LONG-TERM SAFETY, HIGH-RESOLUTION IMAGING, AND TISSUE TEMPERATURE MODELING OF SUBVISIBLE DIODE MICROPULSE PHOTOCOAGULATION FOR RETINOVASCULAR MACULAR EDEMA

JEFFREY K. LUTTRULL, MD,* CHRISTOPHER SRAMEK, PHD,† DANIEL PALANKER, PHD,† CHARLES J. SPINK, MA,* DAVID C. MUSCH, PHD, MPH‡§

Purpose: To determine the long-term safety of high-density subvisible diode micropulse photocoagulation (810 nm), compare the clinical findings with computational modeling of tissue hyperthermia and to report results for a subset of eyes treated for diabetic macular edema (ME) documented pre- and postoperatively by spectral-domain optical coherence tomography.

Method: All eyes treated for ME from diabetic retinopathy (diabetic ME) and branch retinal vein occlusion between April 2000 and January 2010 were reviewed for subvisible diode micropulse laser-induced retinal damage. Therapeutic outcomes were reviewed for a subgroup treated for diabetic ME with pre- and postoperative spectral-domain optical coherence tomography. Laser-induced retinal thermal effects were modeled computationally using Arrhenius formalism.

Results: A total of 252 eyes (212 diabetic ME, 40 branch retinal vein occlusion) of 181 patients qualified. None of the 168 eyes treated at irradiance <350 W/cm^2 and 7 of 84 eyes at ≥ 590 W/cm^2 had retinal damage ($P = 0.0001$) (follow-up 3–120 months, median, 47). Sixty-two eyes of 48 patients treated for diabetic ME with pre- and postoperative spectral-domain optical coherence tomography with median 12 months follow-up had no retinal injury by infrared, red-free, or fundus autofluorescence photos; fluorescein angiography or indocyanine green angiography; or spectral-domain optical coherence tomography. Central foveal thickness ($P = 0.04$) and maximum macular thickness decreased ($P < 0.0001$). Modeling of retinal hyperthermia demonstrates that the sublethal clinical regimen corresponds to Arrhenius integral >0.05, while damage is likely to occur if it exceeds 1.

Conclusion: Subvisible diode micropulse can effectively treat retinovascular ME without laser-induced retinal damage, consistent with Arrhenius modeling of pulsed hyperthermia.

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Diabetic retinopathy (DR) is the leading cause of vision loss in persons aged <50 years in the developed world, and its prevalence is increasing.[1–4] Retinal photocoagulation has been the mainstay of treatment since the publication of the landmark Diabetic Retinopathy Study (DRS, 1976) and Early Treatment Diabetic Retinopathy Study (ETDRS, 1982).[5,6]

Despite remarkable advancements in our understanding of the pathophysiology of DR, the advent of new pharmacologic agents, revolutionary diagnostic imaging, and improvements in the surgical management of DR, little has changed in the protocols of photocoagulation for the complications of DR since the DRS and ETDRS.[7–10] Controlled laser-induced thermal retinal destruction remains the standard of care. However, this same thermal retinal destruction inherent in conventional photocoagulation is the single cause of all laser-induced adverse treatment effects and complications.[11] These well-known effects include immediate and late visual acuity loss, inflammation, scotoma, visual field loss, nyctalopia, choroidal neovascularization, preretinal and subretinal fibrosis, laser scar expansion, tractional retinal detachment, vitreous hemorrhage, choroidal detachment, acute glaucoma, macular edema (ME) or exacerbation of preexisting ME, pain, and loss of light-sensitive retinal ganglion

cells, which may cause sleep disturbance.[12] Yet, the evidence that thermal retinal destruction is necessary to achieve the therapeutic benefits of treatment remains entirely circumstantial. In the decades since the DRS and ETDRS, a number of investigators,[13–22] seeking to minimize post-retinal photocoagulation (RPC) adverse events, have reported effective treatment of DR complications with reduced laser treatment intensity.

In addition to reduced-intensity photocoagulation, several alternative approaches to minimize damage to the retina have been investigated. In selective treatment of the retinal pigment epithelium (RPE; selective retina treatment), damage is confined to the RPE layer with microsecond-duration pulses, thereby sparing photoreceptors and the inner retina.[18] Although damage is initially visible with fluorescein angiography, RPE proliferation and migration restore continuity of the RPE layer after a few days.[23–25] Selective retina treatment has been shown to be clinically effective in applications to idiopathic central serous choroidopathy and diabetic macular edema (DME).[20–26]

Transpupillary thermotherapy, using long (60 seconds) exposures of near-infrared 810-nm laser radiation with a large (1.2–3 mm) spot, has been shown to slow down the progression of exudation and choroidal neovascularization in AMD in several studies. However, transpupillary thermotherapy has not become widely used for treatment of retinal vascular disease because of questions about its safety and efficacy.[27–31]

In the early 1990s, Pankratov et al[32] described a new repetitive micropulsed laser modality leading to studies of selective photothermal therapy of the RPE. Early applications of the micropulsed diode laser used high irradiances, producing visible thermal damage as a treatment end point. The persistently destructive nature of the treatment required continued application of conventional grid and modified ETDRS-style techniques.[15–22,32–43]

