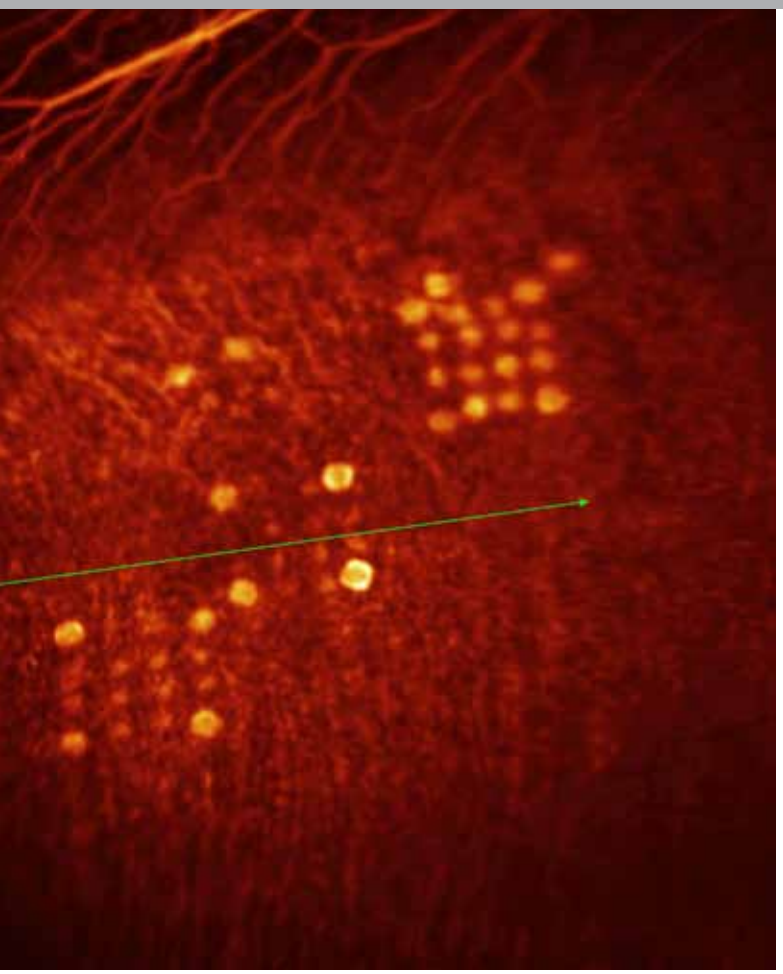
Endpoint Management:
Advanced algorithms for controlled laser treatments



Introduction

Retinal laser photocoagulation was introduced in 1961, a year after the invention of the laser, and remains the standard of care for various retinal diseases including proliferative diabetic retinopathy (PDR), diabetic macular edema (DME), vascular occlusions, central serous chorioretinopathy (CSC), and retinal tears. To minimize the side-effects while retaining the therapeutic benefits, refinements in treatment parameters have been introduced including variations in wavelength, pulse duration, lesion intensity, and localization of the laser effects to specific retinal layers. With advances in laser therapy research, treatment protocols are being continuously improved to provide the best patient care.

Recent successes with micropulsed lasers have demonstrated that visible lesions are not necessary for laser treatment to be effective, and in fact, sub-visible treatment eliminates a host of complications resulting from injury to the neurosensory retina. Extensive research has found that with an understanding of cellular thermal effects and an accurate model of the non-linear processes involved, it is possible to use conventional lasers to perform sub-visible therapy. Advanced calculations can ensure that laser delivery is controlled and treatments remain in the therapeutic realm, even when non-ophthalmoscopically visible.

Photothermal interactions and mechanism of retinal photocoagulation

The working mechanism of retinal phototherapy is an area of active investigation. The pathophysiology underlying a number of retinal vascular disorders has implicated inflammation and hypoxia. These conditions induce angiogenic factors such as vascular endothelial growth factor (VEGF) or inflammatory cytokines that stimulate neovascularization or vascular permeability.[1, 2] Thus, it has been traditionally thought that the destruction of the numerous, metabolically-demanding photoreceptors in poorly-perfused portions of the retina during photocoagulation limits the ischemia and decreases the production of angiogenic factors.

