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Excimer laser radiation for endarterectomy of experimental atheromas.

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Journal

Journal of investigative surgery : the official journal of the Academy of Surgical Research, 4(3)

ISSN

0894-1939

Authors

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Publication Date

1991

DOI

10.3109/08941939109141157

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Peer reviewed

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To cite this article: Yvon Baribeau, John Eugene, Thuc-Trinh Nhu, Scott L. Firestein, Yischon Liaw, Lindy Yow, Marie Hammer-Wilson & Michael W. Berns (1991) Excimer Laser Radiation for Endarterectomy of Experimental Atheromas, *Journal of Investigative Surgery*, 4:3, 247-258, DOI: [10.3109/08941939109141157](https://doi.org/10.3109/08941939109141157)

To link to this article: <http://dx.doi.org/10.3109/08941939109141157>

Published online: 09 Jul 2009.

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Topics and Trends

Excimer Laser Radiation for Endarterectomy of Experimental Atheromas

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Abstract *Open laser endarterectomy produces a smooth arterial surface with welded distal end points. This report evaluates 308-nm excimer laser radiation for the laser endarterectomy operation. Arteriosclerotic New Zealand white rabbits (N = 15) were studied. A thoraco-abdominal exploration was performed, the aorta was isolated, heparin was administered, and multiple endarterectomies were performed in each rabbit. A line of laser craters was created at the proximal and distal ends of an atheroma. Laser radiation was used to connect the craters to form the proximal and distal end points. The atheromas were dissected from the aorta with laser light and the end points were fused. The aortas were removed for light and electron microscopy and the animals were sacrificed. Excimer radiation was delivered by a 600- μ m fiber at 50 mJ/pulse, 120-ns pulses and either 15- or 20-Hz frequency. At 15 Hz excimer laser endarterectomies showed no perforations along the surface or at the end points. The surfaces were smooth but the end points were not welded in place. At 20 Hz, perforations were seen along 7/11 surfaces and at 5/11 end points. Excimer laser endarterectomy is best performed at 15 Hz. The end points, however, cannot be welded with excimer laser radiation.*

Keywords Laser endarterectomy, excimer laser, arterial welding.

Introduction

Early studies of laser radiation for the treatment of arteriosclerotic cardiovascular disease were conducted with continuous wave lasers.^{1,2} As thermal damage to arteries

Presented at the Sixth Annual Scientific Session of the Academy of Surgical Research, Long Beach, California, September 27-29, 1990.

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from continuous wave lasers was identified,^{3,4} attention was directed to excimer laser radiation for the ablation of arteriosclerotic plaque.^{5,6} The 308-nm pulsed xenon chloride laser is reported to offer advantages over continuous wave lasers because the beam is capable of ablating atheromas, even calcified plaques, without inflicting thermal damage upon the remaining artery or surrounding tissues. These reports have concentrated on using excimer radiation to perform transluminal laser angioplasty. Our interest in applying direct laser radiation to the treatment of arteriosclerotic cardiovascular disease has been to perform open laser endarterectomy.⁷ Up to now, only continuous wave lasers have been evaluated for the laser endarterectomy operation.^{8,9} This report evaluates 308-nm excimer laser radiation for the performance of open laser endarterectomy in an experimental arteriosclerosis model.

Materials and Methods

All experiments were performed in the New Zealand white rabbit arteriosclerosis model. The animals received humane care in compliance with the Animal Care Committee of the University of California, Irvine, and the Principals of Laboratory Animal Care formulated by the National Society for Medical Research and the Guide for the Care and Use of Laboratory Animals (NIH Publication No. 80-23, revised 1978). Under general anesthesia (intramuscular acepromazine 0.5 mg/kg, xylazine 3.0 mg/kg, and ketamine 50 mg/kg), 15 rabbits had the right common femoral artery exposed and a No. 4 Fogarty catheter was passed into the thoraco-abdominal aorta to denude the endothelium. Following recovery from anesthesia and surgery, the animals were started on a 2% cholesterol diet. The diet was continued for 16–20 weeks. This regimen has been shown to produce substantial arteriosclerotic lesions in 86% of rabbits.¹⁰