Recently, a new clinical approach to the use of the micropulsed 810-nm diode laser was reported, described as ''low-intensity/high-density'' subthreshold (subvisible) diode micropulse (SDM) photocoagulation.[44–46] In this approach, treatment of retinal vascular disease is performed with the express goal of avoiding any laser-induced retinal damage (''invisible'' photocoagulation). Complete avoidance of thermal retinal injury from such ''low-intensity'' exposures permitted a modification of treatment technique aimed at maximizing clinical effectiveness: complete and confluent (high-density) coverage of the diseased retina, such as the areas of macular thickening constituting DME (previously precluded by the retinal damage produced by conventional and other retina-damaging treatments). In pilot studies, SDM was reported to be effective for the treatment of DME and proliferative diabetic retinopathy without adverse treatment effects, complications, or any evidence of laser-induced retinal damage.[44–46] Subsequent randomized clinical trials corroborated these findings for DME, observing clinical efficacy comparable with conventional photocoagulation without laser-induced retinal damage.[47–49]

The previous studies describing SDM for DME report relatively brief mean follow-up periods of $\leq$1 year.[41–46] Recognizing the unconventional nature of SDM, the absence of laser-induced retinal lesions at 1 year may not necessarily preclude the possibility of latent retinal damage with associated adverse effects becoming manifest later. Therefore, in this study we 1) assess the long-term safety of SDM for the treatment of ME because of DME and branch retinal vein occlusion. We also 2) assess the safety and effectiveness of SDM for DME in eyes evaluated pre- and postoperatively by the more recently available Heidelberg Spectralis (HS) high-resolution retinal imaging system; and 3) compare the clinical findings with calculations of laser-induced temperature rise and associated tissue effects.[30]

Methods

With approval of an Institutional Review Board, the records of all patients in a private vitreoretinal subspecialty practice who had undergone SDM for the primary diagnoses of DME and ME complicating branch retinal vein occlusion were reviewed. This included all eyes undergoing macular photocoagulation for these diagnoses from April 2000 through January 2010. Each record was examined for any indication of laser-induced retinal injury after SDM. Inclusion criteria were availability of pre- and postoperative fundus autofluorescence photographs (FAF) and/or intravenous fundus fluorescein angiography (FFA) and postoperative follow-up of at least 3 months. Exclusion criteria included any other macular disease or imaging failure that precluded determination of possible SDM-associated retinal injury. The clinical results of the eyes treated with SDM for DME from April 2000 to February 2003 have been previously reported in a pilot study.[46] As optical coherence tomography (OCT) is the most useful clinical tool for

From the *Private practice, Ventura, California; †Department of Ophthalmology, School of Medicine and Hansen Experimental Physics Laboratory, Stanford University, Palo Alto, California; and Departments of ‡Ophthalmology & Visual Sciences and §Epidemiology, The University of Michigan, Ann Arbor, Michigan.

J. K. Luttrull, C. Sramek, D. Palanker, and C. J. Spink authors have no financial interest or conflicts of interest.. D. C. Musch has worked as a consultant with Iridex Corporation, Mountain View, CA.

Reprint requests: Jeffrey K. Luttrull, MD, 3160 Telegraph Road, Suite 230, Ventura, CA 93003; e-mail: jkluttrull@aol.com

assessing DME, and the long time-window of the current study spanned the pre-OCT, time-domain OCT and spectral-domain optical coherence tomography (SD-OCT) eras, we did not attempt to analyze the effectiveness of SDM treatment in the whole group because of the difficulty of reconciling such heterogeneous clinical outcome data.

However, a subgroup of eyes was identified that were treated with SDM for DME and had pre- and postoperative high-resolution retinal imaging with the HS (Heidelberg Engineering, Heidelberg, Germany). For this group, in addition to examining the records for evidence of SDM-induced retinal injury, uniform pre- and postoperative testing allowed for an assessment of the treatment effect. The indices of treatment outcome included best-corrected Snellen visual acuity, central foveal thickness (CFT), and maximum macular thickness (MMT) within 2 mm of the foveal center preoperatively and at the last recorded postoperative visit. The retinal thickness measurements used were those calculated by the HS with manual verification of correct automated tissue-plane identification. Additional exclusion criteria from this arm of the study included any vitreous or anterior segment surgery within 6 months of study entry or during the course of the study and other macular disease such as advanced age-related macular degeneration, epiretinal membrane or vitreoretinal interface disease, or pseudophakic cystoid ME. Use of augmentary pharmacologic therapy, such as local depot triamcinolone acetonide and/or intravitreal vascular endothelial growth factor inhibitors in addition to SDM was not exclusionary, nor was a history of SDM at least 3 months before study entry. Eyes that had undergone conventional macular photocoagulation before SDM were excluded. However, previous, concurrent, or subsequent SDM panretinal photocoagulation for proliferative diabetic retinopathy was not an exclusion criterion. The presence of SDM-induced retinal injury was determined by HS imaging including infrared, red-free, and FAF fundus photography, FFA, indocyanine green angiography, and SD-OCT imaging. The risk of SDM-induced retinal injury and treatment effectiveness were tested for statistical significance using appropriate statistical tests for categoric or continuous outcomes, and an alpha probability of 0.05 was used to judge significance of the result.

After informed consent, SDM was administered in all eyes with topical anesthesia using an 810-nm diode laser operating at burst frequency of 500 Hz, with micropulse durations from 0.1 milliseconds (ms) to 0.3 ms, corresponding to duty cycles (DCs) of 5% to 15%, respectively. In eyes treated before the availability of OCT, confluent treatment of all areas of macular thickening visible by contact lens biomicroscopy was performed, excluding the central fovea. With availability of OCT, treatment was directed by the OCT depiction of the location and extent of macular thickening displayed beside the patient at the time of treatment. Retinal microaneurysms were not treated focally. Burst (pulse) duration varied from 100 ms to 300 ms and peak power from 0.78 W to 0.95 W. Aerial spot size was 125 μm, which with the Mainster macular contact lens used (laser magnification factor $\times$1.05) corresponds to a retinal spot of 131 μm. All eyes included in the subgroup with pre- and postoperative HS analysis were treated uniformly with the following standardized laser parameters: 5% DC, 300-ms burst duration, 131-μm retinal spot, and 0.95-W power.

