THE IMPACT OF PULSE DURATION AND BURN GRADE ON SIZE OF RETINAL PHOTOCOAGULATION LESION

Implications for Pattern Density

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Purpose: Shorter pulses used in pattern scanning photocoagulation (10–20 milliseconds [ms]) tend to produce lighter and smaller lesions than the Early Treatment Diabetic Retinopathy Study standard 100-ms exposures. Smaller lesions result in fewer complications but may potentially reduce clinical efficacy. It is worthwhile to reevaluate existing standards for the number and size of lesions needed.

Methods: The width of the coagulated zone in patients undergoing retinal photocoagulation was measured using optical coherence tomography. Lesions of ''moderate,'' ''light,'' and ''barely visible'' clinical grades were compared for 100, 200, and 400 μm spot sizes and pulse durations of 20 ms and 100 ms.

Results: To maintain the same total area as in 1,000 standard burns (100 ms, moderate) with a 400-μm beam, a larger number of 20-ms lesions are required: 1,464, 1,979, and 3,520 for moderate, light, and barely visible grades, respectively. Because of stronger relative effect of heat diffusion with a smaller beam, with 200 μm this ratio increases: 1,932, 2,783, and 5,017 lesions of 20 ms with moderate, light, and barely visible grades correspond to the area of 1,000 standard burns.

Conclusion: A simple formula is derived for calculation of the required spot spacing in the laser pattern for panretinal photocoagulation with various laser parameters to maintain the same total coagulated area.

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The Diabetic Retinopathy Study and the Early Treatment Diabetic Retinopathy Study (ETDRS) established retinal photocoagulation (PRP) as an effective treatment for diabetic retinopathy.[1,2] Ocular neovascular disease and retinal vascular leakage result from angiogenic factors produced in response to retinal inflammation and ischemia. While the exact mechanisms of laser treatment are unknown, one working assumption is that panretinal photocoagulation reduces ischemia and decreases the production of angiogenic factors in the poorly perfused portions of the retina by lowering the metabolic load because of killing of a fraction of retinal cells.[3–6] Photoreceptors are the most numerous and metabolically active cells in the retina, with a large number of mitochondria, having high oxygen consumption. The cells of the inner nuclear layer and the ganglion cell layer represent $<10\%$ of the number of photoreceptors,[7–9] and thus, additional damage to the inner retina is unlikely to significantly improve clinical efficacy. After a laser burn, the photoreceptor layer is partially replaced by glial tissue.[10] This tissue has fewer mitochondria and therefore lowers overall oxygen demand.[11,12] Other theories include improvement of

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oxygenation and metabolic transport between choroid and retina by creating photoreceptor-free glial ''windows'' and stimulation of retinal pigment epithelial and choroidal cells by thermal stress.[13] With all these mechanisms, the clinical effect is likely to be proportional to the total treated area.

Conventional retinal photocoagulation based on the ETDRS standards is typically performed with a 514-nm or 532-nm laser using exposure durations from 50 milliseconds (ms) to 200 ms and spot sizes ranging from 100 μm to 500 μm.[14,15] Initially, rather intense retinal lesions were applied, with thermal damage affecting not only photoreceptors but also often extending into the inner retina. Over time, there has been a tendency to apply more moderate lesions in an attempt to limit damage to the ganglion cell layer and nerve fiber layer. A new method of retinal photocoagulation (PASCAL) has recently been introduced, in which patterns of multiple spots are applied using a scanning laser, with shorter pulse durations in the range of 10 ms to 30 ms.[16] Because heat diffusion with shorter exposures is decreased, these lesions tend to be lighter and smaller than conventional ones.[17,18]

It has been shown in preclinical studies that the size of the retinal lesion is affected not only by selection of the laser beam diameter and type of contact lens but also by pulse duration, power, and intensity (clinical grade) of the lesion.[17] These results have been confirmed in patients undergoing panretinal photocoagulation for proliferative diabetic retinopathy, using fundus autofluorescence and optical coherence tomography (OCT), demonstrating reduction in the width of 20-ms burns by 35% compared with 100-ms exposures.[19]

Retinal photocoagulation with shorter pulses has been shown to be effective in selected smaller series[18–20]; however, its efficacy has not been compared directly with conventional pulse duration used in the Diabetic Retinopathy Study or ETDRS for a large number of patients.[1,2] Studies of diabetic retinopathy patients in the United Kingdom correlating the regression rate of neovascularization with the coagulated area of the retina have shown a more complete and rapid regression in patients with greater areas of photocoagulation.[21] Similar correlation has been shown in treatment of rubeosis iridis: rubeosis regressed in 70.4% of eyes receiving full-scatter (1,200–1,600 spots) photocoagulation versus 37.5% of those receiving mild-scatter PRP (400–650 spots).[22]