Arteriosclerotic rabbits were anesthetized (intramuscular acepromazine 0.5 mg/kg, xylazine 3.0 mg/kg, and ketamine 50 mg/kg) and intubated. They were ventilated with a small animal respirator (Ohio V5A) with oxygen and halothane (Ohmeda VMC anesthesia machine). Oxygen saturation was continuously monitored by an infrared sensor (Ohmeda 5120 oxygen monitor). Supplemental ketamine (50 mg/kg intravenously) was administered as necessary throughout the procedure to maintain anesthesia. A thoraco-abdominal incision was made to expose the aorta. Heparin (3.0 mg/kg intravenously) was administered and proximal and distal vascular control was obtained. A longitudinal arteriotomy was made to expose the diseased segments of the thoracic and abdominal aorta. Open laser endarterectomy was performed. A line of laser craters was created with individual laser exposures proximal and distal to an atheroma. The lines were connected by constant laser exposure to create proximal and distal end points. The atheromas were grasped with forceps and constant laser delivery was used to develop a cleavage plane just beneath the internal elastic lamina. Laser radiation was directed at the cleavage plane as the atheromas were retracted in order to dissect the atheromas from the aorta. The atheromas were removed from the arteries and constant laser exposure was used to weld the end points in place to provide a secure transition from endarterectomy surface to intima. Surgery was performed using optical magnification (3.5 power loupes and 4.5 power loupes).

Laser endarterectomy was performed with a XeCl excimer laser (Spectranetics, Inc., Colorado Springs, CO) with wave length 308 nm. Excimer radiation was directed through a 600- μ m quartz fiber to produce a laser spot approximately 0.75 mm diameter. The optical fibers were freshly cut for each experiment. Power delivery was

measured directly from the laser head and the delivery was verified at the beginning and the conclusion of each experiment with a power meter (Gentec, Inc, Plattsburgh, NY). Prior to performing the laser endarterectomy experiments, preliminary tests were conducted on 5 rabbits to determine the optimum working conditions for the laser and the fiber. Fluence 50 mJ/mm² was tested on arteriosclerotic rabbit aortas and was seen to produce even atheroma ablation without damaging the artery. A pulse width of 120 ns was chosen as the optimum delivery time for this fluence in order to maintain fiber integrity. Frequency was determined to be optimal at 15–20 Hz.

In group I (5 rabbits), endarterectomy was performed with energy density 50 mJ/mm², pulse width 120 ns, and frequency 15 Hz. In group II (5 rabbits), endarterectomy was performed with energy density 50 mJ/mm², pulse width 120 ns, and frequency 20 Hz.

After laser endarterectomy, the aortas were harvested and the rabbits were sacrificed (barbiturate injection). The aortas were rinsed in Ringer's lactate solution and separated into paired surface and end point specimens under a dissecting microscope. The specimens were pinned on Teflon blocks using insect pins. One pair was fixed in 3% glutaraldehyde in phosphate buffer at 4°C for 24 h, rinsed (phosphate buffer), dehydrated (alcohol), removed from the Teflon, and embedded in paraffin. The embedded specimens were serially section at 6- μ m intervals and the slides were stained with hematoxylin and eosin.

The other pair was postfixated for 90 min on 1% osmium tetroxide, dehydrated through an acetone series, and critical-point dried using a Ladd critical-point dryer (Ladd Research Industries, Burlington, VT, Model 28000). Specimens were removed from the Teflon blocks, placed on scanning studs, and gold-coated using a Pelco Pac-1 bench top coater (Ted Pella, Redding, CA). They were examined in a scanning electron microscope (Phillips Company, Mahwah, NJ) using between 15 and 25 kV and 20° to 60° tilt. Photographs of the scanning images were taken using Polaroid-type 55 P/N film (Polaroid Corporation, Cambridge, MA).

The endarterectomy experiments were evaluated by gross and microscopic findings. They were given a score of 1 to 4 according to the following outline. For the surface, 1 = perforation, 2 = wrong cleavage plane, 3 = rough surface, and 4 = smooth surface. For the end points, 1 = perforation, 2 = intimal flap, 3 = rough transition, and 4 = smooth transition. The specimens were examined independently by three of the investigators and the results were averaged to determine the final score for each specimen. The scores for groups I and II were compared by the Wilcoxin rank-sum test. Differences with a value of $p < .05$ were considered significant.

Results

Eight endarterectomies were performed in group I (15 Hz) and 11 endarterectomies were performed in group II (20 Hz). In group I, arteriosclerotic plaques were readily removed with excimer radiation. The plaques could be cut out of the arteries along the cleavage plane leaving a clean surface. The depth of the dissection was predictable and there were no obvious injuries to the arteries or surrounding structures. No perforations were seen. Microscopically the surfaces were smooth and at the appropriate cleavage plane (internal elastic lamina) in nearly all of the cases (Fig 1). There was only one case where the wrong cleavage plane was identified. There was no

Figure 1. Longitudinal sections of arteriosclerotic rabbit aortas following excimer laser endarterectomy. (A) At 15 Hz, the endarterectomy surface is smooth and free of debris. The internal elastic lamina has been removed and the media and adventitia are undisturbed. (B) At 20 Hz, the surface is clean without any signs of injury. The architecture of the media and adventitia appears normal. m, media; a, adventitia. Calibration bar = 50 μ m (hematoxylin and eosin stain).

obvious charring or discoloration of the surfaces and no microscopic perforations were seen.

