**Current Perspective**

**Photoangioplasty**

An Emerging Clinical Cardiovascular Role for Photodynamic Therapy

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**Abstract**—Photodynamic therapy (PDT) has been studied and applied to various disease processes. The potential of PDT for selective destruction of target tissues is especially appealing in cardiovascular disease, in which other existing interventional tools are somewhat nonselective and carry substantial risk of damage to the normal arterial wall. Enthusiasm for photoangioplasty (PDT of vascular de novo atherosclerotic and, potentially, restenotic lesions) is fueled by more effective second-generation photosensitizers and technological advances in endovascular light delivery. This excitement revolves around at least 4 significant attributes of light-activated therapy: the putative selectivity and safety of photoangioplasty, the potential for atraumatic and effective debulking of atheromatous plaque through a biological mechanism, the postulated capability to reduce or inhibit restenosis, and the potential to treat long segments of abnormal vessel by simply using fibers with longer light-emitting regions. The available nonclinical data, coupled with the observations of a new phase I trial in human peripheral atherosclerosis, suggest a promising future for photoangioplasty in the treatment of primary atherosclerosis and prevention of restenosis. (Circulation. 2000;102:591-596.)

**Key Words:** photodynamic therapy ■ photoangioplasty ■ atherosclerosis ■ restenosis

Photodynamic therapy (PDT) is an emergent therapeutic modality for several disease processes. The salutary response is mediated by a photosensitizing drug, typically administered parenterally and selectively absorbed or retained within the tissues targeted for therapy.1 Differential selectivity or retention promotes selective damage when the target tissue is exposed to light of an appropriate wavelength; the surrounding normal tissue, containing little or no drug, absorbs little light and is thus spared injury.1,2 Selectivity renders PDT particularly appealing in coronary artery disease, in which other catheter-based approaches are relatively nonselective and carry a substantial risk of damage to the normal arterial wall. Historically, PDT clinical research has focused primarily and successfully on treatment of cancer.2 Recent advances in synthetic macrocyclic chemistry, laser technology, and endovascular light delivery systems have broadened the scope of PDT to include, among others, ophthalmic, urologic, immunological, and more recently atherosclerotic applications.3,4 PDT may have a viable role as a clinical inhibitor of restenosis and de novo disease.

**Mechanism of PDT Action**

The PDT response begins with a differential accumulation of a photosensitizer in the target tissue, the consequence of either selective uptake of the drug or of preferential retention caused by slower clearance from the abnormal tissue. Subsequently, the tissue is photo-illuminated at the wavelength that favors maximal absorption by the photosensitizer. The resultant photobiological response (direct, rapid cell apoptosis and delayed necrosis from neovascular damage) becomes maximal within several days.1,5-7 Throughout this process, the drug serves simply as a catalyst for energy transfer. Light absorption leads to the release of cytotoxic singlet oxygen, a highly reactive, oxidizing agent with very short diffusion distances (≤0.1 μm). Cell death is thus confined to those illuminated areas in which there is an adequate presence of the sensitizing drug.8

The physicochemical properties of the photosensitizing molecule will predetermine preferential uptake by a target cellular population.5 In atherosclerosis, drug lipophilicity and the high lipid content of vascular plaque both appear to predicate selective uptake. Although these mechanisms have not been established with certainty,4 both passive and active processes have been identified for the uptake of hydrophobic photosensitizers into atheromatous plaque.9 Interestingly enough, the selective accumulation by atheromatous tissue of some lipophilic and hydrophilic agents is comparable.10,11 It is likely therefore that passive diffusion into the arterial wall from the vasa vasorum and from the lumen, as well as impaired endothelial permeability,12,13 can augment active transport mechanisms.

Whether in neoplasm or in atheroma, light of the appropriate wavelength is necessary to activate the drug. The light can originate from collimated sources (eg, lasers) or from diffuse illuminators (eg, high-power lamps and light-emitting diode panels).14,15 The emission wavelength is usually...
matched to the far-red absorption bandwidth of the photosensitizer. The light is then delivered to the treatment site either directly or via hollow wave guides or fibers terminating in optical configurations to achieve either a circumferential, segmental, or conical beam profile. Radially emitting fibers, with a variety of designs, have been used for endovascular PDT in animals and in one case, a 2-patient clinical study. Another important advance in photoangioplasty is the development of compact, portable, and relatively inexpensive diode-based lasers to replace the older, large systems requiring special electrical and plumbing infrastructures; the latter are mostly dye lasers pumped by another laser (argon, KTP YAG) or pulse lasers (copper vapor).

