New Instrument

SEMIAUTOMATED PATTERNED SCANNING LASER FOR RETINAL PHOTOCOAGULATION

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The concept of retinal photocoagulation was introduced by Meyer-Schwickerath for the treatment of diabetic retinopathy in the 1950s and used with some success in the 1960s. The xenon arc photocoagulator utilized for this purpose was large, polychromatic, inefficient, and difficult to operate, prompting a search for a better method of treatment. Further progress was achieved when ruby,[1] argon ion,[2] and krypton ion[3] lasers were coupled to a slit lamp with an articulating arm containing mirrors.[4] A contact lens, aiming beam, and movable joystick were used to place the laser beam on the retina. These innovations allowed for creating single laser spots of variable size, power, and duration on the retina with a high degree of precision and ushered in the modern era of retinal laser photocoagulation in the 1970s. The techniques enabled by these devices, termed focal photocoagulation, grid photocoagulation, and panretinal photocoagulation, were refined and shown to be effective in the treatment of proliferative diabetic retinopathy and advanced forms of nonproliferative diabetic retinopathy associated with macular edema in large, prospective, multicenter, randomized trials—the DRS and ETDRS.[5,6] These trials validated the efficacy and institutionalized the indications and parameters for treatment that have remained the gold standard since that time.

Patients with high risk proliferative diabetic retinopathy who undergo panretinal photocoagulation typically receive between 1,200 and 1,500 laser spots in two to four sessions of 10 minutes to 20 minutes each over the course of 2 weeks to 4 weeks. Because the spots are delivered individually, treatments are time consuming and tedious for the patient and physician alike and can be painful, especially in the retinal periphery. Focal photocoagulation and grid photocoagulation for macular edema are less painful and time consuming, because the spots are applied more posteriorly and are fewer in number, but still are tedious and require a considerable degree of patient cooperation and physician skill to achieve a successful outcome and avoid complications.

Until now, little has changed in the general design of the devices used for retinal photocoagulation aside from the substitution of fiber-optic cables for articulating arms and the use of air-cooled solid state lasers rather than water-cooled gas tubes. These innovations have had limited or no impact from the standpoint of the patient or physician on the technique of treatments and clinical outcomes.

We reasoned that greater precision and safety in retinal photocoagulation might be achieved by delivering a multiplicity of spots in a pattern created by a scanner rather than as a series of individually placed lesions. We also wondered whether the pattern application time and patient discomfort could be further reduced by using shorter pulses than the conventional 100 milliseconds to 200 milliseconds recommended in the DRS and ETDRS.[5,6]

Prior efforts toward improvement in retinal photocoagulation systems were principally directed toward (1) fully automated systems with retinal stabilization based on eye tracking[7–10] and (2) determination of the optimal dose in each spot using the tissue reflectance–based feedback systems.[11] Automated systems required acquisition of an image of the retina before the treatment, planning and aligning all treatment locations with reference to the retinal image, and treating all of these locations automatically. Complex retinal tracking systems were also required in these approaches to ensure alignment between planned treatment locations defined on the acquired image and actual sites on the retina.[7–10] The complexity of these fully automated systems hampered the introduction of

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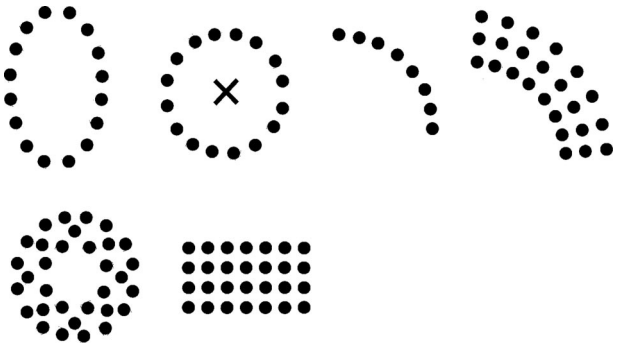

Fig. 1. Examples of patterns for retinal photocoagulation. Patterns can include a fixation spot (shown as X in a second frame) projected by the aiming beam, but not included in the treatment coagulation.

such devices into clinical use. Other approaches to reducing treatment time by simultaneous projection of multiple laser spots using beam splitters or preconfigured fiber bundles[12,13] did not prove practical due to the difficulty in varying the size and spacing of lesions.