At the end points, the laser was used to cut the atheroma and remove it from the artery. This left a sharp transition between surface and intima. In some cases, laser light was used to shape or trim this sharp edge at the end point, but this was not possible in every case. In three cases, obvious intimal flaps were seen and these could not be fused or welded into place with laser radiation. Microscopically, abrupt or rough edges were seen on several of the cases despite trimming or shaping with the laser beam (Figs 2 and 3). Intimal flaps were identified in three cases (Fig 4).

In group II, arteriosclerotic plaques were easily removed with laser radiation, but the depth of the cleavage plane was difficult to control and perforations were common. There was no evidence of damage to surrounding tissues when a perforation occurred. Microscopically, perforations were confirmed in 7 of the 11 surfaces. The cleavage plane was usually irregular and at the wrong depth.

At the end points, most appeared to be grossly irregular and uneven. In trying to trim or shape the end points, perforations occurred. Microscopically, the end points were seen to have a sharp edge (Fig 2), an intimal flap (Fig 4) or a perforation (Fig 5). No evidence of carbonization or discoloration indicative of thermal injury was seen at any of the end points, even at the perforations.

The mean ($\pm$ standard error of the mean) endarterectomy surface score was 3.38 ± 0.26 for group I and 2.0 ± 0.43 for group II ($p < .01$). The mean ($\pm$ standard error of the mean) endarterectomy end point score was 2.75 ± 0.25 for group I and 1.73 ± 0.25 for group II ($p < .05$). The results are summarized in Tables 1 and 2.

Discussion

Laser endarterectomy was developed in our laboratory as a method for the *in vivo* evaluation of laser-atheroma interactions. In performing the laser endarterectomy operation, we learned that the various applications of lasers to the treatment of arteriosclerotic cardiovascular disease could be studied in one procedure. These applications include vaporization, cutting, dissection, and welding. As the procedure has been refined, various lasers have been evaluated by their ability to perform laser endarterectomy and we have seen that the laser technique offers advantages over the standard endarterectomy technique. These advantages include a smooth endarterectomy surface with securely fused end points.¹¹

Several lasers as well as laser knives have been evaluated for the laser endarterectomy operation. These include the argon ion, neodymium YAG, carbon dioxide, and sapphire crystal laser knives.^{8,9,12} The best results, thus far, have been obtained with the argon ion laser delivered as a free laser beam. In the clinical studies of laser endarterectomy for peripheral vascular reconstruction and for carotid artery disease, argon ion laser radiation has been used to perform the laser endarterectomy operation.^{13,14} Several studies have confirmed the laboratory findings of smooth endarterectomy surfaces without any atheromatous debris and welded end points. The argon ion laser endarterectomy operation has been performed both in the laboratory and in the clinical setting with low power and there has been no evidence of thermal injury to the arteries or to surrounding structures. These findings are different from the findings of thermal injury that have been demonstrated by using argon ion laser radiation for laser angioplasty. In studying laser angioplasty, thermal injury has been identified from the continuous wave laser.^{3,4,10} To obviate the thermal injury and also

Figure 2. Distal end points following excimer laser endarterectomy in arteriosclerotic rabbits. (A) At 15 Hz, the transition at the end point is abrupt, not smooth and tapered. There is no evidence of thermal injury and the end point is secure. (B) At 20 Hz, the end point is rough. No thermal change is seen but the area between endarterectomy surface and end point is deep within the media and there are fragments of elastic fibers. i, intima; m, media; a, adventitia. Calibration bar = 50 μ m (hematoxylin and eosin stain).

Figure 3. Scanning electron micrograph of an end point created by excimer laser radiation at 15 Hz. There is an abrupt transmission (arrows) from the arterial surface (s) to the endarterectomy surface (m). There is no evidence of debris or thermal injury. s, luminal surface; i, intima; m, media. Calibration bar = 250 μ m.

Figure 4. Distal intimal flaps following excimer laser endarterectomy. (A) At 15 Hz, the end point (arrow) is not fixed in place so that the intima is separating from the media. (B) At 20 Hz, the end point is loose (arrow) and the intima is lifting off and away from the media. i, intima; m, media; a, adventitia. Calibration bar = 150 μ m (hematoxylin and eosin stain).

Figure 5. Distal end point following excimer laser endarterectomy at 20 Hz. There is a full thickness injury (perforation) without any sign of thermal damage. i, intima; m, media; a, adventitia. Calibration bar = 140 μ m (hematoxylin and eosin stain).

to insure better vaporization of atheromatous plaques (particularly calcified plaques), excimer lasers have been proposed for use for laser angioplasty.

