Photodynamic Therapy of Arteries
A Novel Approach for Treatment of Experimental Intimal Hyperplasia

Paolo Ortu, MD; Glenn M. LaMuraglia, MD; W. Gregory Roberts, PhD; Thomas J. Flotte, MD; and Tayyaba Hasan, PhD

Background. Photodynamic therapy (PDT) uses light activation of otherwise nontoxic dyes for the production of reactive oxygen species that cause cell injury and death.

Methods and Results. The inhibition of intimal hyperplasia (IH) by PDT was studied in the balloon injury model of the rat carotid artery. Chloroaluminium-sulfonated phthalocyanine (CASPr) was the drug chosen for PDT because it does not produce skin photosensitivity and has a high absorption peak of light at 675 nm, a wavelength with good tissue penetration. A pilot study indicated that CASPr administration with laser radiant exposure of 100 J/cm² resulted in a homogeneous, circumferential effect on the whole artery. Male Sprague-Dawley rats received the balloon catheter injury to the left common carotid artery (day 0) and were equally divided into two groups. Nine rats received either CASPr (5 mg/kg i.v., n = 6) or saline (n = 3) at day 2, before IH was present, and nine rats received CASPr or saline in the same manner on day 7, when IH was already present. Twenty minutes after drug injection, the distal left common carotid artery was irradiated under saline with 675-nm laser light at 100 mW/cm² for 10 seconds (100 J/cm²). At this low laser irradiance, there are no thermal effects, but photoactivation of CASPr occurs. The rats were killed at day 14 after balloon injury when IH reaches a maximum. The arteries were harvested after perfusion-fixation for light microscopy, histological and computerized morphometric evaluation, and transmission electron microscopy (TEM) analysis. The cross-sectional areas of the neointima were measured in the PDT-treated arteries and in the laser-only control arteries. There was a significant mean±SD decrease of IH in the PDT-irradiated segments of the arteries (0.06±0.05 mm²) versus the laser-only control ones (0.17±0.07 mm²) (t test, p <0.001), with no statistical difference between the day 2 and day 7 treated rats. Lack of IH was correlated in 90% of cases with histological absence of medial smooth muscle cells or inflammatory cells, but no other structural injury was identified. TEM analysis showed early evidence of PDT-mediated cytotoxic effects at 4 hours and the absence of collagen or elastic tissue structural alterations.

Conclusions. These data demonstrated that PDT can effectively inhibit the IH response when it is used before or during induction of cellular proliferation in this acute model. Although the long-term implications of PDT in arteries need to be defined, this technique may offer a new method for understanding and treating IH. (Circulation 1992;85:1189–1196)

Key Words: intima • hyperplasia • photodynamic therapy • phthalocyanines

Proliferation of smooth muscle cells (SMCs) is the major cause of early restenosis in vessels after the therapeutic interventions of percutaneous transluminal angioplasty, endarterectomy, and coronary artery bypass graft surgery. The anatomic and pathological findings of these restenotic conditions are commonly referred to as intimal hyperplasia (IH). The development of a therapeutic option that can effectively obviate the occurrence of IH after vascular interventions has generated considerable interest. Platelets were found to play a significant role in the development of IH by adhesion and subsequent release of platelet-derived growth factor, which can stimulate SMC replication. Several clinical trials investigating the possibility of inhibiting the development of IH have been based on the use of drugs such as aspirin and dipyridamole to interfere with platelet function. Although the use of these drugs reduces the incidence of acute failures caused by thrombosis, they do not affect the incidence of early restenosis secondary to the development of IH.

Other drugs presently under evaluation in animals as prophylactic treatments to prevent IH include heparin, calcium channel blockers, eicosapentanoic acid, and inhibitors of angiotensin converting enzyme. Although they have been promising under experimental conditions, none has proved to be effective in the prevention of IH in humans.

Experimental IH has been studied extensively in a variety of animal models. It can be induced by damaging...
the intimal layer of arteries in several ways: balloon catheterization, air drying of the intima, low-voltage electric stimulation, and periarterial cuff application. One of the most extensively studied animal models of IH is the balloon-induced injury of the rat common carotid artery (CCA), which results in endothelial denudation and medial stretching with SMC injury.

