Retinal Sparing by Selective Retinal Pigment Epithelial Photocoagulation

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Objective: To investigate whether photocoagulation of the retinal pigment epithelium is possible with sparing of the photoreceptors.

Methods: Mild laser effects of a neodymium:yttrium-lithium-fluoride (Nd:YLF) laser (527 nm) were applied to 17 patients. To establish the necessary energy, test exposures were performed to the lower macula (laser variables: 1.7 microseconds, 100 and 500 pulses applied in a train at 500 Hz, 20-130 µJ, 160 µm). Of 179 test lesions, 73 were followed up at various time intervals up to 1 year by performing microperimetry directly on top of the laser lesions.

Results: All of the test lesions were at the threshold of retinal pigment epithelial disruption, and none of the laser effects were visible by ophthalmoscopy during photocoagulation; they were detectable only by fluorescein angiography. After exposure with 500 pulses, retinal defects were detected in up to 73% of the patients (100 µJ) after the first day. Most of these defects were no longer detectable after 3 months. After exposure with 100 pulses, no defects could be detected with 70 and 100 µJ after 1 day. The absence of microscotomas in the follow-up period suggests that retinal damage was minimal or, if it occurred, was functionally repaired.

Conclusion: By choosing proper energy and number of pulses, it is possible to produce retinal pigment epithelial effects with no subsequent retinal damage detectable by microperimetry.


Retinal photocoagulation has been performed for more than 30 years in various diseases. Laser power is usually adjusted so that a gray or white retinal lesion appears. The value of retinal photocoagulation in various macular diseases, eg, diabetic macular edema, is well established. However, the benefit of retinal laser treatment is accompanied by severe destruction of retinal tissue. Subsequent heat conduction out of the retinal pigment epithelium (RPE), which is the primary absorption site, leads to irreversible thermal denaturation of outer and inner segments.

The exact biological mechanism by which retinal photocoagulation leads to the therapeutic effect is poorly understood and is probably different in various diseases. In treatment of diabetic macular edema, the beneficial effect is thought to be associated with the restoration of a new RPE barrier. A similar effect is postulated in the treatment of drusen and of central serous retinopathy. In proliferative diabetic retinopathy, the most common hypothesis is the destruction of oxygen-consuming photoreceptors. Another theory tries to explain the beneficial effect by restoration of a new RPE barrier and the subsequent production of a variety of growth factors. If these theories are accepted, the destruction of the photoreceptors would be only an unwanted side effect.

On the basis of these concepts, a photocoagulation technique was experimentally developed to treat the RPE selectively, with sparing of the photoreceptors. In animal experiments it was shown that this is possible only by means of a train of short pulses of a green laser but not with conventional continuous-wave laser exposures of, for example, 100 milliseconds in duration. With short laser pulses, energy remains confined to the RPE and no significant heat conduction occurs. Optimal pulse durations are on the order of microseconds (1 microsecond = 10^{-6} seconds) down to 200 nanoseconds. In animal experiments, it was shown that the RPE can be photocoagulated and that the RPE starts to regenerate with survival of the immediate adjacent photoreceptors in the healing period. This is in contrast to conventional photocoagulation, where even an extremely mild laser burn leads to irreversible photoreceptor damage.
PATIENTS AND METHODS

PATIENTS

All patients gave written informed consent to the test photocoagulation and to the prospective nature of this study. The protocol was approved by the institutional ethical committee. In 17 eyes of 17 patients, test lesions were applied to the macula. The mean age of the patients was 63.1 ± 11.8 years. Treatment was planned in 8 patients because of marked diabetic macular edema, in 8 patients as prophylactic treatment of soft drusen in eyes with a high risk of development of choroidal neovascularization, and in 1 patient because of central serous retinopathy. Seventy-six percent of the patients had visual acuities better than 20/25, and 24% had visual acuities between 20/63 and 20/40. All patients had clear media or only minimal cataract as assessed by slitlamp examination. Pigmentation of the irises appeared uniform. All test lesions were applied in the region of the lower temporal arcades in the macular area. The patients were followed up 2 hours, 1 day, 1 week, 1 month, 3 months, 6 months, and up to 1 year after photocoagulation. Mean follow-up time was 121 ± 103 days.

