Vitreoretinal Ablation With the 193-nm Excimer Laser in Fluid Media

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Purpose. To ablate retina and vitreous membranes using the 193-nm argon fluoride excimer laser in a fluid medium.

Methods. A special delivery system for the 193-nm excimer laser was developed that enabled the delivery of the laser into high-absorption liquid environments. The system was tested on the retina in an in vitro cup preparation of cow's eyes, and also in vivo on retina and vitreous membranes of rabbit eyes. The depth of cut as a function of laser energy was determined for an ablating needle with a 0.25-mm exit diameter.

Results. Gentle cutting of retinal tissue and of vitreous membranes was obtained in an energy range of 0.075 to 0.25 mJ/pulse. At the energy level of 0.075 mJ/pulse, four pulses were required for full-depth cut formation in rabbit retina, whereas at energy levels greater than 0.17 mJ/pulse, one pulse was sufficient for full-depth cut formation. The maximal rate of cutting achieved for the bovine retina was 2 mm/sec at a 20-Hz repetition rate of the laser. Ablation occurred only when the tip was held in contact with the tissue.

Conclusions. The technology described herein appears to be advantageous and applicable to a variety of vitreoretinal surgical procedures. Invest Ophthalmol Vis Sci. 1994;35:3835–3840.

There is a variety of instrumentation for the segmentation, peeling, and removal of vitreoretinal membranes that can grow in conditions such as proliferative vitreoretinopathy and proliferative diabetic retinopathy. These membranes can cover the macular area, causing the deterioration of vision, or can grow elsewhere on or under the retina, causing tractional retinal detachment. The mechanics of membrane removal are such that usually a degree of traction is exerted on the tissue, occasionally inducing damage to the inner retinal layers, iatrogenic tears, and bleeding.

Several attempts were already undertaken of tractionless removal of vitreoretinal membranes using various types of lasers guided through optical fibers.[1-3] The approach using CO_2[1] and Er-YAG[3] lasers that are strongly absorbed in water (approximately 10 μm and

1 μm penetration depth, respectively) has encountered difficulty, in that the effect of the laser on the treated tissue is too distant: the retina was damaged when the laser probe was located approximately 2 mm from its surface. The 308-nm xenon chloride excimer laser was also reported to be capable of cutting the vitreoretinal membranes,[2] but this wavelength is known to cause severe hazards to the cornea, lens, and retina.[4] As a result, all these approaches have failed to achieve widespread acceptance.

The 193-nm argon fluoride (ArF) excimer laser is known for its ability to ablate biologic tissue with minimal damage to the surrounding tissue.[5,6] A 1-μm penetration depth of this radiation in most biologic materials allows for exceptional control of ablation depth.[6,7] Furthermore, the ArF excimer laser has been shown to have no mutagenic effects on mammalian cells.[8-10] Nonetheless, despite these advantages, this laser has been widely accepted in medicine only for refractive surgery.[11]

The lack of microsurgical applications of the 193-nm excimer laser in liquid environments arises mainly from the absence of a convenient delivery system, because this laser does not pass efficiently through opti-

cal fibers.[12] This problem, in addition to the strong absorption of this wavelength by biologic media, has limited the use of this laser to applications in air and to relatively dry tissues such as the cornea.

The development of a delivery system capable of transmitting the 193-nm laser beam in a fashion suitable for microsurgery in a high-absorption liquid environment has been the object of several years of experimentation at the Hadassah Laser Research Center. In a preliminary investigation, we described a system that was capable of working in a gas environment.[13] With this system, it was possible to photoablate retinal tissue in an air-filled eye in a precise fashion without heat deposition in the surrounding tissue. Working in the air-filled eye, it was impractical to remove vitreoretinal membranes, a major objective of these investigations. A few years ago, we applied the 193-nm excimer laser, delivered into a liquid environment through glass micropipettes filled with air, to drilling holes 4 to 8 μm in diameter in the zona pellucida of oocytes.[14] Although this delivery system suits well the tiny scale of microsurgery in liquid environment, it can not withstand the energy fluence and number of pulses required for vitreoretinal membrane removal.

