A Re-classification of CNV
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A Re-classification of CNV


CHOROIDAL NEOVASCULAR MEMBRANE (CNV) has been described as new, pathological vascular proliferation that originates from the choriocapillaries. There are a number of etiologic conditions that may result in CNV (see “Common Causes of CNV,” right). However, age-related macular degeneration (AMD) is the most common associated etiology.

New diagnostic modalities have helped illustrate the diversity of CNV. Today, several forms of CNV may include newly recognized variants, such as polypoidal choroidal vasculopathy (PCV) and retinal angiomatous proliferation (RAP).

Understanding the morphology of CNV and its variants plays a vital role in patient education, diagnosis and management, as well as customization of treatment options.

CNV Classification

Any disorder that affects the choroid, Bruch’s membrane and/or the retinal pigment epithelium (RPE) can lead to the development of CNV. An upregulation of angiogenic growth factors, such as vascular endothelial growth factor (VEGF) and fibroblast growth factor, lead to the formation of a fibrovascular complex that originates from the choriocapillaries.1,2 Due to their lack of structural integrity, these new vessels are prone to leakage and hemorrhage, often leading to scar tissue formation and vision loss.

The network of new vessels may be limited to the sub-RPE space (type 1) or extend further into the subretinal space (type 2).3 Type 1 CNV typically occurs in AMD patients, while type 2 is more prevalent in younger patients and often is linked to entities such as ocular histoplasmosis syndrome (OHS) and angioid streaks. Patients with type 1 carry a worse visual prognosis secondary to the propensity for greater structural damage.4

Angiographic evaluation can further aid in subtyping CNV into either classic or occult membranes. These two subtypes were first identified in the Macular Photocoagulation Study (MPS), which also indicated that laser photocoagulation was indeed effective in treating extrafoveal classic CNV.4

• Classic CNV is described as well-defined membranes with homogeneous hyperfluorescence of the entire lesion that intensifies in the later phases. These membranes are further classified based on location (see “Classic CNV Locations,” page 4). This is critical in determining which CNV would benefit from laser intervention.

• Occult CNV is a poorly defined membrane that is seen on fluorescein angiography (FA), which can be described as either a fibrovascular pigment epithelial detachment (PED) or a late leakage of an undetermined source. The fibrovascular PED consists of irregular elevation with stippled or granular intial staining. The late leakage consists of areas of RPE defect seen as speckled hyperfluorescence. More than 85% of exudative AMD presents as occult CNV.5,6

Beyond the Archetypal Classifications

Indocyanine green angiography (ICGA), an important supplement to FA, has helped to further define the vascular features associated with CNV. On ICGA, CNV appears to manifest a spectrum of morphology that ranges from the capillary to the branching arteriole pattern.7 The branching arteriole pattern is composed of large-caliber feeder arterioles with many branches, while the capillary pattern consists of smaller-caliber feeder arterioles.

An occult CNV demonstrates a branching arteriolar pattern. Mixed-pattern CNV, consisting of both morphological subtypes, has also been described. It is believed that capillary-dominated CNV responds better to anti-VEGF pharmacotherapy, while branching arteriolar CNV is less responsive.7

Optical coherence tomography (OCT) has become invaluable in the detection and evaluation of CNV lesions. The most definitive OCT finding is described as a fusiform hyperreflective lesion that is found in close proximity to the RPE. If the CNV lesion is not well delineated on OCT, the presence of any associated leakage—denoted as cystoid macular edema, retinal thickening, neurosensory or RPE detachments—raises the suspicion of its presence.

Polypoidal Choroidal Vasculopathy

Lawrence A. Yannuzzi, M.D., first described PCV in 1982. Since
then, the condition has been referred to as idiopathic polypoidal choroidal vasculopathy, posterior uveal bleeding syndrome or multiple recurrent retinal pigment epithelial detachment. Initially, PCV was documented in young, black females. Today, however, the condition is recognized across all genders and ethnicities, with a specific predilection for Hispanics, Asians and blacks.