Temperature rise calculations and modeling of thermal retinal damage were performed for the SDM treatment parameters used in all eyes to determine correspondence with the clinically observed findings. A finite-element model of 810-nm laser heating and damage of the human retina was constructed in the COMSOL Multiphysics computational package (Version 3.5; COMSOL, Inc, Burlington, MA). This coupled an axisymmetric heat conduction model with a thermal damage model,[50] similar to homogeneous absorption models described previously.[51–53] Layer thicknesses and absorption coefficients from a recently described human thermal damage model were used[54]; this model was based on previous study estimating chorioretinal temperature distribution during the diode laser treatment.[55]

Thermal cellular damage produced by millisecond exposures can be described with first-order reaction kinetics (Arrhenius law). Such description assumes the absence of cellular repair and is parameterized by an activation energy corresponding to the denaturation of a single critical molecular component.[50] The decrease in concentration of this component is quantified by the integral of the exponential temperature-dependent reaction rate, the Arrhenius integral (Ω). The criterion for cell viability is then estimated as a threshold decrease in concentration of that molecular component, and the Arrhenius integral is typically normalized to 1 at this threshold.

Temperature rise and Arrhenius damage integral at the beam center was calculated for 125-μm aerial beam diameter. The following SDM treatment parameters were applied: burst duration 150 ms and 300 ms, repetition rate 500 Hz, DC 5% to 15%, and laser peak power 800 mW to 950 mW. To assess the risk of thermal injury in the hyperpigmented areas, calculations were also performed with the absorption coefficients in the RPE and choroid increased by 50%. For comparison, calculations were performed for continuous-wave 810-nm exposures of the same duration and same average power as the SDM bursts.

Results

Retinal Burn Risk

Three hundred and seventy consecutive eyes of 274 patients underwent SDM for ME because of DR or branch retinal vein occlusion from April 2000 to January 2010. Sixty-nine patients (89 eyes) were deceased or otherwise lost to follow-up without records available for review. Twenty-nine eyes of 24 patients were excluded because of inadequate pre- or postoperative FAF or FFA documentation or other exclusionary findings. The remaining 252 eyes (212 DME, 40 branch retinal vein occlusion) of 181 patients treated by SDM for ME met inclusion criteria. Follow-up ranged from 3 months to 120 months (median, 47 months). The length of time from SDM treatment to the last postoperative imaging ranged from 3 months to 120 months (median, 40 months) for FAF photography and from 3 months to 120 months (median, 40 months) for FFA (Table 1). Increased probability of retinal damage corresponded to higher retinal irradiance. Laser-induced retinal damage was found in 0% (0 of 168) of eyes with SDM at a 5% DC (irradiance <350 W/cm^2; Table 2) and in 8% (7 of 84) of eyes treated with a 10% or 15% DC (irradiance >590 W/cm^2; Table 3) ($P = 0.0001$, chi-square test; Figure 1).

Subvisible Diode Micropulse–Treated Eyes with Inadvertent Retinal Burns

In the 7 eyes with laser-induced burns, the retinal damage consisting of biomicroscopically visible multifocal macular pigment clumping, hypertrophy, and atrophy was noted clinically on the first postoperative visit (6–12 weeks postoperatively), and even more evident by FAF and/or FFA. In three eyes of two patients, suspicion of inadvertent threshold retinal burns was noted at the time of treatment. Six of the 7 eyes manifesting SDM-induced retinal burns were darkly pigmented. At last examination, 5 eyes had improved by $\geq$2 Snellen lines and 2 eyes were unchanged. Follow-up of these 7 eyes ranged from 4 months to 81 months (median, 71 months). None of the 245 eyes without retinal burns noted on the first postoperative visit developed later retinal lesions.

Eyes Documented by the Heidelberg Spectralis Before and After Subvisible Diode Micropulse for Diabetic Macular Edema

The subgroup of 62 consecutive eyes of 48 patients treated for DME from November 2007 through January 2010 with pre- and postoperative HS imaging had no laser-induced retinal injury by infrared, red-free (pigment disturbance or chorioretinal scarring) or FAF (loss of autofluorescence) photos; fluorescein angiography (window defect hyperfluorescence and/or focal leakage or late staining of the RPE) or indocyanine green angiography (focal hyper- or hypofluorescence); or SD-OCT (focal disruption, discontinuity or scarring of any retinal layers) (Table 2). Follow-up ranged from 3 months to 24 months (median, 12 months). Because of deliberate selection bias by the surgeon, eyes undergoing SDM with drug therapy differed from eyes undergoing SDM only in many baseline characteristics (Table 4), including worse preoperative best-corrected visual acuity ($P < 0.0001$), greater CFT ($P = 0.02$), greater MMT ($P < 0.0001$), and presence of persistent or recurrent DME ($P = 0.0017$), but did not differ in subject age or follow-up (Table 4).