This article describes a semiautomated patterned scanning laser retinal photocoagulator that allows for much greater speed and precision than single spot application but without the liabilities of fully automated systems previously described. Semiautomatic in this context means that the physician has control over the treatment at all times. Each pattern of spots is configured and positioned by means of a joystick. Laser delivery can be initiated and interrupted at any time by activating and releasing the foot pedal. By eliminating retinal tracking and automated lesion reflectance feedback, the device is relatively simple and inexpensive to construct yet significantly more efficient than nonpatterned systems. Most features of the system are identical to those of existing laser photocoagulator systems, except for the ability to deliver either a single spot or multiple spots in a predetermined pattern in a single burst. By using pulse durations in the 10- to 20-millisecond range, multiple spots can be delivered in the time required for a single conventional 100-millisecond pulse. Such short pulses also provide the theoretical likelihood of less pain during treatment due to reduced choroidal heating from the thermal diffusion associated with longer duration burns.

We describe the first results of treatment with this system on rabbit retina in vivo, demonstrating delivery of multiple spots in a predetermined pattern. We also evaluate the threshold power, scanning rate, and optimal pulse duration relevant to this approach and compare the histologic appearance of conventional and shorter burns to ensure an equivalent biologic effect.

Materials and Methods

Instrument Description

A standard Zeiss SL130 slit lamp was used to support the scanning device and provide a view of the fundus. A 514-nm-wavelength argon ion laser (Novus 2000, Lumenis, Inc., Santa Clara, CA) was used. A Pentium III PC (Micron, Boise, ID) running under Microsoft Windows 2000 coordinated the pulse duration, safety shutter control, scanner positioning, pattern geometry, and aiming beam intensity. Scanning of the laser was achieved by mirrors mounted on a two-axis galvanometric scanner. The system's software had a collection of adjustable predetermined pattern shapes and sizes, including lines, squares, circular arcs, as well as user-defined patterns, and an adjustable "foveal exclusion zone" in which no spots could be placed, as shown in Figure 1. The aiming beam pattern had a blinking central fixation spot used

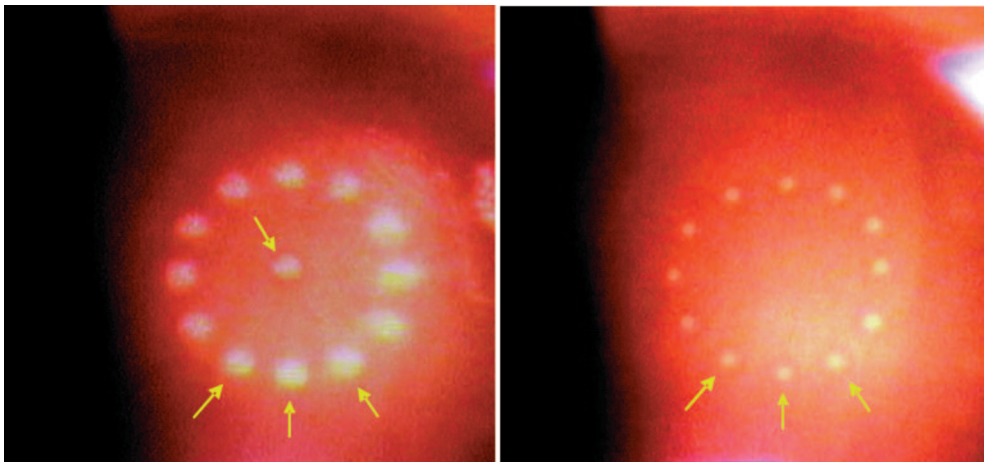

Fig. 2. **Left,** Ring pattern of 12 spots (arrows) with a central fixation point (arrow) projected on rabbit retina by the 632-nm He–Ne aiming beam. **Right,** The completed coagulation pattern with 12 burns in a ring (arrows) but no coagulation corresponding to the central fixation point.