The characteristic finding of PCV is a network of inner-branching choroidal vessels with terminal aneurismal dilations or “polyps.” These lesions have a predisposition for the juxtapapillary and macular areas. Clinically, the lesions may appear as reddish-orange spheroids that lead to chronic, multiple, recurrent serosanguineous retinal pigment and neurosensory retinal detachment.

The diagnostic polyps are best delineated using ICGA and are described as a focal hyperfluorescence that persists into the late phase of the ICGA. OCT helps to further characterize distinct features as well as aids in the evaluation of associated serosanguineous PEDs. The PEDs are sharp, dome-like elevations with underlying moderate hyperreflectivity.

Two distinct indications observed in the OCT, which may be associated with the polyps, include the double layer sign (described as a reflective band below the elevated PED) and the bolas sign (described as an RPE disruption that represents a small polyp, which is located adjacent to the PED).10,11

PCV has often been misdiagnosed as wet AMD, and therefore was long believed to be a type 1 CNV variant. In one study, 23% of patients who were previously diagnosed with exudative AMD had PCV. However, there are distinctive features that differentiate PCV from classic wet AMD. For example, the PCV fundoscopic appearance typically lacks drusen. Also, the lesions frequently are noted in patients of a younger age with darker skin pigmentation.

The pathogenesis of PCV remains controversial. VEGF has been implicated, but it appears to play just a minimal role. When central vision is threatened, various treatment options are available. For years, the only serviceable treatment option was the direct application of thermal laser to the leaking polyps.

More recently, however, researchers have found that anti-VEGF drugs are effective in stabilizing visual acuity by reducing associated leakage. Unfortunately, anti-VEGF treatment yields inadequate efficacy in catalyzing a regression of polyps. This is likely because VEGF plays a limited role in polyp development.

Photodynamic therapy (PDT) seems to be the most effective PCV treatment to date. PDT reduces the associated leakage, as well as the size of polypoidal lesions; however, it may not destroy the polyps completely. The Efficacy of Vasopressin Antagonism in Heart Failure Outcome Study with Tolvaptan (EVEREST) evaluated whether PDT as monotherapy, or in combination with intravitreal ranibizumab, is more efficacious than ranibizumab monotherapy in achieving complete polyp regression. The six-month preliminary results have shown positive data, with complete polyp regression following combination therapy.

Retinal Angiomaticus Proliferation

RAP is a more recently recognized variant of CNV. RAP was first described in 1992 as a deep retinal vascular anomalous complex. Subsequently, Dr. Yannuzzi explicitly defined an RAP to describe a vascular process that originates within the neurosensory retina that begins with capillary proliferation, formation of intraretinal neovas-
cularization and retinal-retinal anastomoses. Like PCV, RAP has been confused with wet AMD, representing approximately 10% to 12% of newly diagnosed neovascular AMD lesions. RAP is often a bilateral condition that exhibits juxtapfoveal lesions. Clinical features of RAP include retinal and pre-retinal hemorrhages as well as neurosensory/pigment epithelial detachments and subretinal hemorrhages. The natural history of RAP is unclear; however, the stages of progression are categorized by the extent of retinal and choroidal involvement (see “Stages of RAP Progression,” right). Similar to PCV, ICGA is essential in the accurate diagnosis of RAP. RAP lesions are best seen in the mid or late phases as focal areas of hyperfluorescence at the terminal end of a retinal vessel. Associated leakage is noted in the surrounding intraretinal and subretinal spaces. OCT evaluation may reveal an abnormal intraretinal hyperreflective lesion. Associated structural alterations may include increased foveal thickness, cystoid macular edema, a serous retinal detachment and an RPE detachment.

Treatment of RAP varies, depending on the stage and associated findings. Stage I and early stage II RAP (outside the fovea) has demonstrated improvement following conventional thermal laser photocoagulation. RAP with PED has been effectively treated with combination PDT and intravitreal triamcinolone injection. Anti-VEGF agents have also been shown to effectively control leakage, but frequent injections are necessary due to rapid recurrences. Surgical ablation combined with PDT has been attempted, but was found to be inadequate in one study due to a high incidence of reperfusion from retinal inflow vessels. A paradigm shift in the evaluation of CNV has taken place over the past decade. OCT and alternative angiography have expanded the CNV spectrum to include RAP and PCV. A more precise diagnosis likely would assist in an improved understanding of the entity as well as help establish a proper natural history and an accurate prognosis.