In the present study, we examined photodynamic therapy (PDT) as a novel approach for the prevention and treatment of IH. PDT is an experimental technique under evaluation for cancer treatment that uses the activity of light-excitable photosensitizers (PS) to produce injury of targeted cells. PS have no cytotoxic biologic effect unless they are activated by the appropriate wavelength of light. Upon absorption of a photon, the activated PS can either be directly cytotoxic or produce reactive oxygen species by way of energy transfer to molecular oxygen. The activated PS or the reactive oxygen species, usually singlet oxygen, becomes the mediator of cellular injury by affecting cellular membranes and subcellular organelles.

Chloroaluminum-sulfonated phthalocyanine (CASpC) is one of many PS currently under evaluation for the treatment of malignant lesions. Its excitation spectrum has a peak at 675 nm, a wavelength at which light has high tissue penetration. CASpC is one of the most potent PS available, but unlike other PS such as hematoporphyrin derivative (HpD) it does not cause skin photosensitization to ambient light or other adverse side effects in vivo. CASpC-mediated PDT was investigated as a method for the treatment of balloon-induced IH in the rat carotid artery model because CASpC is an efficient PS, is well tolerated in vivo, and may be a candidate for future human use.

Methods

Surgical Induction of Intimal Hyperplasia

Male Sprague-Dawley rats (Charles River Breeding Laboratory, Wilmington, Mass.) weighing 350–450 g were anesthetized with an intramuscular injection of ketamine (35 mg/kg), xylazine (5 mg/kg), and atropine (40 μg/kg). The left common, external, and internal carotid arteries were exposed in the neck through a midline incision. A 2F Fogarty arterial embolectomy catheter (Baxter Edwards Healthcare Corp., Irvine, Calif.) was introduced from the external carotid artery through the CCA and into the thoracic aorta. The balloon was inflated with 0.65 ml of air and withdrawn to produce endothelial denudation and medial stretching in the CCA. After three passages, the catheter was removed, and the external carotid artery was ligated. This procedure is not associated with disruption of the internal elastic lamina (IEL). The rats were allowed to recover, after which they had free access to standard rat chow (Purina rat chow 5001, Ralston Purina, Richmond, Ind.) and water, with a 12-hour light/dark cycle.

Animal care in this study complied with the “Principles of Laboratory Animal Care” and the “Guide for the Care and Use of Laboratory Animals” (NIH Publication No. 80-23, revised 1985). All animal procedures were approved by an independent institutional animal care committee.

Figure 1. Schematic of laser irradiation procedure. Left common carotid artery (CCA) is exposed via a midline neck incision in anesthetized animals (a). CCA is then optically isolated from surrounding tissue by black screen (b) and exposed to a 2-cm-diameter spot of 675-nm light (c) delivered by laser apparatus (d).

Photosensitizer Administration

CASpC at a concentration of 300 mg/ml in sterile water (CIBA-GEIGY, Basel, Switzerland) was diluted to a concentration of 5 mg/ml in phosphate-buffered solution (PBS) and stored at −70°C in the dark until use. The drug was administered intravenously to the animals (5 mg/kg) 20 minutes before the irradiation.

Laser Light Delivery System

Laser light was delivered by an argon-pumped dye laser (Coherent Innova I 100 and Coherent CR 599, Coherent, Palo Alto, Calif.) and tuned using a monochromator to emit light at 675 nm. The dye laser output was coupled to a 600-μm-diameter optical fiber, and a 5-mm focal length lens was used to magnify the output end of the optical fiber to obtain a uniform 2-cm spot. An irradiance of 100 mW/cm², as measured by a power meter (Coherent 210, Coherent), was used throughout the experiments because at this power there are no thermal effects.