Severe cellular damage is noted in atherosomatous areas after light exposure. However, there is demonstrable preservation of the intact elastic lamina and of normal collagen in the adventitia, suggesting that the functional integrity of the vessel is conserved. The absence of mural inflammation, despite extensive cell death, is consistent with the regression of atherosclerotic plaque through a hypothesized mechanism of apoptosis, although this has not yet been conclusively demonstrated. Paradoxically, a so-called “dark effect,” ie, a therapeutic response to the drug in the absence of light, has also been described for the inhibitory effect on restenosis of at least one photosensitizer, a benzoporphyrin derivative. The therapeutic implication of this observation has not been delineated.

Photosensitizing Drugs for PDT
Hematoporphyrin derivative (HpD) was the first of a number of photosensitizers with demonstrable, selective accumulation within atherosclerotic plaque. Subsequent studies have underscored the affinity of porphyrin derivatives for diseased arterial wall in rabbits and miniswine. There is maximal drug concentration in the intimal surface layers, diminishing radially into the media. Both hematoporphyrin and Photofrin, a more purified derivative of HpD, also display in vitro preferential uptake by human plaque. Although Photofrin is available for clinical use in antineoplastic applications, its clinical performance in the PDT of atherosclerosis has been somewhat disappointing. Despite obvious, selective damage of the plaque and sparing of the underlying media, the lack of efficacy might be attributable to inadequate penetration of the 630-nm light through endoluminal blood. Clinical application is further hampered by the propensity of treated subjects to display prolonged cutaneous phototoxicity.

Administration of 5-aminolevulinic acid (ALA), a biochemical precursor for protoporphyrin IX, has been accomplished by topical, systemic, and local internal routes in a variety of malignant and dysplastic conditions. However, its administration can elicit hemodynamic changes (depression of systemic and pulmonary pressures and pulmonary resistance) that might limit its ultimate utility in cardiovascular applications.

Newer agents with selective localization, greater PDT efficiency, and minor, self-limited potential for cutaneous phototoxicity are now available. Phototherapeutic capacity in atherosclerosis has been described for a number of these molecules, including the phthalocyanines (photoactivated at 675 nm), chlorin (at 660 nm), purpurins (at 663 nm), and benzoporphyrin derivatives (at 690 nm). However, most of these agents require liposomal or intralipid formulation before administration.

Early PDT agents for cardiovascular disease were activated at wavelengths <700 nm, at which point blood and tissues substantially attenuate the delivery of light to target cells. However, tissue optics dictate that for optimal photochemical response, the ideal photosensitizer should display maximal absorption in the range of 700 to 800 or 950 to 1100 nm. The recent renewal of interest in the therapeutic potential of cardiovascular PDT has been prompted largely by the availability of expanded macrocycles known as the texaphyrins. These drugs circumvent many of the physicochemical limitations of previously studied sensitizers. Texaphyrins are synthetic, water-soluble macrocycles with long wavelength-absorbing properties. They localize both in cancerous lesions and in atheromatous plaque. Incorporation of a diamagnetic lanthanide, lutetium, into the texaphyrin molecule yields a potent PDT agent that is activated by tissue-penetrating far-red light (732 nm). In addition, motexafin lutetium fluoresces at 750 nm (Figure 1); endogenous chromophores do not emit light at 750 nm. Hence, in vivo real-time imaging of target structures is feasible, thus facilitating clinical diagnosis and treatment planning. Similarly, the related, paramagnetic gadolinium texaphyrin might facilitate MRI of atheromatous vascular disease.

Texaphyrins localize in and eradicate diseased tissues, including atherosclerotic plaque (Figure 2). PDT with motexafin lutetium causes selective photodamage and thereby helps to reverse both diet-induced and balloon-induced atheromatous plaque in rabbits. The enhanced efficacy of texaphyrins may be attributable both to a more selective uptake and retention of the photosensitizing molecules and to the depth of light penetration achievable in blood and tissue at the longer 732-nm wavelength illumination. Uptake of motexafin lutetium by the atheromatous plaque occurs in a ratio of 16:1 to 34:1 when diseased and normal segments of the arterial wall are contrasted. One possible mechanism for this selective plaque uptake of texaphyrins is through plasma lipoprotein binding or modification. Unlike HpD-based PDT, there is no evidence of microscopic damage to the arterial wall after PDT with motexafin lutetium.