Knowledge of the expanding CNV spectrum may be useful in designing future studies to determine individualized therapeutic regimens. Clinical trials can now focus on the specific conditions, such as RAP, PCV and AMD, in order to create new, increasingly more effective treatment options for CNV.

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Stages of RAP Progression

1. Stage I: Intraretinal neovascularization (INN). Capillary proliferation within the retina that originates from the deep capillary plexus in the paramacular region.
2. Stage II: Subretinal neovascularization (SRN). Occurs when the INN extends posteriorly, beyond the photoreceptor layer into the subretinal space. A localized, neurosensory retinal detachment develops with increasing intraretinal edema, intraretinal and preretinal hemorrhages, and an associated serous pigment epithelial detachment.
3. Stage III: CNV seen clinically and angiographically, and/or sometimes in association with a vascularized pigment epithelial detachment. During this process, a communication between the retinal and chordial circulations forms a retinal-choroidal anastomosis.
Hydroxychloroquine Retinal Toxicity: A Case Study

By Andrea J. Andrud, O.D.

THE PRESCRIPTION MEDICATION
hydroxychloroquine (HCQ) sulfate (Plaquenil, Sanofi-Aventis) has been shown to cause ocular toxicity.1 The drug is used to treat acute attacks of malaria, discoid and systemic lupus erythematosus, and rheumatoid arthritis.1

To date, there are just 49 published reports of HCQ retinopathy.2-4 Because of the drug’s potential side effects, patients on HCQ therapy must be educated on the importance of thorough and timely ocular examinations. For many patients, the benefits of HCQ therapy outweigh the potential complications—even when the individual exhibits specific risk factors that makes him or her more susceptible to the development of ocular toxicity. So, it is extremely important that both eye care providers and patients are aware of the potential ocular complications of HCQ therapy.

A Review of HCQ Retinopathy

The first case of ocular HCQ toxicity was documented in 1967.5 Due, in part, to the level of retinal toxicity caused by the drug and the potential for concomitant ocular disease, HCQ retinopathy is difficult to define. To date, just two clinicians have attempted to define the parameters of how to diagnose HCQ retinopathy—Michael Easterbrook, M.D., and Howard N. Bernstein, M.D.

Dr. Easterbrook indicates that HCQ retinopathy encompasses “bilateral, reproducible, positive field defects that can be demonstrated by two different tests of visual field examination.”6 His definition suggests that if “reproducible Amsler field defects and reproducible scotomata present on the Humphrey 10-2 white program, [the patient] is considered to have definite retinopathy.”7

Dr. Bernstein classifies true HCQ retinopathy as, “the presence and persistence of paracentral or central visual field scotomas to suprathreshold white stimuli and a duration of treatment of at least nine months when the daily dose was 400mg or less.”8 In the absence of visual field defects, he notes that “a ‘bull’s eye’ lesion or oval pigment epithelial defect in the macula” also is suggestive of true retinopathy.8

The term bull’s-eye maculopathy is used to describe and effect from HCQ’s predecessor, chloroquine. Chloroquine is also an antimalaria
drug. When the chloroquine binds to melanin in the retinal pigment epithelium (RPE), it causes cytotoxicity, resulting in an apparent perifoveal change. Because HCQ is less toxic, it has replaced chloroquine in clinical practice. The few cases of HCQ toxicity that have been reported show similar retinal changes to those seen in bull’s-eye maculopathy secondary to chloroquine use.

Case Report

**History.** A 58-year-old white female presented for an HCQ ocular examination. She had been diagnosed with systemic lupus erythematosus (SLE) in April 2003, and began taking 200mg of HCQ b.i.d. She continued to use HCQ for seven years. Her medical history was negative for both hepatic and renal disease.

There was a two-year gap in our records from January 2008 until April 2010. During this period, the patient reported that she had several ocular examinations elsewhere when she was updating her spectacle prescription.

