboratories, Mountain View, California) was used for all patient studies (Figure 1). This system incorporates real-time laser-excited fluorescence spectroscopic plaque recognition with subsequent pulsed dye laser tissue ablation.11

The diagnostic portion of the system consists of a shuttered 325-nm helium cadmium laser operating at 2.6–5.0 mW, which is coupled into a 200-μm core diameter fused silica fiber. After laser excitation of the tissue in contact with the fiber, the longer wavelength fluorescence light emitted from the tissue surface is transmitted through the same optical fiber and redirected (by mirrors and lenses) into an optical multichannel analyzer. Fluorescence spectra (normalized intensity vs. wavelength) are displayed on a video monitor and are analyzed in real time by a dedicated microcomputer. In a diagnostic mode of the system (probe-and-display), the average of five consecutive spectra is analyzed after correction for background and appropriate adjustment of the detector exposure time (20–90 msec). After a probe-and-display fluorescence diagnostic sequence, a hard copy of the data can be stored in floppy disk format.

Plaque discrimination algorithms (MCM Laboratories) were previously developed and tested in vitro11,12 and in vivo10 by the aforementioned probe-and-display system. Algorithm recognition of abnormal tissue sites required 1) wavelength position of the fluorescence maxima less than 453 nm or more than 466 nm or 2) a change in normalized fluorescence spectra shape. To analyze changes in fluorescence spectra shape, each acquired spectrum was compared with a standard normal curve derived from previous in vitro and in vivo studies10–12 after equalizing peak intensity by amplification and peak position by translation. A numerical index of shape change was quantitated by computing the sum of the squared differences of normalized fluorescence intensity between the standard normal curve and the patient’s curve at various wavelengths. The wavelength positions for the least-squared residuals calculation were selected at five locations relative to the fluorescence maxima position: −42, −36, +52, +83, and +114 nm. By use of this formula, as the shape of the fluorescence spectra became more normal, the shape index value decreased. Algorithm parameters (fluorescence peak position and shape index) were set to provide high sensitivity for normal tissue site recognition. Thus, the treatment laser should never fire against normal tissue but occasionally might not fire against borderline abnormal tissue sites. Importantly, the fluorescence spectra peak position and shape are similar for both the normal artery (nondiseased intima above the media) and the preserved media beneath the atheroma.11,12 Consequently, after plaque ablation, the treatment laser should cease firing; thus, penetration into the media would be avoided. Moreover, as a further safety feature, after background correction, an absolute fluorescence intensity window was individually assigned to prevent treatment laser firing against either low-intensity signals (such as blood) or the normal intima and media, which typically emit higher fluorescence amplitude signals.11,12

The treatment laser consists of a 480-nm flashlamp-exited dye laser capable of generating high energies (up to 1 J) during short pulses (2 μsec). In the treatment mode (probe-and-treat), a 325-nm laser-excited fluorescence spectrum is first analyzed by computer-based algorithms, and a fire or no-fire signal is then sent to the treatment laser based on recognition patterns of either abnormal or normal tissue sites. If plaque is recognized, a single pulse is fired by the treatment laser through the optical fiber in contact with the tissue. A significant advantage of this system is that diagnostic laser light, emitted fluorescence from the tissue, and treatment laser light all travel along the same optical pathway and are transmitted by a common optical fiber (Figure 1). A complete probe-and-treat cycle requires approximately 100 msec, and the system is usually operated at five repetitions per second.

Both lasers are coupled into a single 200-μm fused silica optical fiber with acceptable damage thresholds at the output surface (e.g., for the 480-nm pulsed dye laser, 70 mJ from a 200-μm fiber). The catheter delivery system used in the patient studies was a helical guidewire (0.021-in. or 0.035-in. o.d.) around a central 200-μm silica fiber (MCM Laboratories). The laser fiber-wire design provided good torque control, improved durability of the enclosed fiberoptic, and facilitated passage of subsequent balloon dilatation catheters.
Laser Angioplasty Treatment Protocol