Cardiovascular Applications of PDT
In Vitro Experience
The extent of the short-term angiographic improvement plays a determining role in the durability of the clinical response to standard, percutaneous vascular interventions; however, restenosis still significantly impairs the potential for long-term clinical benefits for many patients. The identified biological determinants of the restenosis response appear to be, in principle, amenable to the mechanisms of phototherapy. These determinants include vascular remodeling, stimulation of the proliferative and migratory response of vascular smooth muscle cells (SMCs), and enhanced production of...
extracellular matrix. Furthermore, neutrophil and platelet activation has been demonstrated with angioplasty in balloon-injured arterial plaque. Moreover, macrophages play an important role in the complex activation of SMCs after vascular injury.

Several studies have shown that PDT inhibits SMC growth and decreases the development of experimentally induced intimal hyperplasia response. The effects of PDT on the injury response seem to be rather complex. Photosensitization can accomplish a complete cellular eradication within the vascular wall without associated inflammation and proliferation, suggesting that PDT may induce changes in the extracellular matrix of the vascular wall. In vitro, exposure to PDT eliminates detectable levels of basic fibroblast growth factor (bFGF and FGF-2) in solution and significantly reduces the smooth muscle mitogenesis inducible by matrix-associated FGF-2. In vivo, PDT of rat carotid arteries produces a loss of bFGF staining compared with control, nontreated arteries. Furthermore, the effect of PDT on the release and activation of transforming growth factor-β, has also been examined in vitro. The data suggest that PDT may inhibit intimal hyperplasia through local inhibition of local cytokine release or activation.

In vitro investigations support the concept that PDT can favorably influence endothelial vascular biology. PDT with Photofrin II substantially impairs the growth of cultured SMCs derived from both atherosclerotic lesions and nonatherosclerotic arteries. The effect on SMCs obtained from atherosclerotic lesions (activated SMCs) is much greater than that seen in the cells obtained from the normal vascular wall. Similarly, studies of SMCs derived from saphenous vein grafts have shown significant inhibition of their growth after photosensitization. In addition, PDT on bovine aortic endothelial cell preparations in vitro induces changes in extracellular matrix; SMC proliferation and migration are inhibited and endothelial cell proliferation is enhanced. These PDT-induced vascular responses may benefit the process of vascular remodeling and reduce the likelihood of a restenosis response. The preferential uptake of the drug in atherosclerotic segments is further accentuated in the highly cellular regions of restenosis, suggesting that the selective cytotoxic effect could be applied to both the therapy and the prophylaxis of restenosis.

**In Vivo Experience**

A benefit after photosensitization with Photofrin in atherosclerotic rabbits has been reported, although others have shown only a slight to modest reduction in plaque burden. The lack of marked therapeutic benefit with Photofrin-mediated PDT in atherosclerosis has been ascribed to the ability of blood to impair light transmission at 630 nm. Thus, suboptimal light transmission would produce subtherapeutic activation of the sensitizer. Furthermore, safety considerations limit the maximum light dose that can be delivered...
ered. In experimental treatments of canine coronary arteries in vivo, light doses >200 J/cm² elicited angiographic spasm, histological necrosis, and even transmural injury. In this study, the cases of premature death were ascribed to the effects of coronary artery spasm, because only minor medial damage was seen in some of these specimens. In fact, even at high light doses, no embolization, vessel perforation, or aneurysmal dilatation was seen.

Efficient reduction of atherosclerotic plaque burden has also been demonstrated after PDT with motexafin lutetium. Histological analysis of the posttreatment specimens reveals selective reduction in plaque area in a hypercholesterolemic rabbit model (Figure 3), whereas in a balloon-injury model, a significant reduction in macrophage density within the treated lesions was observed.

The in vivo studies on intimal hyperplasia have yielded more universally promising results. For example, a substantial reduction in intimal hyperplasia has been shown in the rat carotid artery injury model with chloroaluminum-sulfonated phthalocyanine and 675-nm light at a fluence (the power density of light over time) of 100 J/cm². No thermal injury was identified in the treated vascular segments. In most cases, inhibition of intimal hyperplasia correlates with histological absence of inflammatory and SMCs in the media. Similar benefits have been observed in other experimental model systems with Photofrin and ALA. PDT at the time of angioplasty leads to an acellular media despite regeneration of the endothelial lining. On the basis of the latter study, it would appear that it is not necessary to delay PDT after balloon injury to prevent the injury response of restenosis, because photoactivation at the time of angioplasty completely abolished the expected intimal hyperplasia after this injury. In addition, both short- and long-term benefits of PDT have been demonstrated.