Recently, we have developed a type of laser tip that allows the 193-nm excimer laser to be applied to microsurgery in the high-absorption liquid environment. In this article, we present preliminary in vitro and in vivo data on this intravitreal device capable of cutting retinal and membranous tissue in the fluid environment of a live eye in a fast, precise, and reproducible fashion.

MATERIALS AND METHODS

All investigations involving animals conformed to the ARVO Statement for the Use of Animals in Ophthalmic and Vision Research.

A model 103 MSG Lambda Physik (Gottingen, Germany) ArF excimer laser with 193-nm wavelength and pulse duration of approximately 20 nsec was employed. The laser beam was directed with a specially designed articulated arm.[13] At the arm's exit were fixed special ablating needles of the following dimensions: length 37 mm, entrance outer diameter 1.0 ± 0.1 mm, tapered to a closed tip of diameter 250 μm. The energy transmitted through the tips was measured by the Ophir DGX energy meter (Jerusalem, Israel) with 03AP head. The maximal energy that could be delivered through the tip without damaging it was found to be approximately 0.3 mJ/pulse.

Various pulse energies and repetition rates were investigated to optimize the retinal and membranous cutting conditions. We found it necessary to touch the tissue gently with the tip of the ablating needle to cut it. This feature arises from the high absorption of the

radiation by the surrounding liquid and is actually an advantage, because it protects the surrounding and underlying tissue from the laser radiation. A helium–neon laser-aiming beam was used to guide the transparent ablating probe to the desired position and to control the distance between the tip and the tissue. This was accomplished by fusing two points of helium–neon light, one at the tip of the probe and the other on the tissue.

Retinal Ablation In Vitro

In this set of experiments, we attempted to determine the maximum rate of cutting retinal tissue without concern for the additional factors that a procedure with live animals would normally entail. Ten postmortem fresh bovine eyes were obtained from a local slaughterhouse. The anterior segment of the eyes was removed. Each eye was prepared as an eyecup preparation, the vitreous was removed, and the eyecup was filled with saline (0.9% NaCl), which normally would have prevented ablation of the retina by its strong absorption of the 193-nm radiation. For measurements of the rate of cutting, four to five cuts of approximately 1-cm length were produced in each retina. Energy of approximately 0.25 mJ/pulse and a repetition rate of 20 Hz were used.

Vitreous Membrane Ablation In Vivo

To demonstrate the applicability of our methodology in vitreoretinal surgery, experiments were performed in vivo on anesthetized rabbits. Two albino rabbits weighing 2.0 to 2.5 kg each underwent chorioretinal injury through the sclera to create vitreous hemorrhage with subsequent proliferative vitreoretinopathy. Two weeks later, a lensectomy and pars plana vitrectomy were performed. The ablating needle was inserted through a 1.4-mm sclerotomy located 3.0 mm away from the limbus. Energy of 0.25 mJ/pulse and a repetition rate of 20 Hz were used in this case as well. In these experiments, we found that our system was capable of removing the vitreous membranes.

Retinal Ablation In Vivo

In a further set of experiments, we investigated histologically the dimension of cut as a function of laser energy and the possible side effects in the surrounding tissue. These experiments were performed in two different ways. First, the retina was irradiated when the tip was held at a small (approximately 1 mm) distance from the retina surface. Six rabbits were used in this experiment. The energy at the tip exit was approximately 0.2 mJ/pulse, and a repetition rate of 10 Hz was used. Approximately 25 points were irradiated in the posterior pole of the fundus in each eye, with approximately 10 pulses at each point. Two of the rabbits were killed immediately after the irradiation

procedure, two were killed after 2 weeks, and the remaining two were killed 4 weeks after the irradiation. The eyes were taken immediately for pathologic examination.

In the second experiment, the retina was irradiated with single laser pulses in contact with the tip, with the energy varying from 0.05 to 0.2 mJ/pulse. This experiment was also performed on the retina of intact rabbit eyes in six anesthetized animals. Approximately 25 points were irradiated at constant energy in the posterior pole of the fundus in each eye. All the animals were killed immediately after irradiation, and the eyes were taken for pathologic examination. Eyes were fixed in 4% buffered formaldehyde for at least 48 hours. The tissue was processed and embedded in paraffin. Sections were produced 5 to 6 μm thick and were stained with hematoxylin–eosin.