Noninvasive peripheral arterial evaluations (segmental pressures and Doppler waveforms) were performed in all patients immediately before treatment. Acetylsalicylic acid (325 mg q.i.d.) and dipyridamole (50 mg t.i.d.) were given orally 24–48 hours before procedures. Patients were taken to the Interventional Radiology Department in a fasting, mildly sedated state (oral diazepam), and after local anesthesia, antegrade puncture of the ipsilateral common femoral artery was performed with subsequent guidewire entry into the superficial femoral artery and insertion of a hemostatic introducer sheath. Before further catheter manipulations, combined systemic and intrarterial heparin was administered (total dose, 5,000 units). Diagnostic angiograms were obtained through the sheath to characterize the treatment site and the distal vasculature. Standard 0.035-in. guidewires were then advanced to the proximal portion of the total occlusion followed by a 5F Van Andel guiding catheter (Cook Incorporated, Bloomington, Indiana). The lesion was probed with various guidewires, as previously described, with the guiding catheter close to the total occlusion for support. In situations in which mechanical guidewire recanalization was unsuccessful (12 of 18 total occlusions), the guiding catheter was left within 1 cm of the total occlusion. After guidewire withdrawal, the laser fiber-wire was inserted into the guiding catheter to a position in contact with the proximal total occlusion. The guiding catheter (e.g., a steam-formed 5F catheter with a slightly curved tip or a 4.3F, 2.5-cm long, 3–4-mm diameter centering balloon angioplasty catheter) was frequently changed based on differing anatomic requirements to achieve a coaxial entry position into the total occlusion. Before laser angioplasty was begun, a series of probe-and-display sequences (from three to five per patient) was recorded from several closely spaced but different tissue sites within the total occlusion. Based on the abnormal fluorescence spectra recorded from the lesion site, occasionally (in three of 12 patients) minor modifications of preset spectral shift and shape parameters were made that optimized abnormal tissue site recognition for each patient. In addition, a peak fluorescence intensity cutoff (30–50% above the abnormal tissue site fluorescence intensity) was assigned to further prevent laser firing on normal tissue. After achieving the most central entry position to the lesion with the laser fiber-wire and confirming an abnormal fluorescence spectra, the guiding catheter was pulled back another 1–2 cm to minimize fiber-wire stiffness during subsequent advancement. Probe-and-treat cycles were initiated at five repetitions per second, and initial treatment laser pulse energy varied from 15 mJ in the first three patients to 35 mJ in the last nine patients. During probe-and-treat cycles, the fiber-wire was slowly advanced with minimal antegrade mechanical force into the lesion. Both fluoroscopy with contrast test injections and digital road-mapping were helpful in establishing initial coaxial position within the vessel and also served as an adjunct to fluorescence spectroscopy for guidance during laser angioplasty. After each 50–100 cycle probe-and-treat sequence (10–20 seconds), fluoroscopic advancement of the radiopaque fiber-wire was reassessed, and repeat probe-and-display sequences from different tissue locations within the lesion were recorded.

If the fluorescence spectra were still abnormal but the fiber-wire was not progressing through the lesion, the treatment laser pulse energy was increased (in 5-mJ increments) to as high as 50 mJ/pulse. Occasionally, during laser angioplasty, abnormal tissue sites manifesting changes in fluorescence spectra shape, peak position, or intensity required further algorithm adjustments to improve percent firing frequency. Repositioning of the fiber-wire was frequently required to maintain a central position within the total occlusion. After each probe-and-treat sequence, the remaining segment of total occlusion was gently probed by the laser fiber-wire, and the laser was reactivated only if tactile resistance of the fiber-wire tip against the lesion was still appreciated by the operator and an abnormal fluorescence spectra was recorded.