to help the physician identify the fovea with the patient's assistance (Fig. 2). The graphical user interface operated in the following fashion: (1) a pattern was selected by pressing upon its representative icon on a touch screen, and the selected pattern was then projected onto the retina with an aiming beam; (2) using an electronic joystick, the physician could adjust the size and location of the pattern, as well as the spot density; and (3) when pattern location and geometry were properly adjusted, the physician activated the therapeutic laser by pressing on a foot pedal, similar to standard photocoagulators.

Experimental Methods

Ten New Zealand Red/Hybrid rabbits (weight, 3.5–4.5 kg) were used in accordance with the Association for Research in Vision and Ophthalmology Statement Regarding the Use of Animals in Ophthalmic and Vision Research after approval from the Stanford University Animal Institutional Review Board. The rabbits were anesthetized using ketamine hydrochloride, xylazine, and glycopyrrolate, which were administered intramuscularly 0.5 hour before the procedure. Pupillary dilation was achieved with one drop of 1% tropicamide and one drop of 2.5% phenylephrine hydrochloride. Only one eye of each rabbit was treated at a time, unless the rabbit was to be immediately killed. We compared the effects of various pulse durations and power provided by a nonscanned single pulse delivery system with the patterned arrays generated by the scanner system. Single spots with pulse durations of 10 milliseconds, 20 milliseconds, 50 milliseconds, and (the standard) 100 milliseconds were used to determine the threshold power levels required to achieve a clinically acceptable standard lesion, in the surgeon's judgment, on the retina.

The Mainster standard contact lens was used. The laser spot diameter in air was 200 μm with a top-hat beam profile. Taking into account a rabbit eye magnification factor of 0.66,[14] the spot size on the retina was $\approx$130 μm. Once appropriate power levels were determined ophthalmoscopically, rectangular scan patterns of 16 spots each were delivered as a 4 $\times$ 4 array using the semiautomated scanner. Thresholds for hemorrhage were also tested at a pulse duration of 20 milliseconds. Rabbits were killed 1 hour, 1 day, 1 week, or 1 month after the treatment. Eyes were fixed in 1.25% glutaraldehyde–1% paraformaldehyde in cacodylate buffer at pH 7.4. The eyes were then cut open, fixed, postfixed in osmium tetroxide, dehydrated with a graded series of ethanol, and embedded in epoxy resin. Sections of 1 μm in thickness were stained with toluidine blue and examined by light microscopy.

Table 1. Range of Power Settings and Corresponding Pulse Energies at Various Pulse Durations Required to Achieve Clinically Visible Light Retinal Burn

Pulse Duration (ms)	Laser Power (mW)	Pulse Energy (mJ)
10	190–240	1.9–2.4
20	110–120	2.2–2.4
50	75	3.8
100	50–60	5.0–6.0

Results

As shown in Table 1 and Figure 3, the power required to produce ophthalmoscopically visible spots decreased with increasing pulse duration. However, the cumulative pulse energy increased with pulse duration, indicating significant diffusion of heat from the laser spot at pulse durations of >20 milliseconds. Another indication of significant heat diffusion was a tendency for the creation of less localized and less homogeneous lesions with longer pulses. The dimensions of the coagulation spots on the retina varied with