The 1.5-cm-long distal segment of the left CCA was surgically exposed in the anesthetized animal and optically isolated to avoid irradiation of surrounding tissue. The CCA was kept under saline and externally irradiated from above for various time intervals (from 10² through 10⁵ seconds) to obtain total radiant exposures from 10 through 10⁶ J/cm² (Figure 1). The rats were irradiated 20 minutes after intravenous injection of CASpC, corresponding to peak serum levels. At the end of irradiation, wounds were closed by standard surgical technique. Although the drug in both the arterial wall and in the circulation is irradiated, because of the short half-life of the free radicals, only the drug activated in the artery is expected to cause biologic effect. The attenuation of the laser light energy across the artery was measured after CASpC injection using an isotropic, photon-detecting probe. This demonstrated a 60% decrease of light energy as it penetrated across the artery.
Pilot Study on Photodynamic Therapy–Induced Effects

To determine the radiant exposure to be used in the PDT treatment of IH, a pilot study was designed to determine PDT-induced effects on cell viability. This was accomplished in the rats 1 day after receiving the balloon catheter injury to mimic CASPc penetration in instrumented, deendothelialized arteries, as in the induction of IH. Eighteen rats received the injury to the left CCA and were randomly divided into six groups (n=3 per group). Five groups were injected intravenously with CASPc and one group was injected with saline (laser-only control group). The distal portions of the CCA were irritated as described, whereas the proximal segments of the CCA were not exposed to the laser light and were considered CASPc-only controls. The irradiation times in the five experimental groups were regulated to obtain the radiant exposures of 10, 25, 50, 75, and 100 J/cm²; the laser-only control group was exposed at 100 J/cm². All rats were killed 24 hours after irradiation, and the arteries were harvested fresh and placed in Tissue-Tek OCT compound 4583 (Miles Scientific Inc., Elkhart, Ill.) before freezing at −70°C. Cross sections were cut from the frozen specimens (Cryostat Microm 500 OM, Heidelberg, FRG) and stained with hematoxylin and eosin.

PDT-induced effects on cell viability were examined by comparing the number of SMC nuclei remaining in the media after the PDT treatment with the number of SMC nuclei in the nonirradiated control segments. The results were graded as follows: grade 0, no evidence of loss of SMC nuclei in the media; grade 1, loss of less than 50% of SMC nuclei in the media; grade 2, loss of 50–75% of SMC nuclei in the media; grade 3, virtually complete loss of SMC nuclei in the media.

Photodynamic Therapy Treatment Protocol

The radiant exposure of 100 J/cm² was selected for the IH treatment experiment because it produced a circumferential, homogeneous effect on the whole artery in the pilot study. Eighteen rats received the injury to the left CCA (day 0) and were randomly divided into two groups: nine rats received intravenous administration of either CASPc (n=6) or saline as a control (n=3) at day 2 (day 2 irradiation group), and the remaining nine rats received CASPc (n=6) or saline as a control (n=3) on day 7 (day 7 irradiation group) after arterial injury. These two time points were chosen to study the effects of PDT when it was applied before (day 2) and during (day 7) IH growth inside the injured arteries. All rats were then irradiated as described and killed 14 days after surgical induction of IH by an overdose of pentobarbital. Arteries were then perfusion-fixed at 80 mm Hg by the intracardiac injection of 50 ml of PBS followed by 300 ml of 4% glutaraldehyde in PBS. Nine additional rats, which received the induction of IH without other procedures, were killed on day 2 (n=3), day 7 (n=3), and day 14 (n=3), and the perfusion-fixed CCAs were considered balloon-only controls.

Histological and Morphometric Analysis

All vessels were patent and without gross abnormalities. Before harvesting, the adventitia of the irradiated distal segments of the CCA were stained with India ink for orientation of the direction of the laser beam and used for morphometric and histological examination. The excised samples were transversely cut in three segments and embedded in paraffin, and 5-μm-thick cross sections were stained with hematoxylin and eosin. Morphometric evaluation of cross sections was performed using a digitizing measurement system (Sigma Scan, Jandel Scientific, Sausalito, Calif.) coupled by a camera lucida to a light microscope (Labophot, Nikon, Japan) at ×100 magnification. The area of the intima and the diameter of the artery demarcated by the IEL from three different cross sections of each arterial segment were measured and averaged. The residual IH in the PDT-treated rats was calculated as the ratio of the areas of IH between the PDT-treated and the laser-only control rats.