Based on pretreatment angiograms taken with the radiopaque metric ruler placed adjacent to the lesion site, contact of the laser fiber-wire with the nonoccluded reconstituted distal vessel could usually be determined. In addition, contrast injections through the guiding catheter, free movement of the fiber-wire tip, and fluorescence spectroscopy indicating the presence of a blood field were all helpful in confirming successful laser recanalization of the total occlusion. After laser angioplasty, the laser fiber-wire was held in a position approximately 1–2 cm beyond the proximal nonoccluded portion of the parent reconstituted vessel as the guiding catheter was advanced through the total occlusion. Thereafter, the fiber-wire was removed, guiding catheter contact with the distal vessel was reassessed by angiography, and a standard guidewire (0.035-in. o.d.) was inserted to a distal infrapopliteal position in preparation for subsequent balloon angioplasty. The guiding catheter was then removed, and appropriate balloon dilatation catheters (4–6-mm balloon diameter, 2–10-cm length) were advanced across the lesion followed by overlapping balloon dilatations from distal to proximal segments of the lesion. After completion of balloon dilatation of the total occlusion, a posttreatment angiogram was obtained to evaluate the treatment site and the infrapopliteal vasculature.

Catheters and sheaths were removed soon after the procedure, and patients remained at bed rest overnight with slow ambulation the following day. Patients with successful laser-assisted balloon angioplasty were treated with continuous systemic heparin (PTT maintained at approximately twice control values) for 24 hours, repeat noninvasive peripheral arterial evaluations were performed before dis-
charge, and they were given oral acetylsalicylic acid (325 mg q.i.d.) for 6 months.

Follow-up Studies

Patients with successful laser-assisted balloon angioplasty procedures were seen as outpatients in 2 months for repeat clinical examinations including noninvasive peripheral arterial evaluations and angiography of the femoropopliteal treatment site (venous digital subtraction angiography from the right atrium). One patient died from unrelated noncardiovascular causes 6 weeks after a successful procedure and therefore was not available for follow-up studies.

Statistics

Data are expressed as mean±1 SD, and statistical comparisons were made by t test analysis of paired and unpaired data.

Results

Laser Angioplasty

Successful laser recanalization was achieved in 10 of 12 total femoropopliteal occlusions that could not be opened by standard mechanical guidewire techniques (Table 1 and Figure 2). There were two instances of fiber damage at the output surface resulting in sudden loss of power during laser angioplasty without intravascular particulate embolization of the optical fiber.

Laser angioplasty attempts with low energies (15 mJ) in the first three patients indicated that higher energies were usually necessary for in vivo atheroma ablation (Table 1). When the 480-nm pulsed dye laser was used, rapid ablation of noncalcified atheroma required approximately 35 mJ/pulse or 1.1 J/mm²/pulse. During advancement of the fiber-wire against noncalcified total occlusions, a series of short-segment firm obstructions requiring laser recanalization and intervening softer regions, which were easily displaced with minimal antegrade mechanical pressure, were typically encountered.

Historical and clinical factors, lesion length, and laser operating conditions were not predictive of a poor outcome in the two cases of failed attempted laser angioplasty. In each patient, the procedure was
terminated because of an adverse occurrence; in patient 1, there was a mechanical perforation after progressing 3 cm within a 10-cm lesion, and in patient 9, an eccentric laser channel recanalized the total occlusion but did not communicate with the nonoccluded distal vessel.

Success of primary laser recanalization was strongly dependent on lesion composition. Heavy calcification of the treatment area was present in both laser failures, and in three additional patients, (patients 3, 6, and 7), calcification contributed to slow progress in achieving fiber-wire penetration of the lesion. The energy threshold for ablation of calcified lesions was more variable but was always higher than for noncalcified lesions, often requiring 45–50 mJ/pulse or 1.4–1.6 J/mm²/pulse. Moreover, when patients with and without calcified atheroma were compared, the total number of laser pulses fired (328±316 vs. 16±12, p=0.024), the total energy expended during the procedure (10,903±10,002 mJ vs. 492±408 mJ, p=0.018), and the total energy per centimeter of recanalized tissue (1,837±1,251 mJ/cm vs. 90±39 mJ/cm, p=0.0036) were all significantly greater with calcified atheroma (Table 1).

