Non-damaging Laser Therapy of the Macula: Titration Algorithm and Tissue Response

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ABSTRACT

Retinal photocoagulation typically results in permanent scarring and scotomata, which limit its applicability to the macula, preclude treatments in the fovea, and restrict the retreatments. Non-damaging approaches to laser therapy have been tested in the past, but the lack of reliable titration and slow treatment paradigms limited their clinical use.

We developed and tested a titration algorithm for sub-visible and non-damaging treatments of the retina with pulses sufficiently short to be used with pattern laser scanning. The algorithm based on Arrhenius model of tissue damage optimizes the power and duration for every energy level, relative to the threshold of lesion visibility established during titration (and defined as 100%). Experiments with pigmented rabbits established that lesions in the 50-75% energy range were invisible ophthalmoscopically, but detectable with Fluorescein Angiography and OCT, while at 30% energy there was only very minor damage to the RPE, which recovered within a few days.

Patients with Diabetic Macular Edema (DME) and Central Serous Retinopathy (CSR) have been treated over the edematous areas at 30% energy, using 200μm spots with 0.25 diameter spacing. No signs of laser damage have been detected with any imaging modality. In CSR patients, subretinal fluid resolved within 45 days. In DME patients the edema decreased by approximately 150μm over 60 days. After 3-4 months some patients presented with recurrence of edema, and they responded well to retreatment with the same parameters, without any clinically visible damage. This pilot data indicates a possibility of effective and repeatable macular laser therapy below the tissue damage threshold.

Keywords: retinal laser therapy, thermal damage, macular degeneration, macular edema.

1. INTRODUCTION

Retinal laser photocoagulation remains the standard of care, either alone or combined with pharmacological agents, for various retinal diseases including proliferative diabetic retinopathy (PDR), diabetic macular edema (DME), vascular occlusions, central serous retinopathy (CSR), and retinal tears. To minimize the side-effects while retaining the therapeutic benefits, and to improve localization of the laser effects to specific retinal layers, various refinements in the treatment parameters have been introduced, including variations in wavelength, pulse duration, and lesion intensity.

Introduction of the pattern scanning approach to retinal photocoagulation (PASCAL)[1] has advanced the use of shorter pulses (10 – 30ms), which limit heat diffusion, minimizing the inner retinal damage and pain.[2, 3] As a result, less-damaging photocoagulation endpoints have been adopted,[4] which have been shown to decrease residual scarring and result in better restoration of the retinal structure and function.[5, 6]

Selective and sub-visible treatments have been developed to further minimize tissue damage, especially in the macula. These include Selective RPE Therapy (SRT) with microsecond pulses, which allow destruction of the RPE without damage to the photoreceptors and choroid.[7] RPE cells proliferate and migrate from the surrounding areas, restoring a complete coverage of the treated zone within days.[8] Clinical efficacy of SRT has been demonstrated in applications to CSR and DME.[9]

A sub-visible approach to retinal laser therapy was developed based on micropulse 810-nm diode laser, where power is titrated to the levels below clinically-detectable tissue damage using relatively long (100 – 300ms) bursts of 0.1-0.3ms pulses. Clinical trials have shown that sub-visible treatment of DME delivered with high spot density is equal or superior to the standard mETDRS protocol. However, the lack of a well-defined titration procedure is reflected in the variable results of these studies.[10-12]

Significant advantages of the retinal phototherapy with a sub-visible endpoint are the absence of scotomata and scarring, the ability to treat foveal areas, as well as improved preservation of the color vision and contrast sensitivity.[13] The lack of chorioretinal damage permits high-density therapy, which greatly improves therapeutic outcomes, compared to conventional sparse laser treatment protocols in the macula. Confluent laser applications can be safely delivered over the entire edematous areas, including retreatment of the same areas, even in the fovea.

However, the lack of a reliable titration protocol for reproducible sub-visible treatment settings inhibits its adoption in clinical practice. If laser settings are too low, the treatment will be not only sub-visible, but also sub-therapeutic, while if the settings are too high, there is a danger of excessive damage to the retina due to confluent coverage, especially in the fovea.

We developed a titration protocol for adjustment of laser power and duration, based on a retinal thermal model. It ties the subvisible tissue effects to a visible titration point. The protocol was first calibrated in rabbits using OCT, fluorescein angiography, light microscopy, transmission and scanning electron microscopy. Settings corresponding to non-damaging regime where then evaluated in patients with DME and CSR.