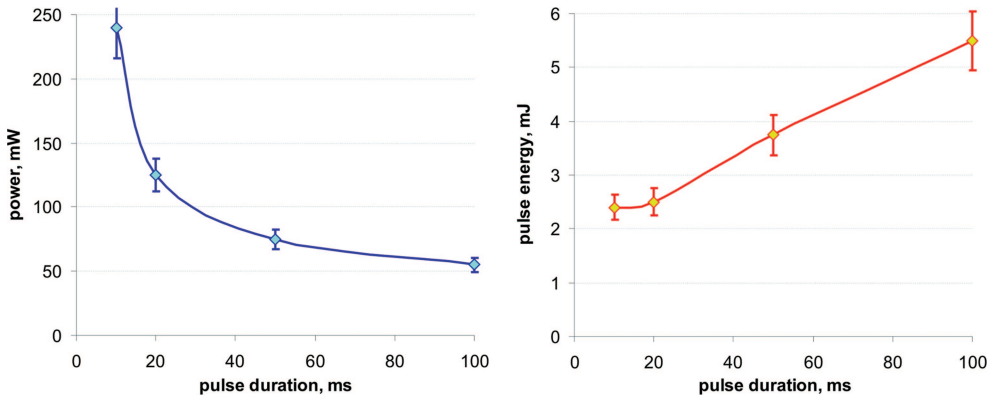

Fig. 3. Threshold laser power (**left**) and pulse energy (**right**) required for producing visible retinal lesions, plotted as a function of pulse duration.

Table 2. Scan Time for the Patterns of 16 and 36 Spots at Different Pulse Durations

Pulse Duration (ms)	Time to Scan 16 Spots (ms)	Time to Scan 36 Spots (ms)
10	310	710
20	470	1,070
50	950	2,150
100	1,750	3,950

the laser power and pulse duration in the range of 110 μm to 170 μm in diameter. At a 20-millisecond pulse duration, the threshold power for producing visible lesion was 110 mW to 120 mW, while the threshold for hemorrhage was 600 mW.

Table 2 summarizes the length of the procedure as a function of pulse duration for the application of 16 or 36 points in evenly spaced rectangular grids with a 10-millisecond interpulse delay. For example, with 10-millisecond pulses, the application of 16 spots took 310 milliseconds, while for 36 spots 710 milliseconds was required.

Histologic Observations

An example of a pattern of lesions produced with a scanning laser system 1 week after treatment is shown in Figure 4. In this case, the pulse duration was 10 milliseconds, and the laser power was 240 mW. The lesions are regularly spaced and have a uniform and similar histologic appearance. There is loss of the outer nuclear layer, inner segments, and outer segments, with visible migration of glial columns and slight displacement of the inner nuclear layer in an outward direction.

Ophthalmoscopically comparable lesions produced with the scanning system at pulse durations of 10 milliseconds, 20 milliseconds, 50 milliseconds, and 100 milliseconds at different power levels required to generate the same visible end point had the same histologic appearance. Two examples of ophthalmoscopically similar light retinal burns produced with pulses of 10 milliseconds at 240 mW and 100 milliseconds at 60 mW are shown in Figures 5 and 6, respectively. There is almost complete loss of the outer nuclear layers with outward migration of glial elements toward the pigment epithelium. The inner nuclear layer appears unaffected, as do the inner plexiform layer and nerve fiber layer. The adjacent regions between burns appear to be essentially within normal

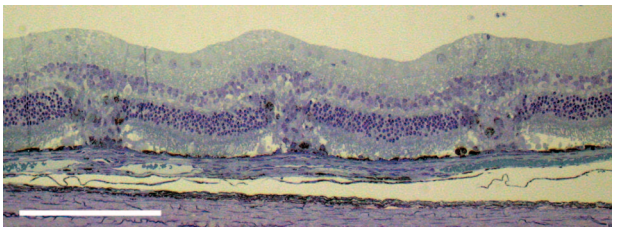

Fig. 4. Histologic section of rabbit retina treated with a patterned scanning laser system. Three very similar lesions were produced by a series of pulses of 10 milliseconds in duration at 240 mW. The eye was enucleated 1 week after the treatment (1-μm-thick section; toluidine blue staining; scale bar, 200 μm; original magnification, $\times$10).