Balloon Angioplasty

Of the 10 patients with primary laser recanalization, successful balloon angioplasty was performed in seven. For these seven patients, all areas of stenosis and occlusion were successfully dilated (<50% post-treatment lumen diameter narrowing) in six (Figure 3, Tables 1 and 2), claudication thresholds were improved before discharge in all, and ankle/brachial indexes increased in all patients, from 0.60±0.12 at baseline to 0.84±0.11 after laser-assisted balloon angioplasty (p=0.0043). In the three balloon angioplasty failures, each of the lesions was heavily calcified, and neither guiding catheter nor balloon catheters could be advanced over the fiber-wire into the nonoccluded distal vessel segment.

Fluorescence Spectroscopy

After firm tissue contact with the fiber-wire was established, fluorescence spectra were recorded from 60 proximal total occlusion interrogation sites from the 12 patients (five sites per patient). Each of these abnormal sites represented an area within the proximal total occlusion presumably consisting of atherosclerosis or thrombus. Tissue contact was indicated by a sudden increase in fluorescence intensity and the appreciation of a recognizable spectrum, both of which could easily be distinguished from the non-descriptive low-intensity fluorescence signals emanating from a blood field. In all 12 patients, abnormal fluorescence spectra triggered the pulsed dye laser to begin tissue ablation. Analysis of the last recorded spectra before laser firing revealed that there was an abnormal shift in fluorescence spectra peak position.
(to wavelengths either >469 nm or <455 nm) in 10 patients and an abnormal fluorescence shape change in five patients (three of whom also had a shifted peak position). The most characteristic fluorescence spectra pattern recorded during fiber-wire contact with firm atherosclerotic obstructions was a reduction in fluorescence intensity (by 30–50% compared with standard normal reference data), minor fluorescence shape changes, and a consistent shift in the fluorescence peak position to higher wavelengths (usually between 469 and 474 nm). Fluorescence spectra findings from regions of heavy calcification revealed an unusual shift in fluorescence peak position to lower wavelengths (<455 nm) and only slightly abnormal shape indexes.

In two patients (patients 4 and 5) in whom the proximal vessel terminated in a large collateral vessel and no distinct entry site into the occluded segment was present, fluorescence spectroscopy was extremely helpful in directing the laser fiber-wire to an appropriate abnormal tissue site, initiating successful subsequent laser recanalization (Figure 4).

Between probe-and-treat cycles, 159 additional fluorescence spectra were recorded from tissue sites within the total occlusion. Treatment laser firing and resultant tissue ablation did not alter the capacity to resolve and interpret subsequent fluorescence spectra. In 10 patients (83%), a sudden increase in fluorescence intensity associated with normal fluorescence spectra shape and peak position indicated proximity of the laser fiber-wire to the vessel wall media at least once during laser recanalization (Figure 5). In each case, the treatment laser did not fire, and fluorescence spectroscopy was the earliest indicator of an eccentric fiber-wire position. X-ray fluoroscopic redirection of the fiber-wire to a different tissue site with an abnormal fluorescence spectra suggested a more central location within the atheroma, and laser angioplasty was resumed safely. Thus, despite the suggestion of an abnormal tissue site by standard fluoroscopic examination, there were many instances when fluorescence spectroscopy prevented the treatment laser from firing. Fluorescence spectra associated with no-fire signals were due to either 1) low-intensity counts (from blood or when the catheter was being advanced too rapidly) or 2) recording of normal spectra (either incorrect recording in areas of

![Fluorescence spectra with intensity plotted against wavelength (left panel) and angiograms (right panel) during laser angioplasty procedure. Before treatment (left angiogram), short femoropopliteal occlusion (outlined segment) terminates in large collateral vessel (arrows). Fluorescence spectra from collateral resembled normal artery reference spectra. Repositioning fiber-wire within occlusion revealed an abnormal spectra and permitted subsequent successful laser angioplasty (right angiogram).](http://circ.ahajournals.org/)

**FIGURE 4.**

<table>
<thead>
<tr>
<th>Table 2. Laser-Assisted Balloon Angioplasty: Follow-up Results</th>
</tr>
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<tbody>
<tr>
<td><strong>Patient</strong></td>
</tr>
<tr>
<td></td>
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<tr>
<td>---</td>
</tr>
<tr>
<td>2</td>
</tr>
<tr>
<td>4</td>
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<td>10</td>
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<td>11</td>
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<td>12</td>
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</tbody>
</table>

Greatest residual stenosis was determined by angiography.