Transmission Electron Microscopy

To determine the effects of PDT treatment on the ultrastructure of the arteries, transmission electron microscopy (TEM) was performed on arterial samples from eight rats. Seven days after surgical induction of IH, eight animals were randomly divided into three groups: 1) intravenous CASPc and laser light irradiation (n=4), 2) intravenous CASPc but no laser light irradiation (CASPc-only control, n=2), and 3) intravenous saline and laser light irradiation (laser light–only control, n=2). Four rats were killed at 4 hours; the remainder of them were killed at 7 days after the treatment. Both left and right CCAs were harvested by perfusion-fixation as previously described, and the right CCA was used as normal artery reference.

The arteries were postfixed in 2% osmium tetroxide for 2 hours, dehydrated in a graded ethanol series, and flat embedded with Epon 812 (Electron Microscopy Sciences, Fort Washington, Pa.). Longitudinal and cross sections were obtained from each sample. One-micrometer-thick sections were cut for light microscopy and stained with 0.5% toluidine blue. TEM sections were cut on an ultramicrotome (Reichert-Jung Ultracut, Vienna, Austria), stained with uranyl acetate and lead citrate, and examined with an electron microscope (model CM10, Philips, Eindhoven, The Netherlands).

Statistical Evaluation

All values were expressed as mean±SD. The statistical significance of morphometric differences between control and PDT-treated arteries was determined using two-tailed Student's t test. Differences were considered significant at p<0.05.

Results

All rats receiving CASPc appeared healthy and had no evident untoward effects. Arteries from all rats were patent with no signs of thrombus, and no inflammatory reaction was present in the vessels.

Pilot Study on Photodynamic Therapy–Induced Effects

Arteries from the laser-only control group, all proximal nonirradiated arteries, and the experimental groups receiving CASPc and radiant exposures of 10 and 25 J/cm² demonstrated no evidence of PDT-induced effects at 24 hours (grade 0). Experimental groups receiving CASPc
and radiant exposures of 50, 75, and 100 J/cm² demonstrated progressive increase of PDT-induced effects and were graded respectively as 1, 2, and 3. In groups 1 and 2, SMC nuclei loss was confined primarily to the portion of the arterial circumference of the CCA that was under direct laser light irradiation. The radiant exposure of 50 J/cm² was considered threshold value. These results prompted us to use 100 J/cm² as the radiant exposure value for the IH treatment experiments.

**Histological and Morphometric Analyses**

To test its efficacy, the CASPe-mediated PDT protocol was applied after induction of IH at two different stages of IH development: at day 2, when medial SMCs...
had already undergone replication but migration across the IEL had not occurred yet, and day 7, when IH made of three or four layers of cells was already present.\textsuperscript{13}

Arterial sections from balloon-only control rats killed at day 2 after induction of IH had an increased number of cells in the media, but no IH was apparent (Figure 2a). By day 14, sections from balloon-only control and laser-only rats irradiated at day 2 demonstrated eccentric circumferential IH (Figure 2b). The intima was expanded by cells with eosinophilic cytoplasm and oval nuclei. The IH was composed of as many as 20 cell layers and the luminal surface was lined by flattened intimal cells. The IEL was intact and the media demonstrated an increased number of cells. The arterial sections from rats receiving CASPc and laser light irradiation at day 2 after induction of IH demonstrated no IH by day 14 (Figure 2c). This effect was associated with loss of SMCs in the media, which appeared collapsed but with intact elastic laminae. The luminal surface was partially covered by endothelial-like cells.

Arterial sections from balloon-only control rats killed at day 7 after induction of IH had an increased number of cells in the media and IH composed of three or four layers of cells (Figure 2d). By day 14, all arterial sections from balloon-only and laser-only rats irradiated at day 7 demonstrated eccentric IH similar to the sections previously described (Figure 2e). The arterial sections from rats receiving CASPc and laser light irradiation at day 7 after induction of IH showed generally absence of IH (Figure 2f). Occasionally, the IEL was lined by clear acellular material measuring less than 20 \( \mu \)m thick, representing residual necrotic IH. There was a loss of SMCs in the media, and eosinophilic staining material was evident between intact elastic laminae.

Occasionally, IH was present and confined to the arterial wall opposite to the external laser light path (Figure 3). In these areas, IH was made of typical neointimal cells, and the adjacent media contained cells with eosinophilic cytoplasm; elastic laminae were intact and normally spaced. No signs of arterial enlargement, aneurysmal degeneration, or inflammatory infiltrate were present in PDT-treated vessels.