RESULTS

To check the applicability of our system to vitreoretinal surgery, we performed the following experiments. First, we determined the maximal cutting rate of retina in vitro to ensure that it was sufficient for real applications. Second, we demonstrated that epiretinal membranes in live rabbit eyes can also be removed at the same energy. Third, we determined the dimensions of cut in vivo in rabbit retina as a function of laser energy, and we determined the distance control that can be achieved with this system.

Retinal Ablation In Vitro

A full-thickness retinotomy was achieved in vitro in postmortem fresh bovine eyes by applying a laser with an energy of approximately 0.25 mJ/pulse and a repetition rate of 20 Hz. The sequence of frames taken from a video recording of the procedure indicated a rate of cutting of 1 to 2 mm/sec, depending on the degree of contact of the tip with the retina. During the procedure, we observed the formation of small bubbles that were released from the point of contact of the tip with tissue. A very small amount of such bubbles was also observed during the irradiation of saline and vitreous at high repetition rates. The retinal tissue in the immediate vicinity of the ablated region looked normal, and the borders of the lesion were quite sharp and clean.

Vitreous Membrane Ablation In Vivo

Vitreous membranes in rabbit eyes were found to be easily cut in vivo under the same irradiation conditions as those used in the first experiment (0.25 mJ/pulse, 20 Hz). The rate of cutting was also similar to that of the bovine retina.
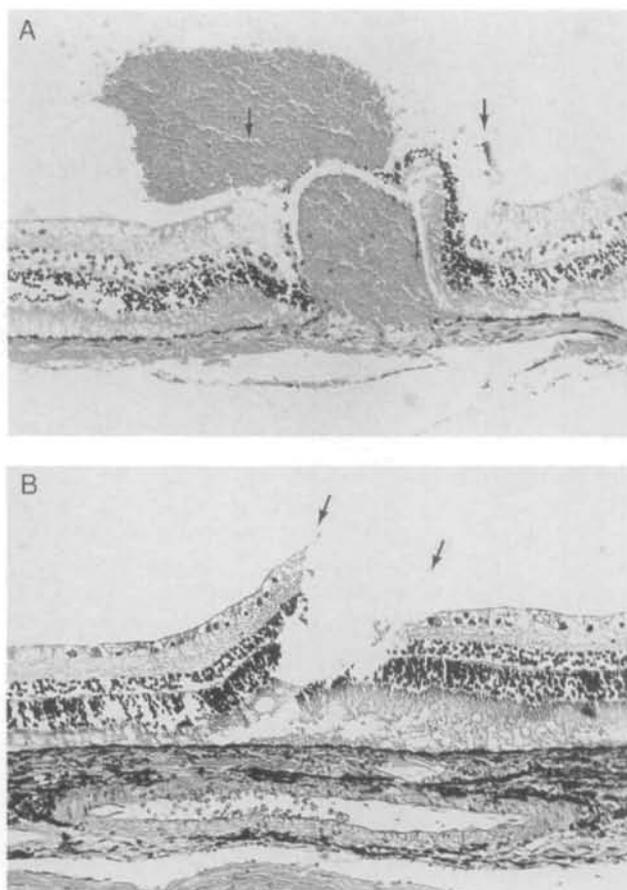
FIGURE 1. Full-depth cuts in rabbit retina caused by 1 pulse of the 193-nm excimer laser delivered through the ablating needle with an exit diameter of 250 μm with an energy of 0.17 mJ/pulse. (A) Cut area (*arrows*) where all the sensory retinal layers and the retinal pigment epithelium are ruptured, and blood burst from the choroid through the retina into the vitreous. The bleeding area width is approximately 100 μm. (B) Cut area (*arrows*) where the whole sensory retina is ruptured, but the retinal epithelium and choroid are intact. The cut width is approximately 100 μm.