Overall reductions were noted in CFT ($P = 0.04$) and MMT ($P < 0.0001$). Of the 24 eyes of 20 patients receiving SDM combination therapy for DME, 17 of 24 eyes (71%) improved and 7 (29%) worsened. The change in CFT was not significant ($P = 0.16$), whereas the MMT improved significantly ($P = 0.0035$). Of the 38 eyes of 28 patients with DME treated with SDM alone, 34 eyes (89.5%) improved and 4 (10.5%)

Table 1. Statistics of the Long-Term Follow-up and Postoperative Imaging of Eyes Treated for ME Because of DR and Branch Retinal Vein Occlusion from April 2000 to January 2010

	Color	IR	RF	FAF	FFA	IGCA
Total number of patients	181	109	181	109	149	71
Total number of eyes	252	154	252	153	212	107
Median F/U	41	40	36	40	40	45
F/U Min	3	3	3	3	3	3
F/U Max	83	120	120	120	115	115

F/U, months follow-up after SDM; Min, minimum; Max, Maximum; color, color fundus photography; IR, HS infrared fundus photograph; RF, HS red-free fundus photograph; FAF, HS FAF photograph; FFA, film or HS digital; ICGA, HS digital indocyanine green angiogram.

Table 2. SDM Laser Parameters of Eyes Without Laser-Induced Retinal Damage

Peak Power (Watts)	Retinal Spot Size (μm)*	DC	Pulse Duration (ms)	Average Irradiance (W/cm^2)
0.95	131	5%	300	351

Average retinal irradiance is calculated as an average laser power (peak power multiplied by DC) divided by the irradiated area on the retina.

*Produced by using a 125 aerial spot projected through a Mainster macular contact lens, laser magnification factor of $\times$1.05 (Ocular Instruments, Mentor, OH).

Table 3. SDM Laser Parameters and Patient Characteristics of the Seven Eyes with Laser-Induced Retinal Damage

Patient	Retinal Spot Size* (μm)	DC (%)	Peak Power (Watts)	Pulse Duration (ms)	Average Irradiance (W/cm^2)	Race
1	131	10	0.78	150	577	Hispanic
2	131	15	0.82	150	910	Hispanic
3	131	15	0.83	150	921	Asian
4	131	15	0.80	150	887	White
5	131	10	0.80	100	592	Hispanic
6R	131	15	0.80	150	887	Asian
6L	131	15	0.80	150	887	Asian

*Produced by using a 125 aerial spot projected through a Mainster macular contact lens, laser magnification factor of $\times$1.05 (Ocular Instruments, Mentor, OH).

worsened. Central foveal thickness ($P = 0.0313$) and MMT ($P < 0.0001$) both improved (Table 5). Visual acuity was unchanged overall and in both the SDM-alone and combination therapy subgroups. When best-corrected visual acuity, CFT, and MMT changes were categorized into improved/unchanged/worsened strata (for visual acuity, >2-line change in Snellen acuity; for CFT and MMT, change in retinal thickness measured by SD-OCT), there were no significant differences between SDM-alone versus SDM combination therapy groups (Table 6).

Tissue Temperature

The calculated temperature rise at the RPE in the center of the laser beam is shown in Figure 2A for the following SDM parameters: 131-μm retinal spot size, 300-ms burst, 5% DC, 950-mW peak power. The temperature produced by the laser oscillates with the rise time equal to 0.1-ms micropulse duration, and repetition period of 2 ms, reaching a maximum rise of 14°C over baseline of 37°C. Average temperature rise over a single oscillation at the end of the pulse is 8°C, rising to 45°C, equivalent to the temperature rise for a continuous-wave exposure with the same average power (47.5 mW).

The corresponding axial profile of the Arrhenius integral, shown in Figure 2B, exhibits a higher value in the RPE, indicating selective thermal effect to this layer. Peak value of Arrhenius integral, $\Omega_{SDM} = 0.08$ is well below the lethal damage threshold level of 1 ($\Omega_{SDM} = 1.0$). Increasing the absorption coefficient of the RPE and choroidal layers to model a hyperpigmented area raises the value to $\Omega_{SDM} = 0.39$. This is consistent with the lack of visible damage observed clinically with these parameters.

Figure 3 illustrates the temperature and Arrhenius traces with more intense SDM parameters: 131-μm retinal spot size, 150-ms burst, 10% DC, 800-mW peak power. The peak temperatures in this case (Figure 3A) are significantly higher (57°C), resulting in an Arrhenius value closer to 1 ($\Omega_{SDM} = 0.27$). Peak temperature for continuous-wave exposure of the same average power (80 mW) was again equivalent to the average over a single cycle at the end of the SDM burst (50°C). Increasing the absorption coefficient by 50% with SDM leads to peak Arrhenius value >1 ($\Omega_{SDM} = 3.8$) (Figure 3B). The Arrhenius integral in the photoreceptor outer segments and choroid is also significantly >1, indicating a high likelihood of damage not only to RPE but also to photoreceptors. Increasing the DC to 15% raised peak temperatures with SDM even further, resulting in an Arrhenius value >1 in the case of normal pigmentation ($\Omega_{SDM} = 3.9$), and even higher assuming hyperpigmentation ($\Omega_{SDM} = 167$). Visible lesions are thus expected in highly pigmented eyes, which is consistent with the clinically observed higher burn risk associated with treatment using these parameters.