However, no clear correlation of the treated area with clinical efficacy has been seen in the ETDRS[2] when patients with varying degrees of nonproliferative diabetic retinopathy with or without macular edema were treated with either mild or full scatter. Patients with macular edema and less severe retinopathy did not show greater degrees of severe visual loss when treated with early mild scatter compared with those receiving early full scatter, both groups accompanied by focal treatment for macular edema. Patients receiving mild scatter showed equal or slightly lower moderate visual loss compared with those with a full scatter and also appeared to have a lower rate of development of paracentral scotomata (20% vs. 34%).

To compare therapeutic benefits and complications profile of the lighter lesions with standard ones in various clinical conditions, larger trials would likely be required. Therefore, it may be important to estimate an appropriate number of lesions for the desired laser settings to coagulate the same total retinal surface area, assuming comparable coverage is desired. Using OCT, we measured the sizes of the retinal coagulation zone with various laser settings in patients treated with panretinal photocoagulation for diabetic retinopathy. Based on these results, we describe below a simple geometric calculation of the required number of lesions for various laser spot sizes, contact lenses, and clinical grades to maintain the total coagulated area as in the earlier ETDRS standards. This calculation does not take into account the lesion thickness and consequent volumetric changes.

Methods

Lesion size depends not only on beam diameter but also on pulse duration and its clinical grade.[17] Using spectral-domain OCT (Spectralis, Heidelberg Engineering, Heidelberg, Germany), we measured the width of the coagulated zone in patients treated with retinal photocoagulation within 1 hour of the procedure. Delay between the laser treatment and the OCT imaging varied from 10 minutes to 60 minutes, with an average of 20 minutes. Forty lesions of the same treatment parameters were averaged: 4 lesions per patient in 10 patients. All patients presented with diabetic retinopathy and were scheduled for panretinal photocoagulation as part of their standard care at the Department of Ophthalmology, Federal University of Sao Paolo, Brazil. The study was conducted according to the Declaration of Helsinki, and the protocol was approved by the Federal University of Sao Paulo Ethics and Research Committee, and patients gave informed consent.

Laser photocoagulation was performed using the PASCAL system, according to physician preference and the clinical presentation. With the aerial beam sizes of 100, 200, and 400 μm and Area Centralis contact lens (laser spot magnification $\times$0.94; Volk Optical Inc., Mentor, OH), the retinal beam size was

94, 188, and 376 μm, respectively. A standard photocoagulation protocol using single exposures of 100 ms producing lesions of ''moderate'' clinical grade was compared with PASCAL 20-ms exposures producing ''moderate,'' ''light,'' and ''barely visible'' lesions. Laser lesions were first titrated peripheral to the retinal arcades to a moderate white–gray lesion. Then, the same power was used to create 2 moderate 100-ms lesions temporal to the macula beyond 3.5 mm from the fovea, and the same titration was performed for 20-ms lesions with the same white–gray pattern. Retinal laser photocoagulation has an inherent subjectivity associated with the determination of the clinical thresholds, and since the Diabetic Retinopathy Study and ETDRS, the ideal laser burn for scatter PRP has been classified as a moderate white–gray lesion or Grade 2 in a 4-category classification.[1] To decrease further subjectivity, we reduced the power from the moderate burn level by fixed amount: 25% and 50% to achieve light and barely visible lesions, respectively. Similar methods were used to create 100-μm burns for focal treatment of macular edema, where clinically indicated.

Results

Figure 1 demonstrates the typical appearance of the various retinal lesions produced with a 400-μm aerial beam size. In addition to the changes in the photoreceptor layer visible in all OCT images, the moderate-grade lesions of 100 ms and, to less extent, of 20 ms show some changes (dark band) in the inner retina (pointed by the arrows in Figure 1, A and B). Table 1 summarizes the ratio of the width of the coagulated zone to the retinal beam diameter. Moderate lesions were significantly larger than the beam size. Thermal spread of the lesion had more significant relative effect on smaller spots. The ratio of the lesion width to beam diameter increased from 1.39 for 400-μm spot size to 3.81 for 100-μm beam. With 20-ms pulses, the thermal spread was reduced, but moderate burns were still larger than the beam diameter. For the 20-ms moderate burns, the ratio varied from 1.15 with 400-μm beam to 2.5 with 100-μm spot. The barely visible burns were smaller than the beam size, varying from 0.99 for a 100-ms 400-μm beam to 0.74 with a 20-ms 400-μm beam and to 0.94 with a 20-ms 200-μm beam. The minimum power of 100 mW in PASCAL laser was too high for reliably producing barely visible–grade lesions with 100-μm spots using 100-ms and 20-ms exposures.