Retinal Ablation In Vivo

Histologic examination of the rabbit retina showed that in the absence of contact between the probe and the retina (distance 1 mm), there were no signs of damage detected in the retina. When the probe was in contact with the retina, a full-depth cut was achieved in the retina (which was generally indicated by choroidal hemorrhage) with four laser pulses at an energy of 0.075 mJ/pulse, whereas at 0.11 mJ/pulse, the same cut was induced by two pulses. At an energy level of 0.17 mJ/pulse, we were able to cut a full depth of retina with one laser pulse (Fig. 1). A half-depth cut in retina produced by one laser pulse at an energy level of 0.11 mJ/pulse is shown in Figure 2. The width of both the full- and half-depth cuts was approximately 100 to 150 μm (Figs. 1, 2). As can be seen on Figure 2, the retinal material is expelled as a result of an
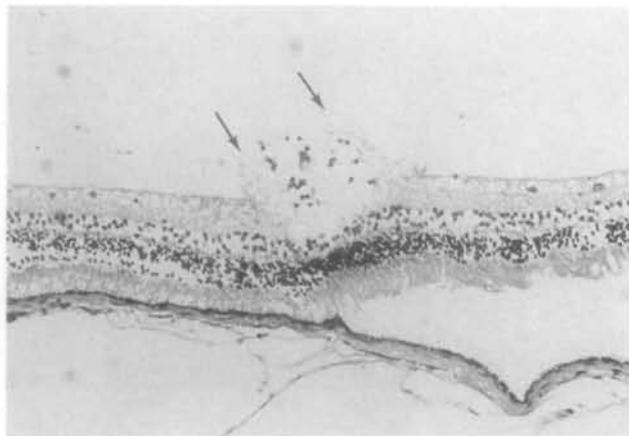
FIGURE 2. A half-depth cut in rabbit retina caused by 1 pulse of the 193-nm excimer laser delivered through the ablating needle with an exit diameter of 250 μm with an energy of 0.11 mJ/pulse. Cut area (*arrows*) with a width of approximately 100 μm. Only the nerve fiber layer, the ganglion cell layer, and the superficial nuclei of the inner nuclear layer are removed. The retinal material seems to be expelled from the tissue, and the inner nuclear layer is slightly compressed.

explosive process, and the nuclear layer under the irradiated area is slightly compressed.

DISCUSSION

The 193-nm excimer laser is well known for its ability to photoablate polymers and biologic tissue precisely in a gaseous environment. Characteristic ablation depths and damage zones in soft tissue are generally less than 1 μm—the same as a penetration depth of this laser radiation.[5,6] In addition, it was shown that at low-energy fluences, this laser is capable of slowly dissolving the zona pellucida of oocytes in a water environment.[14] In this case, the ablation depth was also in the range of 1 to 2 μm per pulse. In the present work, we obtain a cutting depth in the range of 25 μm to greater than 100 μm per pulse, approximately two orders of magnitude greater then the penetration depth of this radiation in biologic tissue.

Such deep tissue removal indicates that the mechanism underlying this process is associated with the formation of cavitation bubbles at the ablating tip exit. Similar effects have been demonstrated for Er:YAG[3] and XeCl[2] lasers delivered by optical fibers into in liquid environments. Such cavitation bubbles can also be produced by dielectric breakdown in liquid caused, for example, by the Nd:YAG laser.[15] These cavitation bubbles grow during a few microseconds after the laser pulse is applied and collapse after a few tens of microseconds, causing a mechanical tissue dissection.[15-17] During the collapse of these bubbles, an energetic water jet is formed that can be considered to be the driving force of tissue dissection in a liquid

environment.[17] This mechanism enables us to reach a sufficiently rapid rate of tissue removal, but in certain cases it could also limit the possible applications.