2. ENDPOINT MANAGEMENT ALGORITHM

Laser power and pulse duration were selected for each energy level using an algorithm (EndPoint Management, EpM) based on the Arrhenius cellular damage model.[14] For pulse durations exceeding 50 μs, thermal denaturation of tissue has been shown to be the primary retinal damage mechanism.[15, 16] In this regime the damage can be described with first-order reaction kinetics (Arrhenius law) parameterized by an activation energy, corresponding to the denaturation of a single critical component, and assuming an absence of cellular repair.

Experiments with heat shock protein expression following non-damaging retinal exposures in mouse,[17] as well as a computational analysis of clinical laser settings[18] indicated that non-destructive thermal therapy corresponds to Arrhenius values approximately $\Omega = 0.1 - 1$.[17] Visible lesions have calculated values $\Omega >> 1$, and the relevant range for retinal thermal therapy spans several orders of magnitude. The EpM algorithm maps a range of calculated Arrhenius integral values to linear steps in pulse energy, normalized to a titration dose specified at a particular duration, as illustrated in Figure 1.

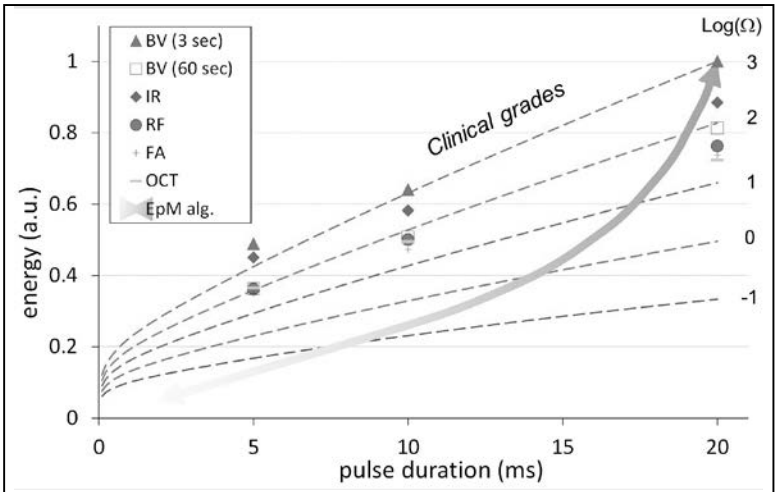

Figure 1. EpM adjustment of the pulse duration and power (solid line) converting the linear steps in pulse energy into the logarithmic steps in Arrhenius integral values (dash lines), corresponding to various levels of the thermal tissue effects.

Retinal treatment begins with titration of laser power to a minimally visible retinal lesion endpoint, which is then assigned the 100% EpM setting. As ophthalmoscopic lesion visibility changes over time, lesion appearance must be evaluated at a consistent time-point after laser delivery. For practical clinical usability, an evaluation time-point of 3 seconds was defined for this protocol. The laser pulse energy for the treatment is defined as a percentage of this titration energy. Each energy level corresponds to a unique pair of laser power and pulse duration, as illustrated in Figure 1. Retinal lesions produced by various pulse energies were imaged *in-vivo* during the follow-up period using fluorescein angiography (FA), fundus autofluorescence (FAF) and OCT (HRA2-Spectralis), and then analyzed histologically and with Electron Microscopy.

3. CALIBRATION IN RABBITS

Ophthalmoscopically, only the burns of titration level (100%) and higher were visible within 3 seconds of laser application. However, tissue effects at 75% and occasionally at 50% energy were identifiable with FA and OCT, as well as ophthalmoscopically in a follow-up longer than 3 seconds after laser application. In-vivo imaging did not show any

signs of tissue damage below the 50% level. Histologically, a 50% burn after 1 hour demonstrated pyknotic nuclei of the photoreceptors, and SEM revealed some damage to the RPE, as shown in Figure 2. At 30% energy no damage could be found histologically. SEM at 1 day consistently identified a single damaged RPE cell in the center of the laser spot, however at 7 days no signs of damage to RPE could be found. We previously determined that enhanced expression of the heat shock protein (HSP-70) in the retina extends down to approximately half of the RPE damage threshold.[17] That study, as well as correlation of the computational model with previous clinical data[18] revealed that Arrhenius integral Ω in the sub-visible retinal therapy was in the range of 0.1 - 1. EpM settings of 30% corresponds to the middle of this range, as illustrated in Figure 1.