Excimer or "excited dimer" lasers use compounds of rare gases and halogens as the lasing medium to produce an ultraviolet pulsed beam. The ultraviolet photon energy from the excimer laser is high enough to cause photodissociation or direct breaking of intramolecular bonds without producing heat.^{15,16} This obviates the potential for thermal damage demonstrated with continuous wave lasers. The excimer beam delivered is also powerful enough to ablate even calcified tissues.¹⁷ The 308-nm xenon chloride laser is undergoing clinical trials for intravascular use and appears to function well for the ablation of arteriosclerotic plaque.¹⁸ In addition, there is experimental evidence that pulsed ultraviolet radiation causes relaxation of vascular smooth muscle even without an intact endothelium.¹⁹ These characteristics might make excimer laser radiation desirable for the performance of the laser endarterectomy operation.

In the present study, 308-nm pulsed radiation was capable of ablating plaque in a predictable and precise fashion. The depth of the photo-ablative process was easily controlled at 15 Hz and there was no gross or microscopic damage evident along the endarterectomy surfaces. The surfaces were clean, smooth, and free of debris, and demonstrated the characteristics that we have come to expect from the laser endarterectomy operation. At 20 Hz, however, the photo-ablative process could not be as easily controlled. The depth of cutting and removal of plaque could not be determined properly and frequent perforations occurred. The operator's hand-eye reflexes were too slow at 20 Hz to control the photo-ablative process so that a cutting

Table 1
Excimer Laser Endarterectomy (Group I)

Experiment	Atheroma	Frequency (Hz)	Energy Density (mJ/mm ²)	Pulse Width (ns)	Surface Score	End Points Score
1	Moderate	20	50	120	3	3
2	Moderate	15	50	120	4	2
3	Mild	15	50	120	4	2
4	Moderate	15	50	120	3	3
5	Moderate	15	50	120	4	3
6	Moderate	15	50	120	4	2
7	Severe	15	50	120	2	2
8	Severe	15	50	120	3	4

maneuver turned into a full thickness perforation before the laser beam could be maneuvered or turned off.

The 308-nm pulsed laser beam did not produce smooth, tapered, and fused end points at either 15 or 20 Hz. With 15 Hz, abrupt transitions were encountered and intimal flaps were seen. In performing the operation, it was noted that the laser beam could be used to sculpt or shape or trim the edge of the end point, but not to weld or fuse it in place. If the atheroma was firmly fixed to the arterial surface by its own disease mechanism, then an intimal flap would not develop; however, once a separation was noted, it could not be secured back in place by phototherapy. Scanning electron microscopy (Fig 3) showed the clean endarterectomy surface obtained with the very abrupt transition that was left at the distal end point. The surface, the

Table 2
Excimer Laser Endarterectomy (Group II)

Experiment	Atheroma	Frequency (Hz)	Energy Density (mJ/mm ²)	Pulse Width (ns)	Surface Score	End Points Score
1	Moderate	20	50	120	4	1
2	Moderate	20	50	120	4	2
3	Severe	20	50	120	3	1
4	Severe	20	50	120	1	2
5	Mod-severe	20	50	120	1	2
6	Moderate	20	50	120	1	1
7	Moderate	20	50	120	1	1
8	Severe	20	50	120	4	1
9	Severe	20	50	120	1	2
10	Mild	20	50	120	1	3
11	Mild	20	50	120	1	3

atheroma, and the end point are all remarkably clean and free of debris, demonstrating the precise cutting mechanism of the 308-nm pulsed beam at 15 Hz. At 20 Hz, perforations frequently occurred at the end points in the same fashion as along the endarterectomy surfaces. As with the surface dissections, the laser beam depth of photo-ablation could not be precisely controlled at this frequency so that perforation was common.

In our laboratory, the rabbit arteriosclerosis model has been reliable in predicting the response of human arteries to the laser endarterectomy operation. The rabbit atheromas are uniform throughout the diseased aorta. There is a thickened and discolored intima which represents fibrous caps overlying areas of inflammation, fatty infiltration, and microcalcification. Often the atheromas involve the internal elastic lamina and even the superficial layers of the media. In the rabbit model, the laser endarterectomy operation is best performed with free beam argon ion laser radiation at power 1.0 W. In the clinical setting, both peripheral vascular and carotid artery reconstructions have been performed with free beam argon ion laser radiation at 1.0 W. The laboratory operations and the clinical operations continue to demonstrate smooth endarterectomy surfaces with fused end points. In the present study, the excimer laser at 308 nm, 15 Hz, 50 mJ/mm², and 120-ns pulses is capable of providing smooth, clean endarterectomy surfaces. The end points, however, cannot be welded. We cannot yet recommend excimer laser radiation for the performance of laser endarterectomy.

Acknowledgments

Statistical consultation was performed by Howard G. Tucker and David R. Noble. Scanning electron microscopy was performed by L. H. Liaw. Gerry Atkinson prepared the manuscript. This work was supported by NIH Grants HL-31318 and RRO-1192.

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