LASER

For setting the test lesions, a clinical prototype of an Nd:YLF laser was used. The wavelength was 527 nm. The pulse duration of a single pulse was 1.7 microseconds (full width half maximum). The laser was coupled in a slitlamp (Zeiss Instruments, Jena, Germany). During each treatment, the pulse shape was recorded by an oscilloscope and saved to a personal computer. The spot size of the laser beam, as analyzed by a beam analyzer (Speron LBA-100A; Polytech, Waldbronn, Germany), was about 160 µm in air. Each test lesion was created by a train of a different number of repetitive laser pulses and different energies. The numbers of laser spots applied were 100 and 500. The repetition rate was 500 Hz. Single-pulse energy, which varied between 20 and 130 µJ, was evaluated before each treatment period. On the basis of the fluorescein angiogram 1 day after photocoagulation, the threshold stimuli were applied on top and in the immediate area of these test lesions. Whether the patient recognized the threshold stimulus was recorded. A defect was noted if the patient did not recognize a stimulus and the retinal location of the defect corresponded to the postoperative (1 day) lesion in the angiogram. Thus, relative or absolute scotomas caused by photocoagulation could be analyzed.

MICROPERIMETRY

Of 179 test lesions, 73 were followed up by microperimetry up to 1 year. All 73 lesions showed disruption of the RPE barrier, as evaluated by fluorescein angiography. All fundus testing was performed with pupils dilated. A standard scanning laser ophthalmoscope (Rodenstock Instruments, Munich, Germany) was used for microperimetry. For retinal imaging, the infrared diode laser (780 nm) was used. Background luminescence was 0.1 candela (cd) per square meter. A helium-neon laser was used as stimulus. During the test procedure, a fixation cross was presented. Fixation and eye movements were controlled by manual fundus tracking with the use of a reference point on the retina. Before application of the test lesions, retinal sensitivity was evaluated in the test area where the laser lesions were intended to be applied. Microperimetry was performed monocularly.

Since no patient recognized a Goldmann I stimulus before photocoagulation, Goldmann II and III test stimuli were used for determining the threshold preoperatively. Ten patients were tested with a stimulus corresponding to Goldmann II and 7 patients with a Goldmann III stimulus. The threshold sensitivity values were defined as the minimal contrast at which a response was obtained. The just-noticeable contrast was recorded by a personal computer after the patient pressed the button. This threshold value was used for evaluating the test lesions in the follow-up period. On the basis of the fluorescein angiogram 1 day after photocoagulation, the threshold stimuli were applied on top and in the immediate area of these test lesions. Whether the patient recognized the threshold stimulus was recorded. A defect was noted if the patient did not recognize a stimulus and the retinal location of the defect corresponded to the postoperative (1 day) lesion in the angiogram. Thus, relative or absolute scotomas caused by photocoagulation could be analyzed.

These data were analyzed by a χ² test. P<.05 was considered significant. Initially, lesions produced by 500 pulses were investigated by microperimetry, and later, lesions produced by 100 pulses were studied. Maximum follow-up time of the lesions obtained by 500 pulses was 1 year, and that of the lesions obtained by 100 pulses was 6 months (Table).
### RESULTS

#### CASE 1

A 37-year-old patient was treated because of a history of blurring of vision for more than 3 months in his left eye. Uncorrected visual acuity was 20/32 and corrected visual acuity was 20/25 (+0.5, +0.25 \(30^\circ\)). Fundus examination showed central serous retinal detachment ([Figure 1, A](#)). Fluorescein angiography as well as indocyanine green angiography showed a spot of hyperfluorescence in the late phase ([Figure 1, B](#)). Central serous retinopathy was diagnosed. Microperimetry showed threshold sensitivity of 14 dB with a Goldmann III stimulus in the test area. Three test lesions (500 pulses, 1.7 microseconds, 500 Hz, 160 µm; 50, 70, and 100 µJ) were applied to the lower part of the macula; 2 of them produced an RPE barrier defect ([Figure 1, C](#)). After evaluation of the test lesions, 6 shots of a train of 500 laser pulses in the immediate neighborhood of the original hyperfluorescent point (1.7 microseconds, 70 µJ). Note the different appearance in hyperfluorescence between the focal point and the retinal pigment epithelial disruption caused by laser photoagulation (curved arrow). Two of 3 test exposures are visible by fluorescein angiography in the area of the temporal arcades (100 µJ [arrowhead] and 70 µJ [arrow]).

Leakage disappeared within 3 weeks ([Figure 2, A](#)). Microperimetry of the 2 test lesions showed relative defects after 1 day in both test lesions ([Figure 3, A](#)), only relative defects at the 100-µJ lesion after 1 week ([Figure 3, B](#)), only a small defect after 1 month ([Figure 3, C](#)), and no defect after 1 year ([Figure 3, D](#)). Uncorrected visual acuity remained stable over 1 year (20/20). Corrected visual acuity (+0.5, +0.25×\(30^\circ\)) was 20/16 after 1 year.