The IH areas and arterial diameters, as determined by morphometric analysis, are summarized in Table 1. These results demonstrated equivalent inhibition of IH in both PDT-treated groups compared with laser light-only controls \((p<0.001)\). Arterial diameters remained equivalent in all groups.

**Transmission Electron Microscopy Analysis**

Specimens from intact right CCA demonstrated normal endothelium and normal SMCs in the media. Instrumented arteries from CASPc-only and laser light–only control rats demonstrated the presence of typical IH. This was composed of cells with abundant rough endoplasmic reticulum, few contractile proteins, and oval nuclei. There also was an increased quantity of collagen. The media contained cells with abundant rough endoplasmic reticulum, contractile apparatus, and oval nuclei with occasional indentations (Figure 4a).

Arteries from rats that were killed 4 hours after PDT treatment presented a distribution of cells, collagen, and elastic tissue similar to that of the nonirradiated control arteries (Figure 4b). The majority of the cells remaining in the intima and the media demonstrated increased density of the cytoplasm, vacuolization of the mitochondria, and dilatation of the endoplasmic reticulum. Rare lymphocytes were noted adhering to the intima. There also were occasional cells in the intima and in the media that did not manifest these cellular injuries. Arteries from rats that were killed at day 7 after PDT treatment presented loss of IH (Figure 5). The luminal surface was either denuded or covered with a layer of platelets. The intima was composed of a thin layer of normal-appearing collagen, and a residual cellular debris was occasionally present. The IEL was intact, and the media demonstrated cellular debris interspersed between normal-appearing collagen and elastic laminae.

**Discussion**

In the present study, we showed that balloon-catheter injured CCAs receiving CASPc-mediated PDT had significantly less IH growth and stenosis as assessed by quantitative histopathology than balloon catheter–injured CCAs receiving laser-light irradiation only. No adverse effects on the rats or on the structural integrity of the vessels results from this procedure, and there were no differences in arterial diameters between experimental and control groups.

In our experimental set-up, the laser light was irradiated from outside of the vessel. This was necessary because of anatomical and technical reasons. Despite the use of light at 675-nm wavelengths, which has good penetration in tissue, we found that light energy was reduced by...
TABLE 1. Comparison of Intimal Hyperplasia Areas and Arterial Diameters Between Photodynamic Therapy-Treated and Control Animals

<table>
<thead>
<tr>
<th></th>
<th>PDT treated on day 2 (n=6)</th>
<th>Control saline on day 2 (n=3)</th>
<th>PDT treated on day 7 (n=6)</th>
<th>Control saline on day 7 (n=3)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Area of intimal hyperplasia (mm², mean±SD)</td>
<td>0.06±0.03*</td>
<td>0.22±0.11</td>
<td>0.04±0.02‡</td>
<td>0.16±0.04</td>
</tr>
<tr>
<td>Residual intimal hyperplasia versus controls (%, mean±SD)</td>
<td>27.8±16.4</td>
<td>...</td>
<td>21.8±9.8</td>
<td>...</td>
</tr>
<tr>
<td>Diameter (mm, mean±SD)</td>
<td>0.78±0.07</td>
<td>0.71±0.13</td>
<td>0.72±0.06</td>
<td>0.73±0.13</td>
</tr>
</tbody>
</table>

PDT, photodynamic therapy.
*<p<0.001 for all treatments versus controls.
†Ratio of the areas of intimal hyperplasia between the PDT-treated and laser-only control animals.
‡Measured at the internal elastic lamina.

60% after crossing a 0.8-mm-diameter artery. This probably resulted from light absorption and scattering by serum CASPc and red blood cells. The decrease in light energy across the vessel caused a nonhomogeneous light dosimetry. This light dosimetry explains why occasionally CASPc-mediated PDT of IH was not equally efficacious around the entire circumference of the vessel, thus accounting for the occurrence of IH in the sector of the arterial circumference opposite to the irradiation site (Figure 3).