*Total occlusion proximal to original laser treatment site.
true plaque or correct recording when normal intima or media were sensed).

In six patients (patients 2, 4, 5, 8, 11, and 12), after initial laser ablation of firm short-segment obstructions, subsequent application of minimal antegrade force to the fiber-wire resulted in rapid advancement within the total occlusion when the treatment laser was not firing; this occurrence suggested the presence of fresh or partially organized thrombus. In each case, the accompanying fluorescence spectroscopy revealed striking attenuation of the fluorescence intensity, changes in fluorescence spectra shape due to a reduction in fluorescence intensity at 400–430 nm, and marked fluorescence peak shifting to higher wavelengths (usually >479 nm).

Two-Month Follow-up Studies

In the seven patients with initially successful laser-assisted balloon angioplasty, one died from noncardiac causes, and six others reported sustained improvement in claudication thresholds at two months. Repeat ankle/brachial indexes were still increased in all patients (to 0.88±0.18, p=0.064) compared with baseline values (Table 2). Two-month outpatient angiograms revealed continued patency without restenosis of the prior total occlusion treatment site in each patient with residual worst-site stenosis 50% or less after balloon angioplasty (Table 2 and Figure 6). In a patient with persistent focal stenosis (58% lumen diameter narrowing) after laser recanalization, although ankle/brachial indexes were still improved, follow-up angiography demonstrated a recurrent total occlusion.

Complications

In the seven patients without calcified lesions, the only complications were two procedure-related groin hematomas that did not require blood product transfusions of surgical evacuation and one mechanical dissection during subsequent balloon angioplasty (Table 1). In the five patients with calcified lesions, there were complications in three, including two mechanical fiber-wire perforations and two dissections of the distal nonoccluded parent vessel while attempting to pass guidewires and guiding catheters through the primary laser channel (Table 1). The mechanical perforations sealed spontaneously without clinical sequelae, and distal dissections were without signs of augmented limb ischemia. There were no instances of arterial vasospasm, procedure-induced thromboses, or distal particulate embolization.

Discussion

Since the advent and widespread use of percutaneous transluminal balloon angioplasty in the late 1970s and 1980s, investigators have considered alternative catheter-based devices that would expand our ability to remodel obstructed coronary and peripheral arteries. One of the most promising of these new technologies makes use of concentrated light energy from lasers transmitted by means of small flexible optical fibers within catheters to a distant intravascular target site to vaporize or ablate atherosclerotic lesions. However, the success of laser angioplasty as a therapeutic modality in the future will depend on a convincing demonstration that, compared with balloon angioplasty, laser plaque ablation can improve the risk profile, expand the range of patient candidates, reduce the frequency of restenosis, or achieve all of these. Enthusiasm for the potential benefits of laser angioplasty has been tempered by the recognition that laser-induced artery wall perforations may complicate recanalization procedures, especially in the setting of chronic total occlusions. Therefore, to optimize safety and efficacy, laser angioplasty may require a means of guidance and feedback control such that laser energy can be precisely directed against only abnormal target sites.

New methods of in vivo plaque recognition currently under investigation include the following: direct fiberoptic visualization or angioscopy; the administration of exogenous fluorescent chromophores that are preferentially sequestered in atheroma; the use of miniature intra-arterial high-frequency ultrasound to acquire spatial and compositional data; and several spectroscopic techniques such as absorption spectroscopy, fluorescence spectroscopy, infrared spectroscopy, Raman spectroscopy, and photoacoustic spectral analysis.

