The demonstration that laser light could convert solid-phase atherosclerotic plaque into gas-phase vapors that are soluble in blood\(^1\) and that such laser light could be transmitted via flexible optical fibers suggested two means by which lasers might improve upon balloon angioplasty. First, the laser could be used to recanalize totally occluded arteries. Second, if the intuition that removing was superior to remodeling atherosclerotic plaque proved correct, then the incidence of restenosis might be diminished.

Quite paradoxically, most of the efforts expended during the past decade to develop laser angioplasty into a viable clinical entity were focused on the albatross of percutaneous revascularization, the total occlusion; this, despite the fact that restenosis loomed far larger on the dark side of balloon angioplasty. The current flirtation with the excimer laser must be viewed from the perspective of this previous obsession with laser angioplasty as a treatment for total occlusion.

The focus on totally occluded arteries developed for several reasons. First, percutaneous trials of laser angioplasty were initiated in the peripheral vasculature. Total occlusions of the superficial femoral artery are proportionately more frequent among patients with chronic claudication than total coronary occlusion is in patients with chronic angina pectoris. Second, before the advent of hydrophilic guide wires, percutaneous recanalization of such totally occluded vessels was less frequently successful. Third, although too small to obviate balloon angioplasty, the size of the lumen achieved with the earliest prototypical devices was sufficient to serve as a pilot hole. If use of the laser could extend the limits of percutaneous revascularization to include total occlusions refractory to conventional techniques, then the instrument would gain in importance to the interventionalist.

The earliest attempts to use laser angioplasty for totally occluded vessels were carried out jointly by a team of cardiologists and radiologists\(^2\) and produced an unacceptable incidence of mechanical perforations due to the bayonettelike effect of the bare optical fiber. Hussein et al\(^3\) solved the problem of mechanical perforation by applying a corpulent metal cap to the distal end of the optical fiber; this novel tip design promoted coaxial, intraluminal passage of the optical fiber and used the laser light to heat the metal cap, thereby burning away atherosclerotic plaque.

While clinical applications of so-called “hot-tip laser angioplasty” served to focus attention on the issue of long total occlusions in lower-extremity vascular disease,\(^4\) the apparent niche that had developed for laser angioplasty was rendered nonexclusive by two concurrent developments. First, McNamara and Fischer\(^5\) demonstrated that adjuvant thrombolytic therapy frequently converted total occlusions to subtotal occlusions, which were then easily treated by conventional angioplasty. Second, development of the hydrophilic (“glide,” “eel,” or “slime,”) wire dramatically improved the capability of the interventionalist toatraumatically recanalize long total occlusions with just a guide wire.\(^6\) While issues of cost and logistics have blunted what might otherwise have been the full impact of adjuvant thrombolytic therapy, use of hot-tip laser angioplasty in most interventional laboratories, including our own, has declined to a negligible level as operators have gained experience and facility with the “glide wire.”

Furthermore, studies with the hot tip proved difficult to duplicate in the peripheral vasculature and nearly impossible to extrapolate to the coronary circulation, despite multiple iterations in probe design. A body of experimental work has helped to clarify the basis for these disappointing clinical results. Tobis et al\(^7\) demonstrated that the route of hot-tip recanalization typically involved creation of a false intramural channel rather than recreation of a true lumen. Pathologic analyses from our laboratory showed that in the peripheral vasculature, angiography sometimes failed to identify necropsy-proven vessel wall perforations.\(^8\) The decisive blow, however,
was the demonstration in vitro and in vivo that the potent vasoconstrictive effects of heat on vascular smooth muscle simply could not be tolerated in coronary-caliber vessels.9

It was in the context of this grim experience that the downsloping curve of enthusiasm for laser angioplasty crossed the upsloping curve for directional atherectomy. Clinical trials in both the peripheral10 and coronary11 arteries confirmed Simpson’s earlier claim that percutaneous removal of plaque was not unique to the laser. Similar capability for percutaneous plaque removal was found with alternative (non-directional) atherectomy devices.12 The atherectomy catheters had only one limitation: All were wire guided; none addressed the issue of the guide wire–refractory total occlusion. But was this a limitation? Suddenly, it was clear that the atherectomy experience held the clue to prevent the rock of Sisyphus from rolling down on the laser every time the latter was activated. Forget total occlusions; instead investigate the likelihood that wire-guided laser angioplasty would have little short-term morbidity and would yield long-term patency rates superior to those achieved with either balloon or mechanical devices.