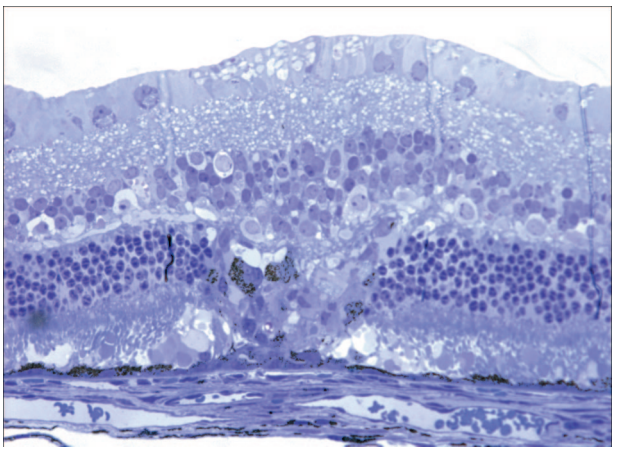

Fig. 5. Single retinal lesion produced with a 10-millisecond pulse at 240 mW, 1 week after the treatment. Note almost complete loss of the outer nuclear layer with outward migration of glial elements toward the pigment epithelium. The retinal pigment epithelium is disturbed with some inward migration of phagocytic retinal pigment epithelium macrophages, which have ingested pigment. The inner nuclear layer appears unaffected, as do the inner plexiform layer and nerve fiber layer. There are a few hypertrophic pigment epithelial cells adjacent to the lesion, some containing increased numbers of melanosomes (original magnification, $\times$20).

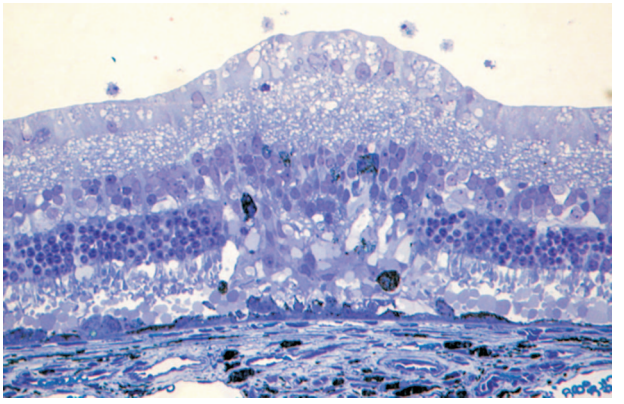

Fig. 6. Retinal lesion produced with a 100-millisecond pulse at 60 mW, 1 week after the treatment. Similar to the lesion produced with a 10-millisecond pulse, there is almost complete loss of the outer nuclear layer and migration of glial elements toward the retinal pigment epithelium. There is some inward migration of phagocytic retinal pigment epithelium macrophages, which have ingested pigment. The inner nuclear layer, inner plexiform layer, and nerve fiber layers appear unaffected (original magnification, $\times$20).

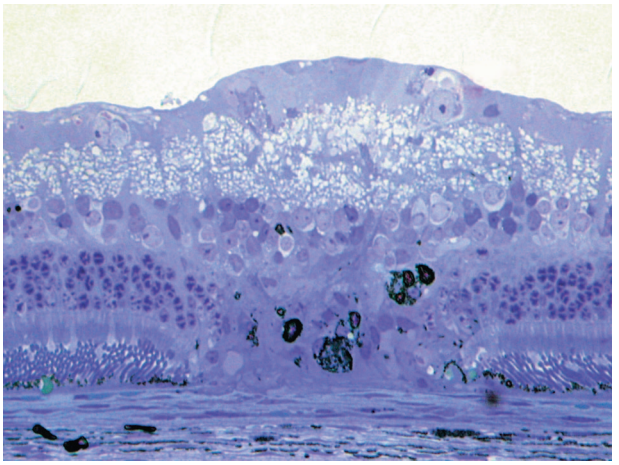

Fig. 7. Retinal remodeling 1 month after laser treatment with parameters of 55 mW and pulse duration of 100 milliseconds. There is a complete loss of photoreceptors and some hyperplasia and hypertrophy of the remaining pigment epithelium. There appears to be excellent preservation of the inner nuclear, plexiform, ganglion cell, and nerve fiber layers. The margins between the laser scar and the adjacent normal remain retina fairly discrete (original magnification, ×20).