The area of the coagulated zone is proportional to the square of its diameter. Therefore, to maintain the same total coagulated area as in 1,000 standard burns with a 400-μm beam (100 ms, moderate grade), one needs to apply a larger number of 20-ms lesions with the same beam diameter: 1,464, 1,979, and 3,520 of the moderate, light, and barely visible grades, respectively. Lesion size also decreases with lighter clinical grades using 100-ms pulses, as shown in Table 1, but to a smaller extent than with shorter pulses. Because of the stronger effect of heat diffusion with smaller beam sizes, with a 200-μm beam, this

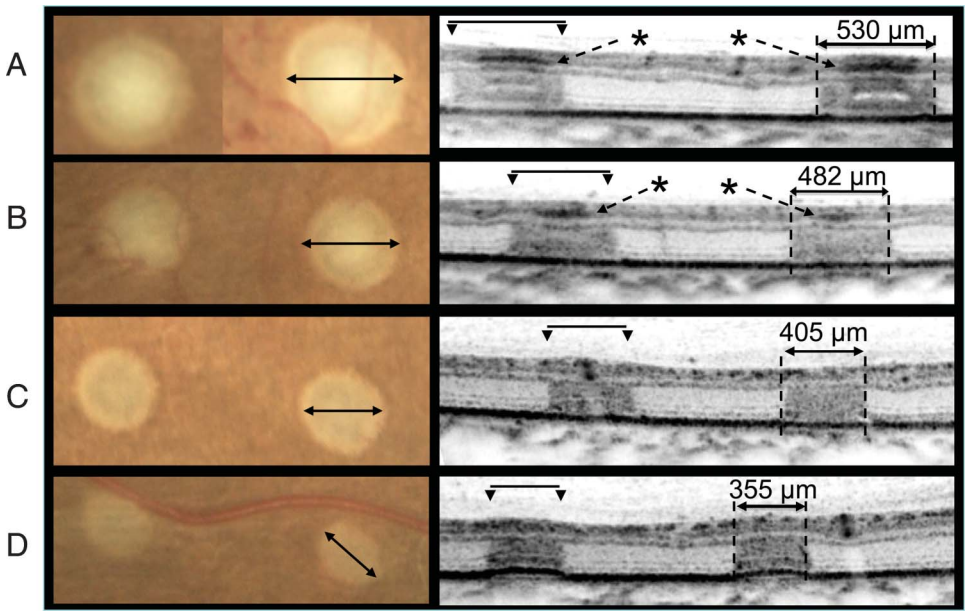

Fig. 1. Typical OCT appearance of the acute retinal lesions produced with a 400-μm aerial beam size using Area Centralis contact lens. Solid arrows show the width of the coagulated zone, with numbers in micrometers. **A**. 100 ms, moderate grade. Dash arrows (*) point at the dark bands indicating some effect in the inner retina. **B**. 20 ms, moderate grade. **C**. 20 ms, light grade. **D**. 20 ms, barely visible grade.

Table 1. Ratio of the Lesion Width to the Retinal Beam Size for Various Pulse Durations and Clinical Grades

		Moderate		Light		Barely Visible	
Beam in Air (μm)	Beam on Retina (μm)	100 ms	20 ms	100 ms	20 ms	100 ms	20 ms
100	94	3.81 ± 0.98	2.50 ± 0.30	—	2.08 ± 0.24	—	—
200	188	2.08 ± 0.22	1.49 ± 0.09	—	1.24 ± 0.08	—	0.93 ± 0.08
400	376	1.39 ± 0.08	1.15 ± 0.07	1.19 ± 0.11	0.99 ± 0.09	0.99 ± 0.08	0.74 ± 0.12

Coagulation was performed with Area Centralis lens (magnification ×0.94). Error is calculated as 1 standard deviation.

ratio becomes larger: for every 1,000 standard burns (200 μm, 100 ms, moderate grade), it requires 1,932, 2,783, and 5,017 exposures of 20 ms in duration with the moderate, light, and barely visible grades, respectively.

A diagram of a pattern of 4 laser spots is shown in Figure 2, where P is the period of the laser pattern, D_L is the diameter of the laser spot on the retina, D_R is the diameter of the retinal lesion, S_L is the relative spacing between laser spots (edge-to-edge, in units of beam diameter), and S_R is the resulting relative spacing between the retinal lesions (in units of lesion diameter).