While these working mechanisms of photocoagulation have been generally accepted for treatment of PDR, alternative mechanisms have been postulated for macular therapy. Recent studies of the healing response of the RPE to thermal injury suggests that the therapeutic cellular cascade is activated by the still-viable RPE cells surrounding the treated areas that are heated to sub-lethal temperatures, implying photoreceptor destruction may not be necessary.[3, 4]

Temperature governs all thermal laser-tissue interactions. Depending on the duration and magnitude of hyperthermia, different tissue effects may occur, including necrosis, coagulation and vaporization. Heat generation in tissue is determined by a variety of factors including laser parameters, such as exposure time, power and wavelength, and the optical absorption and scattering characteristics of the treated tissue.

Retinal photocoagulation typically involves the application of laser pulses with durations ranging from 10 – 200 ms and powers from 0.1 – 2 W. Various lasers have been used in the past: ruby (694 nm), argon (488, 514 nm), krypton (647 nm), and dye (e.g. Rhodamine 6G, 570 – 630 nm). The most common lasers used currently are frequency-doubled Nd:YAG (532 nm) and optically pumped semiconductor lasers (577 nm). The laser energy is absorbed primarily by melanin in the retinal pigment epithelium (RPE) and choroid, and by hemoglobin in blood. At 532 nm wavelength, approximately half of the laser energy incident on the retina is absorbed by the RPE, and the rest in the choroid[5]. The heat generated diffuses from the RPE and choroid into the retina and causes coagulation of the photoreceptors and, with conventional 100 – 200 ms pulses, of the inner retina.

This lateral and axial thermal diffusion into surrounding structures results in collateral thermal damage. During 100 ms exposures, the heat diffuses distances of up to 200 μm, extending the coagulated zone laterally beyond the boundaries of the laser spot, termed “thermal blooming”. The visible endpoint of a conventional retinal laser burn signifies that the axial thermal spread has reached the overlying retina with a temperature high enough to affect the natural transparency. This blanching is typically associated with a temperature rise of 20° to 30°C above baseline.[5-7]

Traditional intense photocoagulation with pulses of hundreds of ms in duration has been associated with several complications, including reductions in visual acuity, visual field, color vision, night vision, and contrast sensitivity.[8-12] Others include choroidal neovascularization, hemorrhage, epiretinal fibrosis, and serous detachment of the peripheral retina.[13] These complications have led to the adoption of alternative protocols. The introduction of patterned scanning treatment with the PASCAL® photocoagulator in 2006[13] has advanced the use of short duration pulses (20 – 30 ms). Short pulses limit heat diffusion to the photoreceptor layer, thereby minimizing inner retinal damage as well as pain due to heating of the cilliary nerves.[14, 15] In addition to shorter pulse durations, less-damaging photocoagulation endpoints have been adopted, from "light" visible lesions,[16] which have shown to decrease residual scarring and result in better restoration of retinal structure and function,[17, 18] to sub-visible treatment.

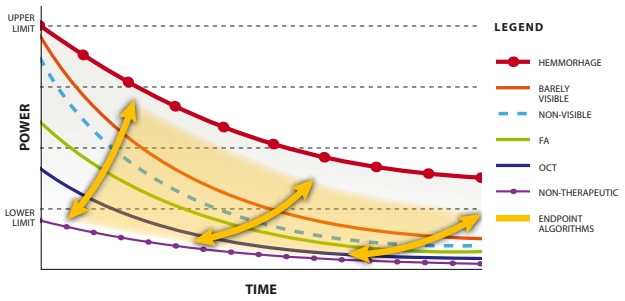
Sub-visible retinal therapy

Sub-visible thermal laser treatment of the retina has predominantly been performed with micropulsed lasers, where repetitive short bursts of NIR radiation (810 nm) are applied during 50 – 300 ms exposures. For many clinicians practicing this treatment, the express goal is non-damaging "sub-threshold" phototherapy, avoiding any detectable cellular destruction (i.e. angiographically or OCT invisible effect). Despite the departure from conventional visible coagulation endpoints, sub-visible micropulse has been shown to be effective in pilot studies for DME, CSC, and macular edema secondary to retinal vein occlusions,[19] with subsequent randomized clinical trials corroborating these findings for DME.[20, 21] The origin of the beneficial effects of sub-visible treatment remains unclear, but the recent observations of PEDF up-regulation and TGF-β down-regulation after sub-lethal laser in RPE cell cultures[22, 23] support the hypothesis of RPE-derived mechanisms. Future studies of sub-lethal tissue hyperthermia are necessary to understand the cellular response mechanisms responsible for the observed therapeutic benefits.