At the April visit, her chief complaint was blurred vision in both eyes that had persisted for the past year. Additionally, the patient said that the glasses she purchased from the other eye care provider were unable to improve her vision to the desired level.

**Diagnostic data.** Upon evaluation, her best-corrected visual acuity was 20/30 O.D. and 20/40 O.S. She exhibited no improvement in visual acuity upon pinhole testing. The pupils were both equal, round and reactive to light, with no evidence of afferent defect. Confrontation visual fields were full to finger counting O.U. Extraocular motility testing found no restrictions of muscle movement.

Ishihara testing revealed color vision deficits that were not observed during previous ocular examinations (11/14 plates O.D. and 8/14 plates O.S.). Two years earlier, Ishihara testing revealed only one missed color plate in the left eye.

Intraocular pressure measured 18mm Hg O.U. Anterior segment evaluation revealed a grade I nuclear sclerotic cataract O.D. and a grade II nuclear sclerotic cataract O.S. Both corneas were negative for vortex keratopathy. A dilated fundus examination revealed crisp optic nerve head margins and a 0.3 x 0.3 cup-to-disc ratio O.U. The fovea light reflex was absent in both eyes. Both maculae exhibited RPE changes that appeared greater superiorly and temporally (O.S.>O.D.) (figures 1 and 2). The RPE changes were significantly more evident when viewed with a red-free filter (figures 3 and 4).

Because HCQ retinopathy is a somewhat rare presentation, I ordered a retina consultation.
The retinal specialists confirmed the aforementioned findings. Additionally, a retinal fluorescein angiogram was performed, which revealed hyperfluorescence surrounding both foveae (figures 5 and 6).

**Diagnosis and follow-up.** I diagnosed the patient with HCQ retinal toxicity, and notified her internist and rheumatologist. All the doctors involved agreed with the recommendation to discontinue the HCQ therapy.

We informed the patient of this decision and scheduled a follow-up appointment with her rheumatologist to consider an alternate therapy.

After the patient was asked to discontinue the HCQ, she was started on methyltrexate. The drug proved to be a failure secondary to a side effect of thrombocytopenia. The rheumatologist found that the combination of prednisone 20mg b.i.d. and Neurontin (gabapentin, Pfizer) 300mg t.i.d. was the best medicinal therapy in this patient’s case.

Because the patient initially was diagnosed with HCQ retinal toxicity, she presented for a six-month and a one-year follow-up examination. At the six-month evaluation, the patient’s ocular assessment was consistent with that at the previous examination, except that her visual acuity decreased from 20/40 to 20/50 O.S. The one-year evaluation showed no change in the anterior segment or fundus findings; however, the patient’s color vision and visual acuity continued to decrease.

On Ishihara testing, the patient scored 4/14 O.D. and 6/14 O.S. Additionally, her visual acuity measured 20/60 O.D. and 20/80 O.S. The patient was asked to return to the retinologist, because she missed her previous appointment secondary to a SLE related hospitalization. I also referred her to a low vision specialist.

**Discussion.** An analysis of studies indicates that the incidence of HCQ retinopathy ranges from 0% to 4%. This variation is believed to be secondary to frank variations in the population, definition of retinopathy and the dosing quantities. The most recent study analyzed nearly 4,000 patients on HCQ therapy and showed a greater than 1% increase in the incidence of HCQ retinopathy occurring after a dosing duration of five to seven years or a cumulative dosage of 1,000g. All told, it appears that HCQ has a well-established safety profile and that an associated retinopathy is rare.

A report by the American Academy of Ophthalmology (AAO) outlined important risk factors for the development of HCQ toxicity. They include use of a dosing regimen that is greater than 6.5mg/kg/d; taking the drug for more than five years; having a high body mass index (unless dosage is appropriately low); a history of renal or liver disease or an accompanying retinal condition; and being older than 60 years of age.