limits aside from a few hyperplastic pigment epithelial cells adjacent to the lesions with increased numbers of melanosomes. These changes were commonly encountered in lesions produced with 10-millisecond, 20-millisecond, and 100-millisecond pulses. In rare instances, at higher power densities, we saw evidence of full-thickness retinal injury, including pyknosis of the inner nuclear and inner plexiform layers. In virtually all instances, the nerve fiber layer and ganglion cells appeared intact. At 1 month after treatment, there was remodeling of the laser burns into a typical mature chorioretinal adhesion, with discrete margins between the center of each laser scar and the adjacent normal retina (Fig. 7). In no instance was there evidence of rupture of Bruch membrane, epiretinal membrane, or ingrowth of new choroidal vessels. The adjacent retina appeared to be relatively uninvolved.

Discussion

Although recent advances in pharmacologic treatment with intravitreal steroids and VEGF inhibitors have suggested new avenues for the management of diabetic retinopathy, laser grid photocoagulation and panretinal photocoagulation remain the gold standard of therapy for diabetics with vision-threatening retinopathy.[15] Unfortunately, photocoagulation for diabetic retinopathy, branch and central retinal vein occlusions, and retinal tears remains a time-consuming, tedious, and uncomfortable procedure in many instances. Difficulties and complications related to focal and grid treatments include the occasional inability to accurately identify the foveal center due to loss of landmarks, making it critical to avoid inadvertent treatment to the center of the fovea.

In this report, we demonstrate that it is possible to improve significantly upon the precision, safety, and efficiency of these procedures by modifications to the slit-lamp delivery system that permits for the rapid application of a large number of spots in a preconfigured pattern distribution. The potential advantages of such a system are severalfold. First, by applying multiple burns with each depression of the foot switch, the duration of the treatment can be reduced by a factor equal to the number of burns applied at a time. For example, with a 7×7 array, theoretically the treatment time could be reduced by nearly 50-fold, assuming burn durations of 10 milliseconds separated by 10-millisecond intervals or just <1 second for 49 spots. In a best case scenario, if one array per second with 1 second between the applications could be delivered safely and comfortably, then an entire treatment of 1,500 spots could be applied in 1 minute with the scanner, compared with 25 minutes when using a conventional system delivering one pulse per second, a typical rate for a physician of moderate experience.

The advisability of placing a whole pattern of panretinal photocoagulation in a single session remains uncertain. In the DRS and ETDRS,[5,6] it was recommended that no more than 900 applications per session be applied, typically separated by 2 weeks because of concerns relating to the potential complications of macular edema, choroidal detachment, exudative retinal detachment, and shallowing or closure of the anterior chamber angle.[16] However, a subsequent study comparing a complete application of argon laser panretinal photocoagulation in a single session with multiple treatment sessions of equal total spot numbers suggested that there was no long-term detriment associated with a single session treatment.[17] Exudative retinal detachment, choroidal detachment, and angle closure occurred more commonly in single session group eyes during the first several days after treatment than in multiple session group eyes but resolved quickly; visual acuities at 7 days, 21 days, and 180 days were not significantly different between the two treatment groups, each consisting of 25 eyes. In fact, eyes receiving single session panretinal photocoagulation were more likely to have visual acuity in the range of 20/20 to 20/40 at 6 months (64%) than eyes receiving treatment in multiple sessions at a similar time point (48%), although these differences were not judged to be statistically significantly different. Similarly, eyes receiving single session panretinal photocoagulation were slightly less likely to have moderate or severe NVD 6 months after treatment

(16%) than eyes receiving multiple session treatments (24%) and more likely to have either complete regression (52.6%) or partial regression (25.3%) than multiple session eyes (45% and 20%, respectively). Practically speaking, because of the time, duration, and discomfort associated with single session treatment, in clinical practice this technique is used less frequently than multiple session treatment and invariably requires retrobulbar anesthesia.