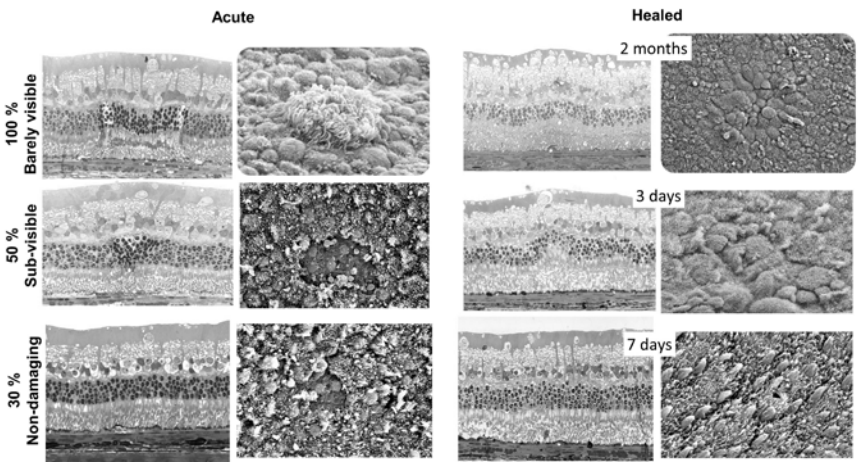

Figure 2. Histology of the retina and SEM of the RPE with acute (left columns) and healed (right columns) lesions at pulse energies of 100%, 50% and 30% of the titration level.

4. INITIAL CLINICAL EVALUATION

EpM algorithm has been integrated into the software control of PASCAL laser (Topcon Medical Laser Systems, Santa Clara, CA). Its clinical utility was assessed in patients with Diabetic Macular Edema (DME, n=10) and Central Serous Retinopathy (CSR, n=16) using the yellow wavelength (577nm) laser. The study adhered to the tenets of the Declaration of Helsinki. Patients were older than 18 years of age, with symptoms presented for more than four months. Best corrected visual acuity (BCVA) measured by the ETDRS protocol was below 20/40 but better than 20/400.

After initial titration to barely visible lesion at 3 seconds using 15ms pulses, the energy was switched to 30% for the treatment, allowing the EpM to adjust the pulse duration and power accordingly. Typical power range in titration: 90-150 mW, average 126±17 mW. Retina was treated over the edematous areas at 30% energy, using 200μm spots with 0.25 diameter spacing in the patterns, with the average number of spots per treatment being 532. No signs of laser damage have been detected with any imaging modality. In CSR patients, subretinal fluid resolved, on average, within 45 days, as illustrated in a typical example shown in Figure 3. Central macular thickness decreased, on average, by 64μm at 3 months. Patients gained, on average, 12 ETDRS letters in best corrected visual acuity at 3 months, which remained steady by 6 months. In 75% of patients the subretinal fluid was completely resolved, in 19% there was some minimal fluid left, and only one patient (6%) did not respond to the treatment.

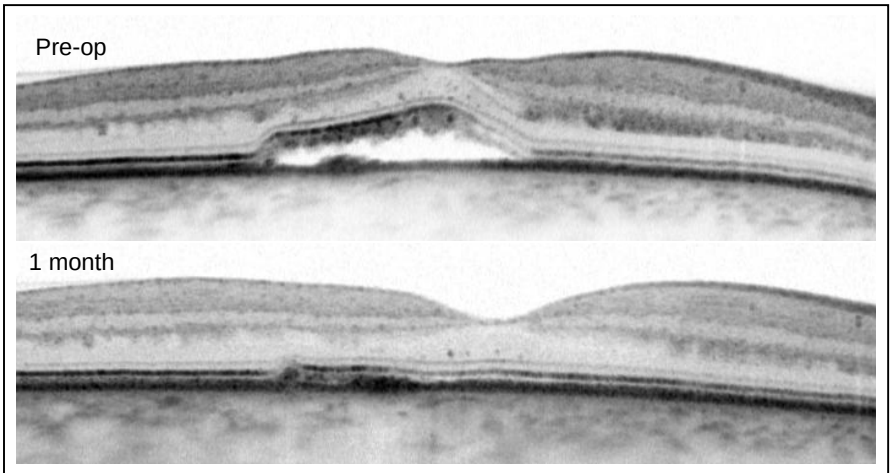

Figure 3. Patient with CSC treated at 30% level, with 200μm spots at 0.25 diameter spacing (total 358 spots). Complete resolution of the subretinal fluid was observed at 1 month, with vision improving from 20/40 to 20/20.