#### DOSIMETRY

[Figure 4](#) shows the fluorescein angiogram 1 day after several different test exposures were performed and the corresponding fundus photograph of a patient who was treated because of soft drusen. None of the lesions were visible as gray or white laser burns during photocoagulation. [Figure 5](#) summarizes the statistical results of all test lesions in a probit plot. Figure 5 gives the probability of producing an RPE defect that can be detected only by fluorescein angiography as a function of the energy per single pulse (microjoules) at various numbers of pulses. The effective dose to achieve a 50% probability of RPE damage is 60 µJ with 500 pulses. The probabilities of producing RPE disruption with a train of 100 pulses and with a train of 500 pulses were not significantly different, as Figure 5 shows.

#### MICROPERIMETRY

The threshold stimuli in the test area, as obtained before laser photoagulation, were 10.2 ± 7.5 dB with the

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### Number of Relative Defects as Detected by Microperimetry After Application of Test Exposures (160 µm, 527 nm)

in the Lower Macula in the Follow-up Period

<table>
<thead>
<tr>
<th>Follow-up</th>
<th>500 Pulses 70 µJ</th>
<th>500 Pulses 100 µJ</th>
<th>100 Pulses 70 µJ</th>
<th>100 Pulses 100 µJ</th>
<th>100 Pulses 130 µJ</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. Tested</td>
<td>No. of Defects</td>
<td>No. Tested</td>
<td>No. of Defects</td>
<td>No. Tested</td>
<td>No. of Defects</td>
</tr>
<tr>
<td>1 d</td>
<td>28</td>
<td>18</td>
<td>11</td>
<td>8</td>
<td></td>
</tr>
<tr>
<td>1 wk</td>
<td>25</td>
<td>7</td>
<td>10</td>
<td>8</td>
<td></td>
</tr>
<tr>
<td>1 mo</td>
<td>25</td>
<td>9</td>
<td>10</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td>3 mo</td>
<td>21</td>
<td>1</td>
<td>8</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>6 mo</td>
<td>18</td>
<td>2</td>
<td>6</td>
<td>2</td>
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<tr>
<td>1 y</td>
<td>2</td>
<td>0</td>
<td>3</td>
<td>0</td>
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*Retinal pigment epithelial effects were obtained by a train of 1.7-microsecond short laser pulses at a repetition rate of 500 Hz. NT indicates not tested.
Goldmann II stimulus and 10.7 dB ± 10.4 dB with the Goldmann III stimulus. Figure 4, C, shows an example of a microperimetry photograph after 1 day. Defects are detectable, for example, with 500 pulses and 100 µJ, but not with 100 pulses and 100 µJ. The Table summarizes the results for detecting relative defects after photocoagulation in all patients. There was no statistical difference in number of defects after photocoagulation between lesions tested with Goldmann II and III stimuli (P < .05). Therefore, they are listed together. After 1 day, defects were detected regularly after exposure with 500 pulses (70-100 µJ) in contrast to 100 pulses (70-100 µJ), where no defects were detected (P < .001). After photocoagulation with 500 pulses (70-100 µJ), the number of
lesions that could be detected by microperimetry was significantly lower after more than 3 months compared with the first month (P < .001). With 100 pulses (70-100 µJ), no significant additional defects were detected in the follow-up period.

**COMMENT**

The purpose of this study was to evaluate whether selectivity is possible in retinal photocoagulation. Dosimetry was used to establish the necessary power for producing lesions at the threshold of RPE damage. If the RPE is damaged, the tight junction of the RPE barrier will break up and fluorescein can pool from the choriocapillaris in the subretinal space. Thus, fluorescein angiography was used to detect a break of the RPE barrier, and it defines an exact end point. As in animal experiments, lesions at the threshold of RPE disruption were not visible by ophthalmoscopy during or 2 hours after photocoagulation.11 Ophthalmoscopic visibility of a white laser lesion always means a change in scattering properties of the retina caused by tissue coagulation. Since none of these lesions showed a white or gray ophthalmoscopic appearance, as recommended in photocoagulation of diabetic macular edema,19 the retinal damage produced by these mild RPE lesions is different from that with standard laser photocoagulation techniques. Dosimetry showed that energies used for producing these lesions are at or about 50% above the threshold of RPE damage. The threshold energy is the per-pulse energy necessary to achieve a 50% probability of RPE damage as detected by fluorescein angiography.