Significant advantages of sub-visible phototherapy are the absence of scotomata and scarring, as well as preservation of color vision and contrast sensitivity. The lack of chorioretinal laser damage also permits high-density therapy, with confluent applications over entire edematous areas and retreatment of the same areas, even in the fovea. However, a considerable disadvantage is the lack of a direct, titratable endpoint to help guide laser dosimetry. With sub-visible treatment, there is a potential for application of clinically irrelevant levels of laser energy, operating in a sub-therapeutic (and equally sub-visible) regime. The wide range of titration protocols used in published studies highlights concerns about repeatability, which may have inhibited the widespread adoption of sub-visible treatment.

Quantifying cellular damage – arrhenius integral

The risk of sub-therapeutic treatment when using laser exposures in the sub-visible regime emphasizes the need for an understanding of cellular thermal effects, and a mathematical description of the laser-tissue interaction linking treatment parameters (in terms of power, duration and spot-size) and the desired tissue effect.



Endpoint Management algorithms adjust power and duration simultaneously, maximizing the ability to safely and accurately control the desired endpoints.

Required number of spots and pattern density

The precise delivery and reduced collateral damage in laser treatment enabled by PASCAL photocoagulators has generated the need for new treatment protocols. Recent OCT measurements of retinal photocoagulation lesions of various clinical grades provided guidance regarding the number of spots and pattern density required to treat a fixed retinal area.[1] Moderate (white-gray) lesions were found to be significantly larger than the laser spot-size, and thermal spread of the lesion had a more significant relative effect on smaller spots. In addition, 20 ms duration resulted in considerably smaller lesion diameters at all grades. Therefore, to maintain the same total coagulated area as in 1000 conventional burns with a 400 µm retinal spot-size (100 ms, moderate grade) for a full scatter PRP treatment, a larger number of 20 ms lesions are needed with the same beam diameter. PASCAL technology, together with appropriate dosimetry, provides unparalleled rapid, precise and effective retinal laser treatment.

Table 1: Spot number requirements for PASCAL treatment

Pulse duration	100 ms	20 ms	20 ms
Lesion grade	Moderate	Moderate	Light
Number of lesions	1000	1464	1979
Percent increase		40%	100%

1 Palanker, D., et al., *The Impact of Pulse Duration and Burn Grade on Size of Retinal Photocoagulation Lesion: Implications for Pattern Density.* Retina, 2011. **31**(8): p. 1664-9.

Temperature rise induces conformational changes in various proteins, which denature at characteristic rates specific to protein species and lead to cellular damage. Millisecond-regime thermal cellular damage is modeled using the Arrhenius integral.[5, 24] The rate of decrease in concentration of a critical component for cellular metabolism D(t) is assumed to change with temperature T(t):

$$dD(t) = -D(t) \cdot A \cdot \exp\left(-\frac{E^*}{R \cdot T(t)}\right) dt$$

where E* and A are the activation energy and rate constant parameterizing the process, and R is the gas constant, 8.3 J/(K·mol). Tissue damage, i.e. decrease in critical molecular component D(τ), relative to its initial value D0 over the pulse length τ is encapsulated in the Arrhenius integral Ω:

$$\Omega(\tau) = -\ln\left(\frac{D(\tau)}{D_0}\right) = A\int_0^{\tau} \exp\left(-\frac{E^*}{R \cdot T(t)}\right) dt$$