In another study of PDT in a balloon-injured rodent arterial model, the media remained acellular for several weeks to months, and intimal hyperplasia did not occur. Although endothelial regeneration occurred by 2 weeks, SMCs failed to repopulate the media. During PDT, retraction of endothelial cells does allow adherence of neutrophils by their β₂-integrin adhesion receptors to the subendothelial matrix, leading to the hypothesis that successful prevention of intimal hyperplasia by PDT relies in part on the presence of the neutrophil at the site of the lesion. Recently, Photofrin PDT was performed with continuous external laser irradiation in the rabbits either 1 (prevention) or 6 (treatment) weeks after balloon injury. PDT was quite effective in the treatment of established intimal hyperplasia but did not prevent it. The authors concluded that refinements in dosimetry will be necessary to achieve long-term benefits.

The importance of the selection of the correct arterial region in the prevention of restenosis has been examined in the balloon-injured rat carotid artery. The results of that study indicate that a hypercellular injury response in a treated lesion can originate from a remote source; consequently, successful elimination of restenosis by PDT may require inclusion of the entire injured artery in the treatment field, perhaps including a section of uninjured margin.

**Human Clinical Applications**

Photoangioplasty for arterial diseases, including de novo atherosclerosis and potentially restenosis, has reemerged because of promising new drugs and safer, less expensive optical devices. This approach has the intriguing potential for invoking separate but interrelated mechanisms of benefit from one therapeutic intervention: safe debulking of the atheroma through selective injury and destruction of the atherosclerotic material; inhibition of the restenosis process through an effect on macrophages, intimal hyperplasia, and the inhibition of SMC proliferation; and further inhibition of restenosis through a hypothesized dark effect of some photosensitizers.

The clinical trials of motexafin lutetium (Antrin) were propelled by early preclinical indications of selective and efficacious resolution of plaque in rabbits. Clinical evaluation of motexafin lutetium is also ongoing in patients with recurrent breast cancer (Lutrin) and age-related macular degeneration (Optrin). In these latter studies, the drug has been well tolerated. The maximum tolerated dose proved to be 5.5 mg/kg on the basis of elicitation of pain in the treatment field and dysesthesias in light-exposed areas. Plasma pharmacokinetic data taken from these patients showed the drug to be cleared relatively quickly, exhibiting a T₁/₂α and T₁/₂β of 0.32 and 12.9 hours, respectively. Early observations from a phase I trial in claudicants with peripheral arterial atherosclerosis suggest that the therapy is well tolerated and has the capacity to invoke a therapeutic response in these patients. Intravascular ultrasonography has confirmed measurable improvement in lumen cross-sectional area after Antrin photoangioplasty. The therapeutic changes are achieved without documented adverse vascular responses or any treatment-limiting phototoxicity. In these ongoing trials, doses of 1 to 5 mg/kg of Antrin have been administered intravenously before...
PDT, although preclinical data also support the feasibility of local endovascular drug delivery. This may ultimately be more clinically advantageous. Endovascular light is delivered through a cylindrical diffuser fiber, typically 24 hours after systemic, intravenous administration of Antrin. The fiber is positioned adjacent to the lesion of interest by percutaneous delivery through a standard 5F to 8F guiding catheter. Light treatment is sustained for 941 seconds to achieve 400-J/cm diffuser fiber over a 3-cm diffuser length fiber. A portable, relatively inexpensive 730-nm diode system facilitates these illumination requirements.

Of paramount interest may be the capacity of photoangioplasty to prevent the cellular responses of restenosis after conventional endovascular procedures. Future investigation will also determine the synergistic role of photoangioplasty when performed at the time of standard endovascular procedures. The available preclinical investigations, coupled with recent and continuing improvements in laser and fiberoptic technology, suggest a promising role for photoangioplasty in the future prevention and treatment of restenosis. Further clinical investigation must evaluate therapeutic outcomes and exclude a significant potential for coronary artery spasm in human applications. Although the time needed for full cytotoxic effect may limit applicability to short-term, primary therapeutic interventions, one can envision a potential role of photoangioplasty as an adjunct to the standard percutaneous techniques for revascularization. Additional, ripe clinical scenarios might include interventions for vulnerable plaque, long coronary lesions, diffuse and distal vascular disease, and stabilization of vulnerable plaque.

References

11. Rockson et al. Photodynamic Therapy in Cardiovascular Medicine 595
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