In the present study, laser-excited fluorescence spectroscopy was used as an in vivo guidance-control modality within an integrated laser angioplasty treatment system. There are several advantages to this approach, including 1) rapid data acquisition and analysis providing real-time feedback control to the pulsed treatment laser, 2) use of a common optical pathway such that fluorescence diagnostics and treatment laser light can be transmitted through a single optical fiber, thereby miniaturizing catheter delivery systems, and 3) use of fluorescence spectroscopic data both as a trigger for treatment laser firing when surface atheroma is sensed and, perhaps more importantly, as a signal to disable the treatment laser when the laser fiber-wire approaches underlying artery wall media.
Fluorescence-Guided Laser Angioplasty

To examine the clinical utility and limitations of this "smart" laser angioplasty system, we treated patients with chronic total femoropopliteal occlusions after standard balloon angioplasty techniques were unsuccessful. This initial patient group was selected to provide an in vivo study environment wherein procedure-related risks could be minimized and the concept of fluorescence-guided laser angioplasty could be rigorously evaluated. Our preliminary results demonstrated successful laser recanalization in 10 of the 12 chronic total occlusions that were resistant to mechanical guidewire penetration. Moreover, the feasibility of real-time fluorescence spectroscopy for guidance of the treatment laser was established, which in the future may reduce the risks of laser-induced perforations.

Although absolute tissue ablation thresholds cannot be determined accurately in vivo, the pulse energy requirement of 35 mJ through a 200-μm fiber to advance the fiber-wire in noncalcified lesions is similar to previous in vitro studies of tissue ablation thresholds with a 480-nm pulsed dye laser that were performed in our laboratories. In the first three patients, we initiated tissue ablation using 15 mJ/pulse. This value was based on in vitro experiments by us and others indicating that in some atheromas there is preferential absorption of 480-nm laser light.
by yellow and red chromophores that results in ablation thresholds that are less than half of those found in normal tissue and in nonpigmented atheromas. Our observation that higher pulse energies are necessary for effective plaque ablation in vivo strongly suggests that in these patients with chronic total femoropopliteal occlusions, carotenoids (producing a yellow surface color) and hemoglobin were not the primary constituents of plaque. More likely, the lesions were white fibrous atheromas with ablation thresholds similar to normal tissue. Recent data indicate that advanced atherosclerotic lesions in carotid arteries manifest a 50-fold increase in plaque β-carotene levels after short-term administration of low-dose oral β-carotene. Perhaps introduction of this exogenous chromophore with resultant enhanced light absorption between 450–500 nm may be a potential future technique to improve selective plaque ablation using a 480-nm pulsed dye laser.

Moreover, the consistent in vivo finding that even higher pulse energies (45–50 mJ) were required to penetrate heavily calcified lesions directly contradicts previous in vitro reports in which preferential ablation of calcified arterial plaque was demonstrated at low pulse fluences because of nonthermal photoacoustic plasma formation. Perhaps fragmentation of calcified materials by photoacoustic shock waves, as is seen with pulsed dye laser disintegration of urinary and biliary calculi, is less effective for bulk atheroma removal when the calcium is impregnated within a tissue matrix.

From these patient studies, given the indeterminate contribution of mechanical tissue displacement as the fiber-wire is advanced, it becomes difficult to ascertain the precise mechanisms of tissue ablation. In calcified lesions, in which fiber advancement was dependent on laser ablation, an average of 5.9 J was required to ablate a cubic millimeter of tissue through a 200-μm fiber. The high-pulse energies and low-ablation efficiencies for removal of calcified atheromas would be most compatible with a photothermal process of tissue decomposition, with lesser photoacoustic shock-wave effects.

**Fluorescence Spectroscopy**

Although several investigators have now shown that low-power midultraviolet laser-excited fluorescence spectroscopy can differentiate plaque from surrounding normal vessel in vitro, this is the first attempt to incorporate real-time fluorescence diagnostics for guidance of a treatment laser during clinical laser angioplasty. Therefore, the investigational utility and practical value of fluorescence spectroscopy in these patient studies must be critically examined.