This strategy was facilitated by the advent of clinically useful pulsed lasers, which offered an alternative power source capable of facile tissue ablation without pathologic heating of boundary tissues. That ablation is accomplished with little change in tissue temperature makes light rather than heat the predominant vasomotor stimulus; as a result, pulsed laser light causes photorelaxation rather than vasoconstriction of vascular smooth muscle.13 Moreover, the finding that thermal injury was absent even at the higher peak powers characteristic of pulsed lasers made these lasers more appropriate for ablation of heavily calcified lesions.14

While most of these features have been shown to be common to pulsed lasers in general,15 most were originally demonstrated with the excimer laser.14 Why the excimer laser remained relegated to the in vitro sphere for so long, however, is no mystery. The difficulties inherent in transmitting high peak powers via diminutive fused silica fibers, the uncertainties regarding transmission of ultraviolet light through a blood field, and the specter of mutagenicity all led experts to predict that the excimer laser was not appropriate for use in clinical trials of laser angioplasty.

Laboratory and clinical investigations performed during the past 3 years have conclusively refuted this earlier skepticism. Novel means of laser–fiber coupling permitted successful fiberoptic transmission of industrial-standard, short-pulse–duration excimer laser light at 308 and 351 nm via commercially available fused silica fibers.16 Longer-pulse durations of “stretched” excimer lasers further facilitated transmission of higher peak powers via lower profile fibers suitable for wire-guided fiber bundles.17 In vitro analyses demonstrated that excimer laser tissue ablation could be reproducibly accomplished in a blood field without fiber-tissue contact as the result of dynamic optical cavity formation at the blood–tissue interface.18 Subsequent studies performed in two atherosclerotic animal models confirmed that energies of pulsed ultraviolet light (again, 308 and 351 nm) could be transmitted via conventional fused silica optical fibers and used successfully to recanalize totally occluded vessels in an intact circulation.19 With the first published report of percutaneous, peripheral excimer laser angioplasty in humans by Wollenek et al20 and subsequent reports of percutaneous, coronary excimer laser angioplasty,21–23 initial concerns regarding the feasibility of the excimer laser for vascular recanalization were laid to rest.

The risk inherent in the atherectomy strategy, however, is illustrated in the superb clinical investigation reported by Karsch et al24 in this issue of Circulation. Despite the fact that 44 of 60 procedures (73%) were acutely successful—including 23 patients treated by laser angioplasty alone (i.e., no supplementary balloon dilation)—short-term angiographic follow-up of 28 patients disclosed evidence of restenosis in 16 (57%). Moreover, although the number of cases was small, excimer laser angioplasty in patients with unstable angina, and perhaps unstable plaque morphology, was not without risk. Finally, contrary to the in vitro and in vivo animal data cited above, excimer laser angioplasty was in certain instances complicated by apparent spasm.

The explanation for the latter finding remains enigmatic but has also been observed by those using the two other systems currently approved for investigational use. Previous reports from our laboratory demonstrated that even with a pulsed laser such as the excimer, excessive irradiation resulting from either protracted cumulative exposure or excessive repetition rate could produce thermal injury.14,25 Consistent with this finding is the recent European experience (with the system used by Karsch et al24) that the incidence of spasm may be diminished by reducing the duration of individual exposures. Alternatively, spasm in patients treated by pulsed laser angioplasty may result from focal heating at a site where the character of the lesion or contour of the artery resists facile advancement of the multifiber catheter. Finally, the possibility that spasm may have resulted from the relatively large (9F) guiding catheters or excessive coronary intubation used to power a multifiber catheter with a relatively stiff and inflexible tip cannot be excluded.

Whatever the reason, it is important to put these exceptional results in perspective. First, in pointed contrast to experience with the hot-tip technology, spasm did not complicate most cases of coronary laser angioplasty in this series. Second, while Karsch et al24 did not attempt to do so, it is possible that the excimer laser might have been used to reverse spasm in these cases by exploiting the photorelaxation property of low doses of excimer laser light.26 That excimer laser angioplasty failed to obviate the problem of restenosis is due at least in part to certain
features of the prototypical multifiber catheters presently used with these systems. As Karsch et al acknowledge,24 the flexibility of the catheters used for their procedures was suboptimal. Consequently, most cases (41 of 55, or 74%) involved the left anterior descending coronary artery, the proximal segment of which has been previously recognized to be an independent anatomical risk factor for restenosis.