The February 2011 revision of the AAO’s recommendations stressed the importance of monitoring cumulative dosing levels. It is now thought that a total lifetime dose of 1,000g or more increases the likelihood of toxicity and is often independent of the original dose/kg model. The exception to this is in patients of short stature. An exact metric to define “short” was not included in the literature. Additionally, multifocal electroretinogram, spectral-domain optical coherence tomography (SD-OCT)
Our patient weighs 150lbs and is 5’3” tall, which constitutes an elevated body mass index. The dosing should be based on lean (ideal) body weight, because only a small portion of the drug is able to bind to fat.13 Lean body weight is defined as 110lbs plus 5.1lbs per inch over 5ft for men and 100.1lbs plus 5.1lbs per inch over 5ft for women.14 Using this guideline, the patient should have been taking up to 340.6mg of HCQ per day. The average adult dose for HCQ is 200mg b.i.d.9 The patient displayed a second risk factor for HCQ retinopathy by taking the drug for more than five years (seven years). The patient’s adequate liver and renal function was important, because the two organ systems are responsible for 60% of the drug’s uptake and excretion.13

Long-term studies have shown that if an ocular toxicity caused by an antimalarial medication is detected early enough, vision can be preserved upon immediate dosing discontinuation.15 The prognosis is good if the patient has normal central and color vision, and a shallow sco- toma.15 When retinopathy presents with decreased visual acuity, abnormal color vision, absolute scotoma and RPE dropout on a fluorescein angiogram, some continued visual deterioration is likely.15

The prognosis for HCQ patients is difficult to determine because there are very few reports of definitive retinopathy. Of the 49 published cases, just 22 reported the prognosis after medication cessation.15 Of those, one report documented a slight improvement, 14 documented stabilized vision and seven documented further visual deterioration.3

When ordering a Humphrey threshold visual field for a patient who is taking HCQ, you must be certain to test macular function. To do this, perform the central 10-2 threshold test with a red stimulus. This test measures the centermost 20° of visual field. The red stimu- lus has been shown to be more sensitive in detecting chloroquine retinopathy compared to the white stimulus.16

The retinal fluorescein angiogram is an important diagnostic tool in the diagnosis of HCQ retinopathy. During an angiogram, an intact RPE will keep fluid in the choriocapil- laris, away from the retina. When the RPE becomes compromised, hyperfluorescence of the choriocapillaris will be visible.17 In one study, the researchers used an SD-OCT on patients with HCQ retinopathy.18 Structural abnormalities were found in the perifoveal inner segment/outer segment photoreceptor junction. In the most severe cases, there was thinning of the outer nuclear layer and perifoveal hyperscattering as well as increased penetration of the SD-OCT beams into the external limiting membrane, photoreceptors, RPE and choroid.19

At this time, there is no “magic bullet” for HCQ retinal toxicity. Once ocular toxicity secondary to HCQ therapy is suspected, the only effective course of action is to discontinue the medication. Even then, visual deterioration may continue.

There is a fine line to walk when it comes to patient education on HCQ therapy. It is your responsibility to emphasize the importance of timely and thorough ocular examinations, while still informing the patient that the incidence of toxicity is rare. You should stress this information at every follow-up visit, because consistent reiteration will increase patient compliance with his or her ocular examination schedule. All potential complications aside, HCQ therapy often is the best option for many patients with rheumatoid arthritis, lupus and other conditions that require off-label dosing. Should HCQ retinopathy develop, early detection will ensure that the patient has the highest probability of a good visual prognosis.

As eye care providers, close communication must be maintained with primary care physicians and rheumatologists to maximize the patient’s overall wellness. Ultimately, however, it is your obligation to provide the best care possible so that the patient may experience a good quality of life.

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A Review of Micropulse Laser Photocoagulation

By Carolyn Majcher, O.D., and Andrew S. Gurwood, O.D., F.A.A.O., Dipl.

GERMAN OPHTHALMOLOGIST GERD MEYER-SCHWICKERATH first pioneered retinal photocoagulation in the 1940s when he focused natural sunlight into the eye.1,2 Using a heliostat (reflective concave mirror with a central viewing ocular), he constructed a functional sunlight photocoagulator.1,3 Later in his career, Dr. Meyer-Schwickerath assembled the first xenon-arc photocoagulator with Hans Littmann of Zeiss Laboratories in 1956.3 The first xenon-arc photocoagulator produced light comprised of various wavelengths within the visible and infrared spectrum.3 This beam produced destructive, full-thickness retinal burns. Theodore Maiman, Ph.D., designed the first ophthalmic laser in 1960 at the Hughes Research Laboratory in Malibu, Calif.1,3 It emitted monochromatic energy of 694nm.1 Monochromatic lasers allowed tissue-specific photocoagulation, so certain layers of the retina could be targeted—particularly the retinal pigment epithelium (RPE).