Unexpectedly, there were fewer distinctive fluorescence spectra shape patterns associated with abnormal tissue sites than noted in previous in vitro experiments. This suggests more homogeneous plaque-related fluorophores in femoropopliteal occlusions with less intrasession and interpatient variability. Specifically, in these lesions there was a virtual absence of yellow atheroma, which can be distinguished by a broad fluorescence maxima and a secondary shoulder appearing at 498–506 nm. This finding agrees with our inability to ablate tissue effectively at 15 ml/pulse, as would be expected from in vitro measurements on pigmented yellow atheroma. Firm atherosclerotic occlusions in patients were most consistently associated with fluorescence spectra revealing diminished intensity, minor changes in shape, and shifting of the peak position to higher wavelengths (between 469 and 474 nm). Based on necropsy and in vivo studies, these lesions almost undoubtedly were chronic white fibrous atheroma. Alternatively, after beginning laser recanalization, we often encountered softer areas within the total occlusion, which exhibited much lower fluorescence intensities, greater changes in fluorescence shape, and even greater shifts in fluorescence peak positions to higher wavelengths (usually >474 nm). The fluorescence shape changes were attributed to diminished fluorescence intensity at 400–430 nm, which was probably caused by hemoglobin absorption at these wavelengths. Thus, the distinctive spectra often seen in softer lesions, some of which could easily be penetrated by mechanical advancement of the fiber-wire, probably represent fresh or partially organized thrombus or both. This conclusion is further supported by the observation of similar fluorescence spectra patterns in two patients with mechanical guidewire and balloon catheter recanalization who required adjunct intra-arterial thrombolytic agents to lyse residual thrombus. Heavily calcified lesions were less sensitively detected by fluorescence spectroscopy than other plaque morphology subtypes because of greater interlesion compositional heterogeneity of calcified plaques and less distinctive changes in spectra shape.

There were two clinical situations in which fluorescence spectroscopy was most helpful in achieving safe and effective laser recanalization of femoropopliteal occlusions. In vessels that terminate in a large collateral branch at the origin of the lesion, proper direction of the laser fiber-wire away from the collateral vessel and into the nonvisualized flush-occluded parent vessel could only be accomplished with fluorescence spectroscopic monitoring. Similarly, frequent eccentric fiber-wire positioning during laser angioplasty of an occluded vessel was usually heralded by fluorescence intensity and shape changes indicating proximity to the media. The sudden change in fluorescence spectroscopy was correctly interpreted, and the treatment laser did not fire; thus, laser penetration into the media and resultant perforation were prevented. The fiber-wire was then redirected to a more advantageous coaxial position within the neolumen of the vessel. This situation was most common in the distal superficial femoral artery (within the adductor canal) where the vessel courses more obliquely and is firmly engaged by intertwining muscle bundles.
An important design consideration for fluorescence-guided laser angioplasty systems is synchronous fluorescence depth sensing and pulse tissue ablation. That is, the treatment laser should ablate with each pulse only that tissue mass sensed by the diagnostic laser. Recent work measuring the depth of laser-excited tissue fluorescence at 325 nm\(^{30}\) estimates that most of the emitted fluorescence arises from a tissue zone 150 \(\mu\)m beneath the transmitting fiber. From the present study, in calcified lesions in which there is relatively little mechanical displacement of tissue, the fiber tip advanced an average of 243 \(\mu\)m/pulse (range, 102–459 \(\mu\)m/pulse). Although these are only crude estimates, and previous in vitro work\(^{11}\) has demonstrated fluorescence sensing and 480-nm dye laser pulse ablation of comparable depths, careful additional experiments are required to ensure that tissue ablation does not “outdistance” the feedback sensing system. This assumes greater importance in smaller vessels such as atherosclerotic coronary arteries in which the media thickness averages only 150 \(\mu\)m, and a laser pulse removing more than the sensed depth may result in media penetration despite accurate fluorescence recognition of the surface target sites.