According to ETDRS recommendations, full-scatter PRP typically involves spacing the retinal lesions by half of the lesion diameter apart and mild scatter by one diameter.[2] The fraction of the coagulated area in the retina is determined by the ratio of the area of a lesion ($\pi D_R^2/4$) to the area of one period in the pattern (P^2): $F = \pi D_R^2/4P^2$ (Figure 2). Because $P = D_R\ (1 + S_R)$, $F = \pi/4\ (1 + S_R)^2$. For example, mild scatter ($S_R = 1$) involves coagulation of approximately 20% of the retina, while full scatter ($S_R = 0.5$) involves up to 34% of the retina in the treatment zone.

For planning of a semiautomated pattern application, one needs to relate spacing between the laser spots (S_L) to the resulting spacing between the lesions (S_R). The pattern period can be expressed as a function of both parameters: $P = D_R\ (1 + S_R) = D_L\ (1 + S_L)$. Relating the resulting lesion size to a beam diameter: $D_R = D_L \cdot g$ (coefficient g is a function of the lesion grade, pulse duration, and retinal beam size, shown for some parameters in Table 1) allows expressing the

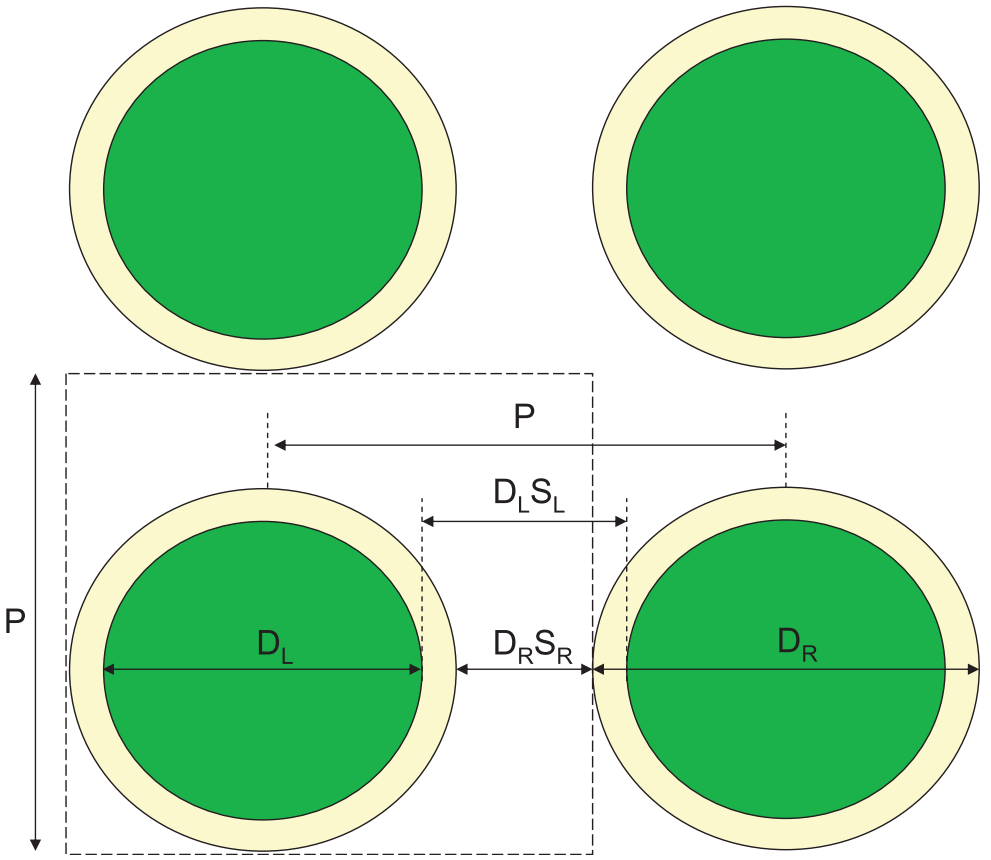

Fig. 2. Diagram of a laser pattern on the retina including four spots. Period of the pattern is P, laser spot diameter D_L, retinal lesion diameter D_R, spacing between the lesions is $D_R \cdot S_R$, and spacing between laser spots is $D_L \cdot S_L$.

spacing between the laser spots as the following: $S_L = g\ (1 + S_R) - 1$. For example, for light 20-ms lesions with a 400-μm beam, g is very close to 1; therefore, the beam spacing is equal to the resulting lesion spacing. A spacing of barely visible lesions ($g = 0.74$) should be much tighter, if a comparable area is to be coagulated: $S_L = 0.11$ instead of 0.5 diameter for a full scatter and $S_L = 0.48$ instead of 1 for a mild scatter.