Perhaps most important, however, is teasing out the contribution of adjunctive balloon angioplasty to restenosis after excimer laser angioplasty. One of the major dilemmas that has confounded the development of fiber-catheter delivery systems is how to reconcile the requirement of diminutive, flexible optical fibers or fiber bundles with the intent to achieve an adequate-size lumen with laser irradiation alone. A key question is the extent to which restenosis is an independent function of residual luminal diameter narrowing. Liu et al27 recently reviewed the incidence of restenosis as a function of residual luminal diameter narrowing in more than 2,000 patients treated by balloon angioplasty for one-vessel disease; among patients with less than 50% luminal diameter narrowing after angioplasty, the incidence of restenosis was the same for those with 35–49% as it was for those with 0–19% residual diameter narrowing.

This finding has been implicitly incorporated into many current clinical trials of excimer laser angioplasty to determine whether the long-term outcome of a patient with an arbitrary noncritical percent of residual luminal diameter narrowing achieved with excimer laser angioplasty alone is superior to no (or least) residual luminal diameter narrowing achieved by combined laser-balloon angioplasty. Karsch et al24 analyzed a small subgroup (23) among their cohort in whom this strategy had been used and still found a restenosis rate of 32% (six of 19) among patients in whom angiographic follow-up was available after laser angioplasty alone.

Until catheters designed for excimer laser angioplasty approach a stage of development similar to that of balloon angioplasty catheters, any assessment of restenosis must be regarded as premature. It is important to understand that for more than two decades, the principal thrust of research in fiberoptics was aimed at satisfying the telecommunications industry; accordingly, this involved transmission of low powers by large-diameter fibers.16 In contrast, percutaneous vascular therapy requires transmission of peak powers in the megawatt or kilowatt range by fiberoptics sufficiently small to traverse the angles and bends of the coronary arteries.

Postprocedural testing of the fiberoptic catheters used by Karsch et al24 revealed that in most cases there was a significant decrement in energy output compared with preprocedure energy output. We and others (unpublished data) have noted similar findings with alternative excimer systems now undergoing clinical trial. Such reduced energy transmission typically represents fiber-face damage due to light back-scattered from the target atherosclerotic lesion or mechanical trauma from direct contact with calcified plaque. Losses related to positioning of an intact fiber across a successfully negotiated bend may further compromise predictable energy delivery over a long segment of diffusely diseased artery. Novel design features that are intended to increase the ratio of cross-sectional fiber face to the total cross-sectional area of the catheter tip, augment spot size with lens-tipped fibers, provide on-line feedback of the magnitude of energy transmission, and accomplish all of these with a larger number of smaller fibers are still in the earliest stages of investigation.

At the very least, the results reported by Karsch et al24 convincingly confirm that excimer laser angioplasty is a realistic percutaneous form of vascular recanalization. Further investigation will be required, of course, to determine whether it is superior to alternative atherectomy technology, including other pulsed lasers.28–30 Contrary to what is often alleged, experimental data do not support the concept that excimer laser ablation involves a unique mechanism of laser-tissue interaction.25,31 In terms of anatomical outcomes—specifically, the absence of thermal injury—light microscopic and ultrastructural findings indistinguishable from excimer laser ablation have been documented with wavelengths ranging from the visible to the infrared.15 That some of these waves (e.g., 2.1 μm from a holmium:YAG laser) may be generated from solid-state rather than gas lasers may have important implications in terms of expense and maintenance, both of which are typically optimized with solid-state instruments. The issue of debris resulting from pulsed laser irradiation compared with mechanical atherectomy has not been fully defined; while this has not been noted to be problematic in clinical trials of excimer laser angioplasty, this issue warrants close attention as attempts to create a larger lumen at sites of highly calcified obstructions become more ambitious. While definitive data are still pending and conventional wisdom suggests that unscheduled DNA synthesis is an unlikely consequence of ultraviolet laser synthesis,32 the possibility that certain wavelengths may be more likely to facilitate accelerated smooth muscle cell proliferation (i.e., restenosis) remains unresolved. Finally, from the standpoint of delivery devices, it must be remembered that none of the three ongoing clinical trials of excimer laser angioplasty involve a device designed to recanalize totally occluded arteries.

Despite these unresolved issues, ongoing clinical investigation of excimer laser atherectomy has restored credibility to the concept of percutaneous laser revascularization. The most sophisticated biomedical lasers yet engineered have resuscitated a technology that is now closer than ever before to fulfilling the promise that has intrigued both investigators and investors for more than a decade.
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Excimer laser atherectomy. The greening of Sisyphus.
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doi: 10.1161/01.CIR.81.6.2018

Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 1990 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circ.ahajournals.org/content/81/6/2018.citation

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