PDT was found to be effective when applied at both day 2 and day 7 during the development of IH. The efficacy of PDT at day 2 can be interpreted as inhibition of IH growth because of injury caused to medial SMCs, whereas the efficacy showed by PDT when it was applied at day 7 can be interpreted as a summation of medial and intimal SMC injuries. In fact, histological specimens from rats treated at day 7 after induction of IH showed generally complete absence of IH, although an acellular residue occasionally lined the luminal surface. This treatment modality was able to remove the already developed hyperplastic tissue from inside the artery.

The effect on IH tissue appeared to be an immediate phenomenon, which was already evident 4 hours after PDT treatment, as shown by TEM analysis. The consequences of this SMC depletion in the media are unknown. Because TEM analysis showed normal-appear-

![Figure 4](http://circ.ahajournals.org/)

**Figure 4.** Transmission electron micrographs of rat common carotid arteries (CCA) on day 7 after the induction of intimal hyperplasia (IH). Panel a: CCA from laser light-only control animal; there is increased quantity of collagen and cells with abundant rough endoplasmic reticulum within region of IH superior to internal elastic lamina (IEL). Panel b: CCA from rat killed 4 hours after receiving photodynamic therapy treatment; majority of cells in intima and in media have hyperchromatic cytoplasm with nuclear and cytoplasmic vacuolization. Occasional cells (arrowheads) show lesser degrees of injury. *IEL; magnification bar, 3 μm.
Photodynamic Therapy of Intimal Hyperplasia

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Phthalocyanines are now being considered to overcome some limitations inherent to HpD, such as skin photosensitization and poor light absorption in the red spectral region. Phthalocyanines are synthetic porphyrin-like molecules. From data accumulated on in vitro and in vivo systems, CASPc and, to a lesser degree, zinc-PC (Zn-PC) have emerged as the most potent PS of this class as they have the best combination of cellular uptake, retention, and photosensitization activities. Recently, rabbits fed a cholesterol-rich diet have been found to accumulate injected Zn-PC in the atherosclerotic aorta.

In this experimental model of IH, the balloon catheter-induced injury to the CCA is followed by SMC replication and migration across the IEL into the intima, where cellular proliferation continues. During this process, SMCs undergo a change in phenotype, exhibiting ultrastructural and functional properties equivalent to the synthetic SMCs in culture. This change in phenotype and the replication and migration activities are noted in only approximately 50% of the medial SMCs. Thus, not all of the medial cells are committed to replicate and migrate, and 50% of them remain in the contractile phenotype. The change in phenotype is accompanied by the expression of new genes and specific cellular membrane receptors in vitro, which may help in developing a targeting system to selectively interfere with the activity of the replicating SMC.

In this first use of PDT as a method to treat the experimental IH in an animal model, no attempts were made to selectively target the replicating SMCs. In fact, in this study, the short time between CASPc administration and laser light irradiation (20 minutes) was chosen because it corresponded to the plasma peak concentration and maximized the occurrence of PDT effects. At this time point, it was likely that the CASPc concentration was equivalent in the replicating and quiescent SMCs. This lack of selective targeting may explain why usually all of the medial SMCs had to be affected by PDT to achieve maximal IH inhibition.

One of the major advantages of PDT is spatial selectivity, that is, only cells in the irradiated field are affected. With the development of a system to specifically label cells in the field, a double selectivity of action can be obtained, thereby fully exploiting the potentials of PDT in the treatment of IH. Further experiments using PDT are needed to provide more insights into the biology of IH and potentially develop it into an effective therapy for IH in humans.

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FIGURE 5. Transmission electron micrograph of common carotid artery from an animal receiving photodynamic therapy (PDT) treatment on day 7 after induction of intimal hyperplasia (IH). Artery was perfusion-fixed on day 7 after PDT treatment. Luminal surface is covered with platelets and no IH is present over an otherwise normal internal elastic lamina (IEL). Media is composed of normal collagen, elastic tissue, and cellular debris. C, cellular debris; *IEL; magnification bar, 2 μm.

Plaques and Plaque Formation

Plaque development in arteries, sclerotic vessels, and atherosclerotic arteries is a continuous process. Inhibition of proliferation and migration of SMCs is helpful in reducing plaque formation, but raising these two processes is needed to achieve a reduction in plaque extent because of the fluorescing properties of HpD.

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