Discussion

Two pivotal clinical trials, the DRS and ETDRS, established not only the safety and efficacy of retinal photocoagulation for treatment of the complications of DR but also the standard of care about the technique of retinal laser application. This "conventional" technique used the argon laser to produce a visible treatment end point, constituting suprathreshold photocoagulation, which resulted in chorioretinal scarring. Despite the inherent adverse effects of thermal retinal destruction, the substantial benefits of conventional photocoagulation, not only supported its use but also suggested by implication that laser-induced thermal retinal damage was required for the therapeutic effect.[11,52,53,56] The DRS and ETDRS investigators also observed that, within limits, the therapeutic effect increased with the treatment density and that adverse effects increased with treatment intensity.[5,6,57–62]. Using these principles, variations on conventional photocoagulation have been studied aiming at improvement in both the safety and effectiveness of photocoagulation.[13–16] Principally, photocoagulation has been modified by reducing treatment intensity.[60] However, visible laser-induced retinal damage continued to be

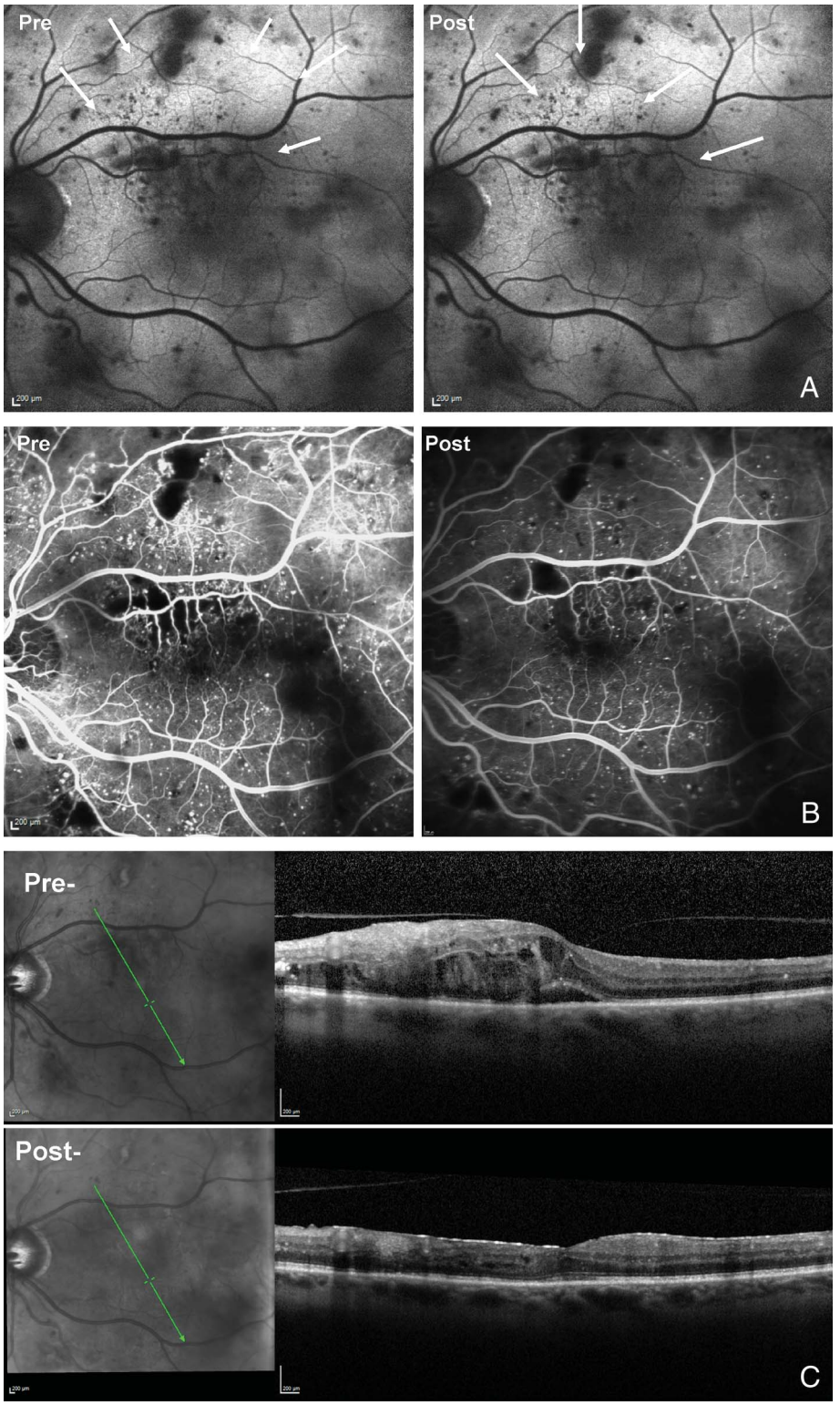

Fig. 1. Heidelberg Spectralis images of an eye treated for DME with SDM. This 66-year-old white man received 648 applications in a single session of macular SDM. Laser parameters: 131 retinal spot size, 0.93-Watt peak power, 5% DC, 500-Hz micropulse repetition rate, 0.3-second pulse (burst) duration. Visual acuity preoperatively was 20/80; 3 months postoperatively, it was 20/50. The images on the left were taken before treatment and those on the right 3 months after treatment. Note resolution of DME and the complete absence of laser-induced retinal injury postoperatively in all images. **A**. Autofluorescence fundus photographs (FAF). Arrows denote area of ME treated by SDM. **B**. Intravenous FFAs. **C**. Spectral-domain OCT before (top) and after (bottom) treatment.