**Clinical Implications**

The standard treatment of symptomatic femoropopliteal disease has evolved over the past decade; retrospective surgical series have indicated an improvement in 5-year patency of autologous vein grafts to 63–78%\(^{31–37}\). Moreover, percutaneous balloon catheter dilatation has gained acceptance as an efficacious and “lesser invasive” therapeutic alternative.\(^{38}\)

However, in patients treated with balloon angioplasty for femoropopliteal lesions, combining initial failures and chronic restenosis, the overall success rate after 2 years falls to approximately 60%.\(^{39–44}\) The results are particularly disturbing in chronic femoropopliteal occlusions for which initial failure rates alone are greater than 50% for long lesions (>3-cm length) and restenosis rates are higher than for comparable length stenotic lesions.\(^{39,41,44}\) Thus, modifications in angioplasty procedures are necessary to achieve initial and long-term results that are comparable with recent surgical reports, especially in patients with chronic femoropopliteal occlusions. In the present report, the study group was too small to elicit worthwhile conclusions concerning the relative efficacy of primary recanalization by fluorescence-guided laser angioplasty techniques. Importantly, although primary laser recanalization was successful in 83% of our patients, definitive angioplasty was only successful in 58%. Future catheter designs (either larger fiber-wires or multifiber catheters) capable of bulk tissue removal should improve this overall success rate by facilitating introduction of guiding and balloon catheters for subsequent angioplasty. It seems likely that fluorescence-guided laser angioplasty will be most useful in technically difficult situations including tortuous vessels, eccentric lesions, and flush occlusions terminating in large branch collaterals.

Importantly, the treatment of heavily calcified lesions by using current methodology was disappointing. Pulse energy requirements were higher in calcified occlusions, and there was more than a 10-fold increase in the number of laser pulses fired, total energy used, and energy per centimeter of recanalized tissue compared with noncalcified occlusions. Moreover, attempts to redirect the fiber-wire within calcified lesions during angioplasty were more difficult, resulting in two mechanical perforations. In calcified lesions, once primary laser recanalization was accomplished (in three patients), efforts to advance either guiding catheters or balloon catheters over the fiber-wire were problematic, causing distal dissections in two patients. Lastly, fluorescence spectroscopy was more variable and less sensitive in detecting calcified atheroma, an observation confirmed by us\(^{12}\) and others\(^{45}\) during both in vitro and in vivo experiments.

Follow-up data in this small group of patients is difficult to interpret, and there can be no definitive statements regarding the frequency of restenosis. In the six patients with 2-month follow-up angiograms, there was one instance of restenosis or reocclusion, in a patient with significant residual focal stenosis after the initial laser-assisted balloon angioplasty procedure. During these studies, because the primary laser channel is only 0.5 mm in diameter and complete recanalization still requires balloon angioplasty, it seems unlikely that postprocedure restenosis will be favorably influenced by using present techniques. In the future, larger catheters with multiple fibers, designed to create a channel with a diameter of 2 mm or more, may ablate a sufficient mass of atheroma to test the hypothesis that laser angioplasty (either as a stand-alone technique or combined with balloon angioplasty) will reduce the frequency of restenosis.

Although complications occurred frequently in patients with calcified occlusions, both mechanical fiber-wire perforations and intimal dissections were without important clinical sequelae. Even in laser and balloon dilatation failures, distal limb viability was never compromised. Greater operator experience and modifications in delivery systems should reduce such complications in the future.

**Future Directions**

Fluorescence-guided laser angioplasty holds promise as a new technique for catheter-based arterial recanalization in patients with obstructive atherosclerotic disease. This initial report should stimulate interest in the concept of real-time fluorescence plaque detection as a feedback-control component of an integrated laser angioplasty system. However, challenging design refinements are necessary to accomplish improved recanalization efficacy with fewer complications in calcified occlusions and to achieve definitive laser atheroma debunking as a stand-alone procedure without balloon angioplasty, especially in the infrapopliteal vessels and in the coronary arteries. Ongoing system-design modifications include: 1)
improved laser fiber-wire construction with retained flexibility but increased surface ablation area, 3) greater catheter-tip control using fixed J-tip configurations and manual tip deflectors, 4) multiple fiber catheter designs for bulk tissue removal, and 5) examination of alternative pulsed laser sources with improved tissue ablation characteristics (especially for calcified lesions), which may also be more compatible with the fluorescence-guided detection system.

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