The retinal beam size is scaled reciprocal to the lens magnification factor, that is, if the lens magnifies retinal image by a factor of 2, the beam size on the retina is demagnified by the same amount. Table 2 lists the image magnification factor and, its reciprocal, the beam magnification factor (L) for the most common contact lenses. Taking into account magnification of the retinal beam size by a beam magnification factor L (Table 2), $D_L = L{\cdot}D$, where D is a laser beam diameter in the air: $P = L{\cdot}D{\cdot}(1 + S_L)$, the total number of required lesions can be calculated simply by dividing the total retinal area S_{ret} by the area of a unit period (P^2): $N = S_{ret}/P^2 = S_{ret}/(L{\cdot}D{\cdot}(1 + S_L))^2$. With an average eye diameter of 22 mm, the area posterior to the equator is $S_{ret} = 760$ mm^2 (the total retinal area is approximately 1,050 mm^2,[23] but its portion anterior to the equator is easily accessible only with an endoscope or scleral depression). Thus, the total number of lesions N can be calculated as a function of beam diameter in air D (in millimeters), lens magnification factor L, lesion grade factor g, and desired lesion spacing factor S_R as follows: $N_¶ = 760/(L{\cdot}D\ g{\cdot}(1 + S_R))^2$.

Table 2. Listof Ocular Contact Lenses and Their Magnifications in a Human Eye

Lens	Image Magnification	Laser Beam Magnification
Ocular Mainster Std*	0.95	1.05
Ocular Fundus Laser*	0.93	1.08
Ocular Karichoff Laser*	0.93	1.08
Ocular 3 Mirror Univ.*	0.93	1.08
Ocular Mainster Wide*	0.67	1.50
Ocular Mainster Ultra*	0.53	1.90
Ocular Mainster 165*	0.51	1.96
Rodenstock Panfundoscope†	0.67	1.50
Volk G-3 Gonio‡	1.06	0.94
Volk Area Centralis‡	1.06	0.94
Volk TransEquator‡	0.69	1.44
Volk SuperQuad 160‡	0.5	2.00
Volk QuadrAspheric‡	0.51	1.97
Volk HRWF‡	0.5	2.00
Goldmann 3 mirror‡	1.00	1.00

*Ocular Instruments Inc. Bellevue, WA.
†Rodenstock GmbH, München, Germany.
‡Volk Optical, Inc., Mentor, OH.

For example, with a beam in air of $D = 200$ μm (0.2 mm) and a lens magnification $L = 2$ (Volk SuperQuad 160, Volk Optical Inc., Mentor, OH), the retinal beam size will be $D_L = 400$ μm. Because for 20-ms light lesions $g \approx 1$, they will have the same diameter $D_R = g\ D_L = 400$ μm. Full scatter ($S_R = 0.5$) will have a period $P = D_R\ (1 + S_R) = 600$ μm, and thus, the number of lesions $N = S_{ret}/P^2 = 760/0.36 = 2{,}111$. With barely visible lesions ($g = 0.74$), the total number for a full scatter would be $N = 3{,}855$. With the same beam diameter, the corresponding number of 20-ms moderate lesions ($g = 1.15$) for a full scatter is $N = 1{,}596$. With the 100-ms moderate lesions ($g = 1.39$), the same area is covered by 1,093 spots.

With the assumption that the therapeutic benefic of PRP originates from the reduction in the number of photoreceptors, this study was focused on estimation of the total coagulated area. Over the years, intense laser scars may slowly expand (so-called atrophic creep),[24,25] leading to additional loss of photoreceptors. This process may contribute to additional reduction in the metabolic load over time. However, because patients typically respond to PRP within approximately 6 weeks, while the atrophic creep does not become noticeable for at least a year,[24] the amount of photoreceptors destroyed by PRP should suffice for a clinical benefit without relying on additional creep later on. However, it will be important to monitor the clinical benefits of photocoagulation with various levels of severity over extended period to assess potential long-term benefits of the atrophic creep.

Conclusions

Pattern scanning with shorter pulses allow for faster treatment with significantly reduced pain.[18,26,27] In lighter lesions, the thermal damage is better confined to the photoreceptor layer, resulting in better healing of the lesions and reduced scarring.[10] To settle the question of the therapeutic benefits and complications of lighter lesions versus the standard ones in various clinical conditions, clinical trials would be required. Results and calculations described in this article can help adjusting the required total coagulated area, the number of lesions, and pattern density.

Key words: laser, photocoagulation, diabetic retinopathy, panretinal photocoagulation, macular grid.

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