Table 4. Comparison of Baseline Characteristics and Results for Eyes Evaluated Pre- and Postoperatively by the Heidelberg Spectralis with SDM Alone and in Combination with Local Drug Therapy

	SDM + Drug Therapy (n = 24 Eyes; 20 Subjects)		SDM Alone (n = 38 Eyes; 28 Subjects)		
Continuous Variables	Mean (SD)	Min, Max	Mean (SD)	Min, Max	*P**
Age (subject based), years	70.9 (10.4)	51, 85	70.6 (11.3)	49, 90	0.9239
Days of follow-up	421.7 (203.3)	100, 693	337.9 (197.3)	97, 715	0.1128
Pre-BCVA	5.9 (2.7)	2, 13	3.0 (1.5)	1, 8	<0.0001
Pre-CFT (μm)	328.8 (125.6)	165, 614	258.4 (65.9)	177, 507	0.0166
Pre-MMT (μm)	528.7 (104.3)	370, 726	429.5 (77.6)	341, 670	<0.0001
Number prior macular SDM	5.1 (5.3)	0, 16	1.0 (3.0)	0, 16	0.0017

SDM, low-intensity/high-density subthreshold diode micropulse phototherapy; age, years; BCVA, best corrected visual acuity; CFT, central foveal thickness, in microns; MMT, maximum macular thickness, in microns; DME, diabetic macular edema; Dx, diagnosis; Sbjs, subjects. Visual acuity: 1 = 20/20, 2 = 20/25, 3 = 20/30, etc.

*t-test (all observations assumed to be independent).

the goal of treatment. Thus, treatment risks and side effects, while possibly reduced, persisted and treatment density—and thus possibly effectiveness—remained constrained by laser-induced retinal damage and the risk of treatment-associated vision loss.

High-density/low-intensity SDM represents a departure from the techniques and assumptions of conventional photocoagulation, for retinal vascular disease. First, avoidance of laser-induced thermal retinal damage is an explicit priority of treatment. To this end SDM applies micropulsed 810-nm diode laser at a low DC to improve tissue selectivity and minimize heat spread and accumulation (''low-intensity'' SDM).[13–16,27,32,44–49,63] Avoidance of laser-induced retinal damage permits a second departure from conventional treatment: Rather than partial ''grid'' treatment, SDM uses confluent ''painting'' of the target retina with a large number of small, densely placed short-duration laser spots (''high-density'' SDM).[44] Unlike the confluent treatment of large–spot-sized long-duration transpupillary thermotherapy, high-density SDM maximizes heat dissipation and minimizes heat accumulation, minimizing the risk of unintended thermal retinal injury.[27] Unlike conventional partial grid treatment, high-density SDM achieves complete treatment of the target retina, maximizing therapeutic effects at the laser parameters used.[44] With SDM, DME may be treated confluently up to the edge of the foveal avascular zone 360°, if indicated by the presence of macular thickening. In the absence of laser-induced retinal damage, no adverse effects, treatment complications, or inflammatory reaction are observed, and SDM may be repeated as necessary without apparent limit. For the treatment of DME, SDM has been shown to be as effective as conventional photocoagulation, and retinal sensitivity increased, rather than decreased, after SDM treatment.[44–49]

While the seven eyes in this study with iatrogenic retinal damage did not suffer visual loss, we believe it is desirable to avoid any laser-induced retinal damage, especially with high-density SDM treatment proximal to the fovea. The pilot studies and recent randomized clinical trials have documented the safety of SDM with average postoperative follow-up periods of up to 1 year.[44–49] In this study, eyes without thermal retinal damage noted at the first postoperative visit continued to demonstrate no evidence of subsequent SDM-induced retinal damage for up to 10 years. Thus, the long-term safety of low-intensity/high-density SDM performed at parameters producing Arrhenius integral values <1 or 810-nm irradiances of approximately 350 W/cm^2 appears to be excellent. By contrast, SDM at higher retinal irradiance levels—$\geq$500 W/cm^2—resulting in

Table 5. Clinical Change Within Groups and Overall for the Subset Treated with SDM for DME with Pre- and Postoperative HS SD-OCT Information

	All (n = 62 Eyes; 48 Subjects)			SDM + Drug Therapy (n = 24 Eyes; 20 Subjects)			SDM Alone (n = 38 Eyes; 28 Subjects)		
Variables	Mean (SD)	Min, Max	*P**	Mean (SD)	Min, Max	*P**	Mean (SD)	Min, Max	*P**
BCVA change	0.02 (2.04)	−7, 6	0.9505	−0.08 (3.03)	−7, 6	0.8942	0.08 (1.05)	−2, 3	0.6456
CFT change (μm)	−25.0 (94.2)	−427, 340	0.0410	−42.7 (143.8)	−427, 340	0.1592	−13.8 (37.9)	−172, 49	0.0313
MMT change (μm)	−49.1 (71.4)	−278, 71	<0.0001	−62.9 (94.9)	−278, 71	0.0035	−40.4 (51.2)	−209, 65	<0.0001

SDM, low-intensity/high-density SDM photocoagulation; BCVA, best-corrected visual acuity; visual acuity, 1 = 20/20, 2 = 20/25, 3 = 20/30, and so on.

*The *t*-test (all observations assumed to be independent).

Table 6. Comparisons of Categoric Clinical Change Between SDM with Drug Therapy and SDM-Only Groups

	SDM + Drug Therapy		SDM Alone		
Variable	Frequency	Column %	Frequency	Column %	*P**
BCVA change					
Improved	8	33.3	10	26.3	0.4717
Unchanged	7	29.2	17	44.7	
Worsened	9	37.5	11	29.0	
CFT change (μm)					
Improved	15	62.5	26	68.4	0.7256
Unchanged	2	8.3	1	2.6	
Worsened	7	29.2	11	29.0	
MMT change (μm)					
Improved	17	70.8	32	84.2	0.2075
Unchanged	0	0.0	0	0.0	
Worsened	7	29.2	6	15.8	

SDM, low-intensity/high-density SDM photocoagulation; BCVA, best-corrected visual acuity; visual acuity, 1 = 20/20, 2 = 20/25, 3 = 20/30, and so on.

*Chi-square or Fisher exact (where cell counts <5) (all observations are assumed to be independent).