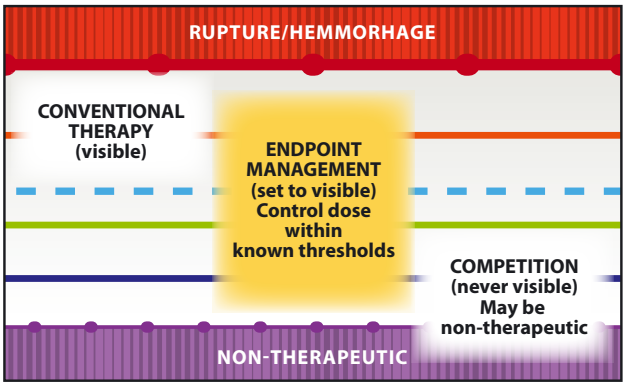
Experiments with heat shock protein expression following sub-lethal retinal exposures in mice, as well as a computational analysis of clinical laser settings, indicated that the therapeutic range of sub-lethal thermal therapy stretches from Ω = 0.1 on the low end to Ω = 1 on the high end.[25] For Ω < 0.1, there is very little effect, while Ω > 1 cells may become irreversibly damaged. The same model applied to micropulse exposures also demonstrated that continuous (non-micropulsed) treatment of the same duration and same average power produces a similar average temperature and Arrhenius integral.[25, 26] This implies that micropulsing may not be necessary, and that similar tissue effects could be produced using more conventional continuous laser exposures, as long as power and duration are appropriately controlled. Single pulse application has the further advantage of a faster overall treatment due to the shorter laser exposures used for each targeted site, rather than longer micropulsed bursts.

Precise titration of therapy

Topcon's Endpoint Management (EM) software uses a computational model of retinal heating and an Arrhenius damage model to determine laser parameters optimized for the PASCAL® and Streamline® lasers. The algorithms modulate power and duration concurrently to maximize the margins between visible and sub-visible photocoagulation endpoints, providing a linear control over an inherently nonlinear process.

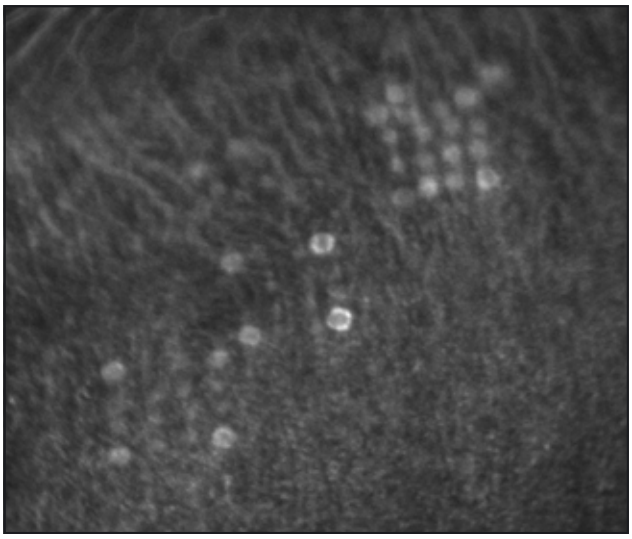
In application of EM, a user first titrates to a comfortable visible endpoint. Establishing a titration endpoint is important as it gives a consistent baseline, ensuring repeatable results between patients. With the Endpoint Management option activated, the laser output in a pattern is a percentage of this titration energy. Power and duration are both modulated to make this energy adjustment, allowing for a fine gradation of laser dosage and control over treatment endpoints. The visible titration endpoint can be referenced throughout the course of treatment by enabling the Landmark feature, which creates reference lesions at the titration dose at the corners a pattern. This provides visible feedback on dosage and positioning of treated areas.

Importantly, the EM approach to laser therapy allows the physician to consistently operate in the realm of therapeutic relevance for sub-visible treatments. When no burns are visible, the biggest risk becomes lack of therapeutic effect. The Arrhenius integral-based algorithms in Endpoint Management adjust power and duration to provide the best "path" between endpoints, moving smoothly from the ophthalmoscopically-visible titration point to angiographically-only, OCT-only, and sub-visible/therapeutic regimes. The Landmark feature allows the user to determine the local effect of the titration dose, and make adjustments as uptake varies across the treated area. The result is more predictable sub-visible laser delivery with the widest window of safe, effective treatment.



Endpoint Management applies advanced algorithms to deliver sub-visible laser applications that stay within therapeutic boundaries.

EM technology provides a significant advantage over other sub-visible laser technologies by delivering greater treatment speeds and providing visible feedback with reference markers. This resulting system provides the physician with better control and more treatment options than ever before.



Laser dose is modulated and controlled to sub-visible levels, with or without peripheral Landmark patterns.

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Endpoint Management is an optional accessory for Pascal, Streamline and Streamline 577 laser systems. Contact your local Topcon representative for information about system upgrade requirements.

IMPORTANT Subject to change in design and/or specifications without advanced notice.
In order to obtain the best results with this instrument, please be sure to review all user instructions prior to operation.

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Item code: 5213401 / printed in Europe / 0112