In this regard, two advantages of our system can be noted in comparison with other lasers that generate cavitation bubbles. First, the confinement of the mechanical action caused by the cavitation bubble is determined by its dimensions and by the amount of energy required for its formation. In our case, the energy required for effective retinal and membranous tissue cutting was in the range of 0.075 to 0.25 mJ/pulse for a tip with a 0.25-mm exit diameter. Regarding Er:YAG and CO_2 lasers applied to vitreoretinal surgery,[1,3] the energy levels used were approximately 15 and 30 times higher, respectively. Second, the cavitation bubbles are formed as a result of strong radiation absorption in the tissue (penetration depth approximately 1 μm). In the surrounding fluid media, such as saline, where the penetration depth is approximately 50 μm,[18] such bubbles cannot be formed at these energy fluences. The medium screens the tissue from the radiation when the tip is held some distance from its surface, and bubble formation with associated effective cutting occurs only when the tip touches the tissue. This feature provides the surgeon with good distance control—approximately 50 μm—for cutting of epiretinal membranes. When the membrane is already cut and the laser radiation begins to penetrate through the lesion, the thin layer of liquid will prevent cutting of underlying retina. In contrast, when the Er:YAG and CO_2 lasers are applied in a fluid media, the vapor bubbles are formed as a result of strong water absorption, and thus the bubbles are produced in the medium independently of the distance from the tissue surface. As a result, retinal lesions were observed with both of these lasers, even when a fiber was located at a distance of 2 mm from the tissue surface.[1,3] The distance control that can be obtained with the 193-nm ArF excimer laser has not be achieved with any other system, including the 308-nm XeCl excimer laser, which has a penetration depth in saline of approximately 5 cm.

In addition to the formation of short-lived cavitation bubbles noted above, we have seen the production of insoluble gas bubbles at the end of the ablating tip during irradiation in absorbing media. In contrast to the 308-nm excimer laser radiation that produces the insoluble bubbles only in tissue,[17] in our case they also appear in saline. The diameters of the bubbles are less then the tip diameter, and their appearance depends on the energy fluence, the repetition rate, and the absorption coefficient of the medium. We have recently shown that when NaCl water solutions are irradiated with the 193-nm radiation, the insoluble bubbles are composed mainly of H_2,[18] and when tissue is cut in a biologic medium, they can also contain

the gaseous products of tissue decomposition. The insoluble bubbles may play an important role in tissue cutting. A bubble formed by a previous laser pulse can collapse from its interaction with a cavitation bubble or with a strong acoustic wave formed by a subsequent pulse in the vicinity of the tissue that is being cut.[17] We are continuing the investigation of these insoluble bubbles produced by the 193-nm excimer laser during vitreoretinal surgery to understand how such bubbles enhances the rate of cutting at low laser energies.

In the present study, we have shown that retinal tissue can be cut with the 193-nm excimer laser in a liquid environment with a rate of approximately 25, 50, and 120 μm/pulse when the energy at the ablating tip is varied in the range of 0.075, 0.11, and 0.17 mJ/pulse, respectively, for a tip diameter of 250 μm. In spite of the fact that the penetration depth in saline is 50 μm, we checked in this work the absence of damage only when the retina was irradiated from a distance of approximately 1 mm in an intact eye. It was difficult to measure much smaller distances between the tip and the retina in a live eye using a regular surgical microscope.

It was also shown in this study that epiretinal membranes can be removed with approximately the same rate as the retina. The obtained rate of cutting and distance control seems to be ideal for vitreoretinal surgery. In the case of very thick membranes or those that are distant from the retina (approximately 1 mm), ablation can be performed directly with no influence on the retina. In the case of thin membranes tightly associated with the retina, the direct ablation of membranes can be dangerous, and in this case the fibrotic connections of the membrane to the retina can be cut when the tip is held tangentially to the retinal surface.

The 193-nm excimer laser-based microsurgical system for vitreoretinal applications, developed at the Hadassah Hospital Laser Center, has several attractive features. The cutting depth of the retina and vitreoretinal membranes that can be achieved with this system is in the range of 25 to 150 μm/pulse, which is sufficiently high and accurate for vitreoretinal applications. This laser cuts tissue in liquid environments only when the tip touches the tissue, making it much safer than the lasers that are absorbed in water (Er:YAG, Ho:YAG, CO_2) or those that penetrate deeply in biologic fluids (XeCl excimer, Nd:YAG). The probe dimensions (37 mm length and 1 mm outer diameter) are similar to standard vitrectomy instrumentation, and the probe can readily reach every point in the fundus using a specially designed seven-joint articulated arm. Thus, we think that the work described in this paper is only the first step in the demonstration of a variety of delicate surgical procedures that will evolve as a result of the application of this new technology.

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