Arrhenius integral values >1, appeared to significantly increase the risk of thermal retinal injury, especially in more darkly pigmented eyes.

Eyes in this study treated for DME with SDM alone or in combination with local drug therapy evaluated pre- and postoperatively with the HS demonstrated significant reductions in CFT (SDM alone) and MMT (SDM alone and combination therapy) without any evidence of laser-induced retinal injury. Thus, the clinical effectiveness of SDM documented by HS SD-OCT appears to be consistent with earlier studies.[44–49] Because of the short follow-up and retrospective, nonrandomized nature of this subgroup, comparison of the results with conventional macular photocoagulation is not possible. Because of deliberate selection bias favoring combination therapy for eyes with worse preoperative visual acuity and greater central fovea thickening, no judgment can be made regarding the benefit of either pharmacologic therapy combined with SDM or of SDM monotherapy in eyes with severe DME. However, recent findings reported by the Diabetic Retinopathy Clinical Research Network suggest that the eyes selected here for combination therapy may not have done as well with SDM alone.[9] While the eyes treated with SDM only had less severe DR at baseline, the majority of eyes treated in this subgroup for DME (38 of 62 eyes) did well with SDM alone, without the expense or risks of additional local medical therapy. No evidence of SDM-induced retinal injury was noted in either group by fundoscopy, red-free fundus photography, or FFA, as reported in previous studies.[44–49] With Vujosevic et al[48] we also documented no evidence of SDM-induced retinal injury by FAF photography. In addition, no evidence of SDM-induced retinal injury was noted by HS infrared fundus photography, indocyanine green angiography, or SD-OCT.

In the pilot study of SDM for DME, the American National Standards Institute "maximum permissible exposure"–based model was proposed for assessing the limits of invisible photocoagulation.[44,64–67] These maximum permissible exposure–based estimates suggested a larger safe therapeutic window (the ratio of threshold powers for resolution of DME and visible coagulation) for micropulsed laser, compared with continuous-wave lasers. In the present report, our calculations of tissue temperature rise and Arrhenius modeling of tissue damage in response to SDM confirm that biologic effects can be elicited below the levels of RPE and other retinal cell death ($\Omega = 1$), consistent with clinical observations. The small difference in temperature and in Arrhenius integral between the micropulsed and continuous laser (Figures 2A and 3A), might suggest that their clinical outcomes could be equivalent. However, temperature and damage calculations are limited by uncertainty in the physical model, such as pigmentation variability, ocular transmittance, and damage model parameters, and this hypothesis remains to be tested clinically. Regardless of the treatment method, observations of the safety and effectiveness of SDM cast doubt on the necessity of producing laser-induced thermal retinal injury to achieve a therapeutic effect in treatment of DME.[11,44–49]

Because the RPE reaches highest temperature and Arrhenius values (Figures 2B and 3B) in response to laser exposure, it is speculated that RPE cells are responsible for beneficial effect of SDM. The clinical results of SDM suggest that, even in the absence of laser-induced retinal damage, SDM may cause the RPE to alter expression of potent locally acting cytokines, such as vascular

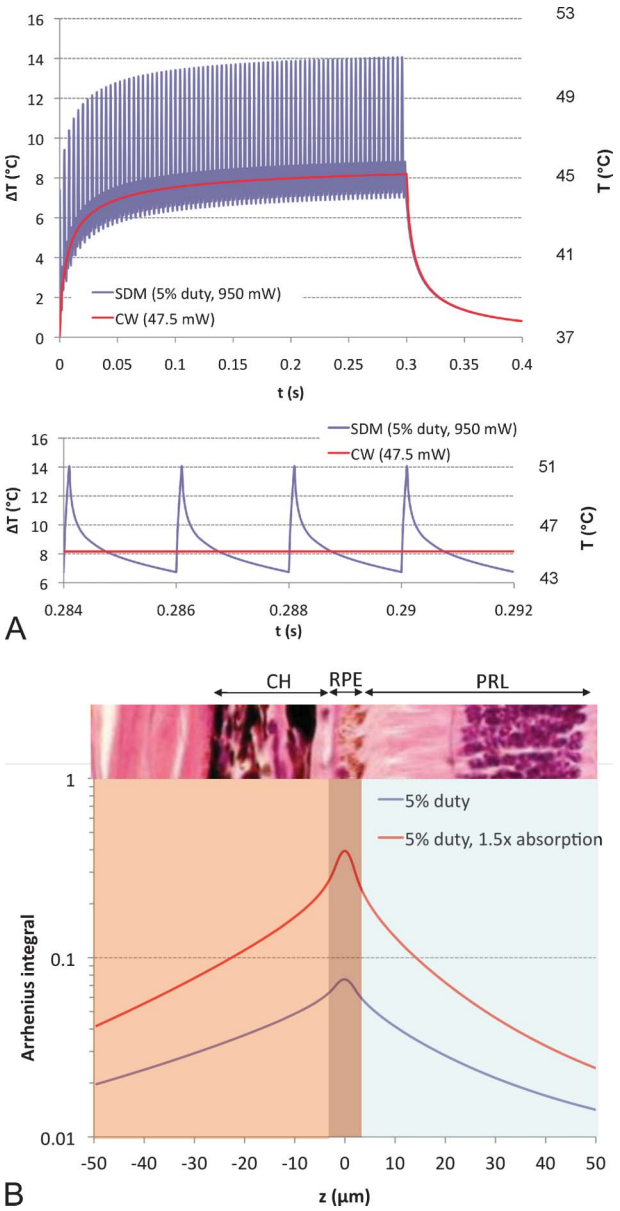

Fig. 2. A. Calculated temperature rise in the beam center at the RPE for low retinal burn risk SDM laser parameters (5% DC). Blue line corresponds to SDM, and red line depicts a continuous laser of the same average power. **B**. Arrhenius integral at low retinal burn risk SDM parameters, showing axial variation in the neural retina, RPE, and choroid. Traces corresponding to hyperpigmented RPE and choroid are shown in red. Peak value remains below the damage threshold Ω = 1, even in the case of hyperpigmentation.