In DME patients the edema decreased by approximately 150μm over 60 days. After 3-4 months some patients presented with recurrence of edema, and they responded well to retreatment with the same parameters, without any clinically visible damage.

5. DISCUSSION

Despite the wide use of retinal photocoagulation in clinical practice, physiological pathways of this therapy have never been well established. Panretinal photocoagulation is thought to help reduce production of angiogenic factors by reducing the number of photoreceptors in peripheral retina and thereby decreasing the hypoxia. Focal grid coagulation was rationalized as a means to seal the leaking microaneurisms, and thereby decrease the fluid influx into the retina. However, therapeutic pathways of the macular scatter photocoagulation, where much smaller area is treated than in PRP, and no leakage is directly addressed, remain a mystery.

We hypothesize that the heat shock proteins (HSPs) upregulated by the thermal stress in RPE and choroid help boost cellular functions, including the enhanced capability of the fluid pumping from the retina. Protein misfolding and aggregation is a fundamental component of the cellular aging process. HSP refold the damaged proteins and thereby protects cells from protein aggregation, proteotoxicity and apoptosis[19]. Aging cells undergo a decline in transcriptional pathways, including heat shock factor (HSF1) potency, and thus lose capacity to synthesize HSP[20]. Decreased HSP concentrations leads to a decline in protein quality control, which, in turn, contributes to protein aggregates formation in cells, commonly observed in neurodegenerative diseases[21].

It has been shown that induction of HSP in aging cells helps maintain protein homeostasis by refolding the damaged proteins, which accumulate during aging and are toxic to cells[22]. The ability of HSP to counteract the proteotoxic effect in tissues can promote longevity and rejuvenate cellular functions[23]. Enhanced synthesis of HSP and co-chaperones in response to sub-lethal thermal stress of RPE can bring back the normal physiology of these cells in aging and disease.

With this hypothesis in mind, we optimized the retinal photothermal therapy to operate within the range limited from below by the threshold of HSP expression (Arrhenius integral Ω=0.1) and from above by the thermal damage to RPE cells (Arrhenius integral Ω=1)[24]. We also assumed that efficacy of the treatment would increase if more RPE cells in the diseased areas are exposed to the thermal stress. Therefore, the treatment was applied at high density – with 0.25 diameter spot spacing, corresponding to 50% of the area covered by the pattern. Radiation was applied not only in edematous area identified by OCT, but also in the areas of enhanced autofluorescence indicating chronic RPE damage. High density coverage of the macula requires a large number of spots - typically between 400 and 700. Since each spot is irradiated with a pulse shorter than 10 ms, such a large number of laser spots can be quickly placed using pattern scanning, especially with automatic pattern advancement option, built into the new software of Synthesis laser (Topcon Medical Laser Systems, Santa Clara, CA).

Previous studies using sub-visible micropulse laser treatment have demonstrated a 70% success rate in patients with chronic CSR[25, 26], and a retreatment rate of approximately 50%. However, the use of EndPoint Management software has several advantages over manual treatment with micropulse laser: (1) proper titration protocol based on the actual level of energy necessary to stimulate RPE in each patient, (2) shorter pulses and the use of patterns result in much faster and more reproducible treatment, and (3) possibility of placing barely visible landmarks at the corners of the patterns for documenting the treatment location.

Recurrence of the subretinal fluid after a few months in some cases indicates that the improvement provided by the photothermal treatment may fade over time. Re-treatment with the same parameters was found safe, and no cumulative retinal damage was detected over the follow-up period. Very encouraging was our observation that the retinal response to re-treatment was as strong as that of the first treatment, and in some cases even better than the initial result, which could represent a cumulative therapeutic effect of several treatments.

In conclusion, the EpM algorithm and associated titration procedure provide an approach to reproducible sub-visible retinal laser therapy. This pilot clinical data indicates a possibility of effective and repeatable macular laser therapy below the tissue damage threshold.

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