To investigate how selective these lesions are, microperimetry was performed directly on top of the laser lesions in the follow-up period up to 1 year. Histological examination after conventional laser photocoagulation shows initial thermal damage of the outer and inner nuclear layer and later scar tissue in the photocoagulated area.6,9 Therefore, it is not surprising that such lesions show absolute scotomas if they are tested by microperimetry. Our study tested only whether the threshold stimu-
lus would be recognized in the follow-up period. We did not investigate the absolute depth in the follow-up period, since we were only interested in whether selectivity is possible by this laser technique. Most of our patients had excellent visual acuity; 76% had visual acuity better than 20/25, and fixation was excellent. A stimulus of Goldmann II and III size is small enough to detect a defect produced by a 160-µm spot size. The actual sizes of the Goldmann II and III markers are about 60 µm and 120 µm on the retina, assuming a nodal point distance of 17 mm to the retina of a reduced schematic eye.

Most of our patients treated with a train of 500 repetitive laser pulses showed relative defects with 70- and 100-µJ single-pulse energy after the first day (up to 72%). These defects can disappear during the first week, as testing of the 70-µJ lesions showed, but most of the lesions produced by a train of 500 pulses can be detected during the first month. This is different from lesions produced by exposures with a train of 100 pulses, where most of the lesions could not be detected by microperimetry. The difference in percentage of defects after 1 day between 100 pulses and 500 pulses is highly significant (P < .001). The number of defects after 500 pulses that can be detected by microperimetry decreases statistically significantly after more than 3 months compared with the first month (P < .001). Obviously, most of the defects are relative rather than absolute, because otherwise no disappearance of these defects would be found. It is known that neural connecting and regrowth of ganglion cells can occur in the retina, and cross-talking between spatially adjacent image parts can also occur. However, this explanation seems unlikely, since the stimulus was tested directly on top of the laser lesion, the test stimulus was 53% to 75% smaller than the laser lesions, and the intensities of the stimuli used were at threshold. If the RPE barrier is disrupted after laser photocoagulation, fluid from the vessels of the choriocapillaris can lead to retinal edema. In animal experiments with selective RPE photocoagulation, intraretinal fluid accumulation has been shown. In theory, this could subsequently lead to a higher threshold at least during the first days. However, this explanation does not hold, since nearly no defects could be detected after application of a train of 100 repetitive laser pulses, where the RPE barrier is also severely damaged. With a train of 100 pulses of 70- and 100-µJ single-pulse energy, none showed any defects as tested by microperimetry.

One explanation for the relative defects in the early stage, which are most frequently found after 500 pulses, could be that in most situations during the early stage, direct and immediate damage of the outer segments of the photoreceptors occurs with 500 pulses. Tissue interaction of 1.7-microsecond laser pulses is thought to be primarily through a thermal mechanism, with an additional mechanical mechanism such as bubble formation around melanin granules, which has been shown with 200-nanosecond laser pulses of an Nd: YAG (532-nm) laser. This could lead to outer segment damage, eg, by compression. Outer segment damage could also occur with the average power of 1-second total exposure time, if 500 pulses at 500 Hz are applied. If photocoagulation is performed by a train of 500 pulses and 100-µJ single-pulse energy, some damage may also occur with the corresponding average power of 50 mW. Whatever the direct damage mechanism, in most cases the defect is obviously only a transient one, since the defects disappear in the follow-up period. It is known that outer segments regenerate as long as the inner segments are not damaged. The regeneration of a complete outer segment takes about 1 to 2 weeks in rats. This can explain the reduction in relative defects in the early stage, eg, with 70 µJ and 500 pulses. If the damage is more pronounced, but only parts of the photoreceptors are damaged in the irradiated area, the photoreceptors at the edge of a laser lesion tilt in, and subsequently the defect will be filled in the follow-up period. This regeneration mechanism is different from the healing process after photocoagulation with white laser burns. This could also explain the reduction of the relative defects as examined by microperimetry.

A train of 100 pulses (1.7 microseconds) with 70- and 100-µJ energy per pulse is obviously more appropriate to photocoagulate the RPE selectively, with sparing of the photoreceptors, since in most of the lesions investigated no immediate defects could be detected. In animal experiments, photocoagulation of the RPE with complete sparing of the outer segments has been demonstrated. Whether these areas where no defects could be detected by microperimetry correspond to such lesions cannot be answered definitively. The use of a smaller Goldmann I stimulus is not possible, since no patient recognized such a small stimulus in this macula region, even if the retina was healthy. Nevertheless, retinal exposures with 100 repetitive pulses and appropriate energy represent laser lesions that are different from conventional photocoagulation burns. Whether complete sparing of the outer segments is really necessary is difficult to answer. If the defects disappear in the follow-up period, this may not be necessary. However, our patients represent a group of patients with clear media. Therefore, in patients with opaque media such as cataract, a broader therapeutic range in selective photocoagulation would be desirable. The therapeutic range is obviously smaller with 500 pulses than with 100 pulses.

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REFERENCES