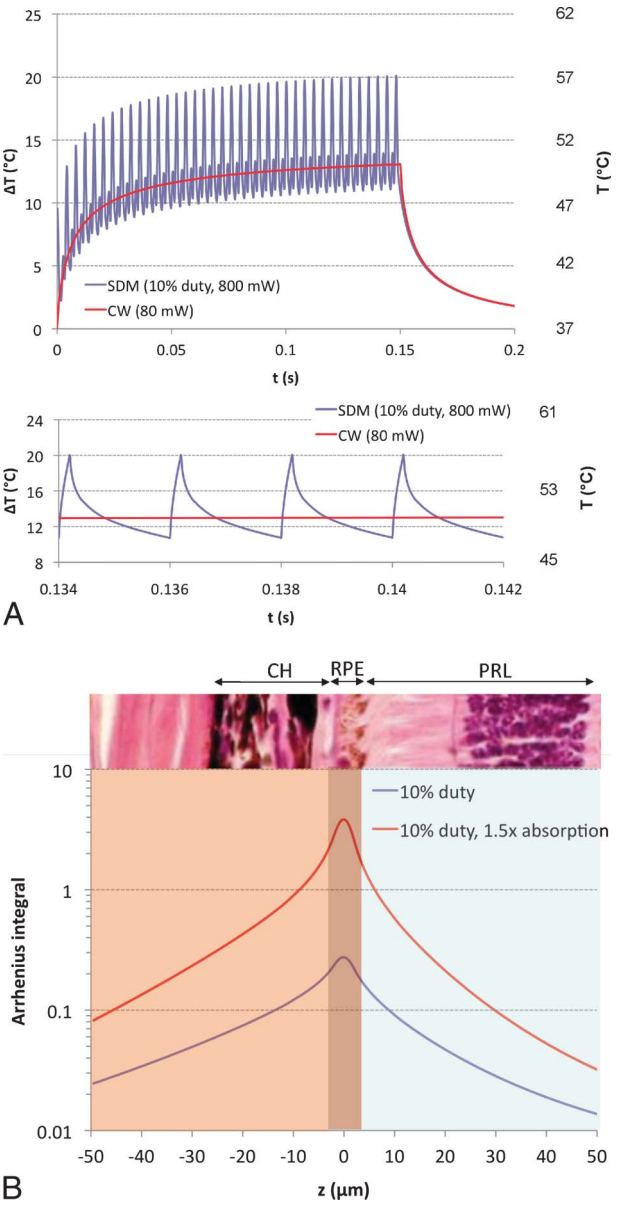

Fig. 3. A. Calculated temperature rise at higher retinal burn risk SDM laser parameters (10% DC). Temperature rise is higher, reaching a peak of 57°C in the normal pigmentation case. **B**. Arrhenius integral at higher retinal burn risk SDM parameters. Maximum value of the Arrhenius integral in RPE does not exceed the damage threshold (Ω = 1) for the normal pigmentation case. With hyperpigmentation, the damage threshold is exceeded, which may lead to an ophthalmoscopically or fluorescein angiography–visible lesion.

endothelial growth factor, pigment epithelial–derived factor, matrix metalloproteinases, and tissue inhibitor of matrix metalloproteinases known to be influential in the development of the complications of DR. This assertion is supported by 1) recent observation of vascular endothelial growth factor, pigment epithelial derived factor (PEDF), and matrix metalloproteinases (MMP) production from laser-treated RPE in cell culture and 2) the clinical observation that, absent thermal retinal injury, pharmacologic agents such as vascular endothelial growth factor inhibitors produce therapeutic effects similar to photocoagulation in the treatment of DR and other retinal vascular disorders.[7–10,44–49,67–70]

This study has significant limitations. These include the long period of study resulting in loss of some subject data, reliance on data collected retrospectively, and reliance on the experience of a single surgeon

performing a novel treatment in a single center. However, the large number of subjects, long length of follow-up, retinal imaging methods used, correspondence with tissue temperature calculations, and consistency with earlier studies of low-intensity/high-density invisible SDM corroborate the reported observations. Continued investigation into subvisible, sublethal retinal photocoagulation may lead to safer, more effective treatment of DR and other retinal vascular disorders, and a better understanding of the mechanisms of retinal laser therapy.

In summary, in a long-term retrospective review of eyes treated for ME because of DR and branch retinal vein occlusion with SDM, the risk of iatrogenic laser–induced thermal retinal injury was found to be low and could be effectively eliminated by using low (5%) DC with a small retinal spot diameter and retinal irradiance levels not >350 W/cm^2. No eye without retinal damage at the first follow-up visit developed late lesions. A subgroup of eyes treated for DME and evaluated pre- and postoperatively with HS high-resolution imaging, including SD-OCT, FAF, infrared and red-free fundus photography, indocyanine green angiography, and FFA, demonstrated clinical efficacy in the absence of laser-induced retinal injury. Calculations of tissue temperature and associated thermal damage are consistent with the clinical observations of this and previous studies of SDM.

Key words: Arrhenius integral, diabetic retinopathy, diode, laser, macular edema, micropulse, retinal photocoagulation, safety, subthreshold, subvisible, tissue temperature.

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