The availability of a retinal photocoagulator capable of significantly improving the efficiency of treatment by the rapid sequential application of a large number of spots in an array makes single session panretinal photocoagulation practically feasible with or without retrobulbar anesthesia. Although total treatment time is unlikely to be reduced by a factor of 36- to 49-fold using a 6×6 or 7×7 array, we estimate that it may be possible to reduce total laser application time by a factor of 7- to 10-fold using these parameters. Thus, a single session treatment requiring $\approx$25 minutes to 30 minutes of laser treatment could be reduced to 3 minutes to 5 minutes, or multiple sessions of 10 minutes to 20 minutes could be reduced to 1 minute to 3 minutes each.

Treatment with reduced pulse duration may also be associated with less pain. Reduced pulse energy requirements associated with the shorter pulse durations are likely to reduce the pain due to decreased thermal diffusion into the choroid, which is rich in sensory nerves. There appears to be an adequate safety margin with short duration burns: the threshold for a visible burn at 20 milliseconds was 110 mW to120 mW, whereas the threshold for hemorrhage occurred $\approx$5 times higher at a power level of 600 mW.

In addition to the potential for more efficient treatment and less pain, the use of patterned delivery offers an opportunity for more precise treatment patterns in which the distances between spots are more uniform than can be achieved using manual single spot application. This may allow for better quantitation of treatment.

In applications of the pattern to the perimacular region, the physician can either manually place the blinking fixation spot on the foveal center in eyes in which landmarks are clear or, when there is considerable central thickening or loss of normal landmarks, encourage the patient to reveal their foveal center by fixation on the blinking cursor. The software can set an array with a central foveal exclusion zone in such a way that no burn can be placed closer than a preset distance from the center of the capillary free zone.

Because of concerns related to progressive enlargement of photocoagulation scars over many years applied in the course of grid or focal photocoagulation,[18] there has been a recent trend toward lower intensity or so-called subthreshold burns to treat diabetic macular edema.[19] Pilot studies by Roider et al[20] and Moorman and Hamilton[21] suggest that subthreshold burns may be as effective as more intense focal burns for the treatment of diabetic maculopathy and other diseases. They are also potentially associated with fewer complications including damage to the inner retina, wrinkling of the internal limiting membrane, and inadvertent rupture of Bruch membrane. One of the problems associated with the use of lower intensity or subthreshold lesions is their relative invisibility during placement. The physician is not able to easily identify the location of prior burns, thereby making the placement of a grid potentially inaccurate, because he or she must rely upon memory rather than visualization. A near simultaneous application of an array of spots with a single depression of the foot switch using a central exclusion zone or two to four hemispheres or quadrants of burns obviates this problem.

Clearly, these theoretical benefits associated with either patterned panretinal photocoagulation or patterned grid photocoagulation should be further corroborated by well controlled, prospective, clinical trials with humans.

Conclusions

A new type of retinal scanning photocoagulation system is described, capable of rapid application of an array of spots with a single depression of a foot pedal. With laser pulses of 10 milliseconds in duration, a pattern of 16 spots could be applied in 310 milliseconds, less than a typical eye fixation time, while 36 points required 710 milliseconds.

The ophthalmoscopic appearance of the retinal lesions produced at pulse durations of 10 milliseconds, 20 milliseconds, 50 milliseconds, and 100 milliseconds at appropriate power levels was very similar, except for the tendency for slightly better defined boundaries and more uniform whitening of the lesions produced with shorter pulses. The histologic appearance of the light burns at 10 milliseconds to 100 milliseconds was also very similar, with the damage predominantly confined to outer retina and retinal pigment epithelium.

Patterned photocoagulation with shorter pulses offers the following potential advantages compared with conventional manual application of single spots: (a) significantly improved efficiency, (b) increased safety with a central fixation spot and foveal exclusion zone, (c) increased uniformity and precision of spot placement, (d) more accurate placement of "subthreshold" lesions in a grid pattern, and (d) possible reduced pain and visual field defects due to reduced heat diffusion toward the choroid and inner retina.

Key words: retinal photocoagulation, patterned lesions, scanning laser.

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