Widespread use of ophthalmic laser photocoagulation began following the invention of the argon laser in 1968 by Francis L’Esperance, M.D.4 This platform used an ionized gas lasing medium.4 Today, the more commonly used Neodymium-doped yttrium aluminum garnet (Nd:YAG) and diode lasers use solid-state platforms that utilize crystals and semiconductors respectively.3 Modern laser models were introduced in the 1980s and have become popular because of their portability and ability to deliver laser in both continuous and pulse modes.3

This article reviews the application and therapeutic efficacy of micropulse laser photocoagulation for the treatment of several devastating retinal conditions, including diabetic macular edema (DME), proliferative diabetic retinopathy (PDR), venous occlusion and idiopathic central serious chorioretinopathy (ICSC).

The Lowdown on Lasers

All lasers are comprised of three essential components: a lasing material, a pump source to introduce energy into the lasing material and an optical cavity with reflectors for light amplification.5,6 Population inversion occurs when energy from the pump source is introduced into the lasing material, which excites electrons in the lasing material’s atoms and causes them to go from a steady, low-energy state to an unstable, higher-energy level.6 Decay (the return of electrons to the steady state energy level) stimulates the production of similar-wavelength photons that have the ability to travel in phase as well as in the same direction.6,7 Amplification occurs as photons travel back and forth in the optical cavity through the lasing material between a total reflecting mirror and a partial reflecting mirror.6,7 When sufficient energy has built up, a burst of laser light is released through the partially reflecting mirror. Modifying various laser properties, such as spot size, duration, power and wavelength, creates specific target effects.3

An Overview of Laser Photocoagulation

Photocoagulation is accomplished through protein denaturation that is induced via absorption of radiant energy by the ocular chromophores.3 This process occurs mainly in the melanin of the RPE cells and choroidal melanocytes, where laser...
energy initially is converted into heat. A traditional laser burn creates a heat wave that spreads outward adjacent from the origin of the burn site in the RPE and/or choroid. The “grayish-white” endpoint in conventional threshold photocoagulation signifies that the thermal wave has reached the overlying neurosensory retina with a temperature high enough to damage the natural transparency of the retina. As the transparency is altered, the light placed onto the retina becomes scattered, which creates the white appearance. This appearance typically is associated with a temperature rise of 20°C to 30°C above baseline body temperature. Inevitably, the thermal damage extends beyond the visible burn as collateral temperatures reach 10°C to 20°C above the baseline, contributing to the phenomenon of laser scar expansion over time.

Collateral heat damage from threshold focal photocoagulation for DME causes significant side effects, including retinal scarring. Scars may enlarge progressively up to 300% and can cause significant vision decrease if the fovea becomes involved. Whenever scarring replaces normal retinal architecture with gliotic/fibrotic matrix, irreversible damage to the overlying photoreceptors results. Other potential side effects include the provocation of physiology, which promotes choroidal neovascularization (CNV), subretinal fibrosis and generalized loss of paraxial threshold sensitivity.

Similarly, panretinal photocoagulation (PRP) has been shown to cause a temporary loss in high spatial frequency contrast sensitivity, long-term visual acuity decrease in up to 10% of eyes, tritanopic color vision deficits, elevated dark adaptation threshold and generalized visual field constriction. Patients have reported postoperative difficulty adjusting to dim and bright lighting, sorting dark colors, judging distances, negotiating stairways and avoiding obstacles.

It is unlikely that the effect of conventional argon laser treatment is due to direct closure of retinal microaneurysms. Typically, closure of microaneurysms is delayed following therapy, with a closure rate of just 0.67% at two-week follow-up. Even though closure is incomplete, significant reduction in macular thickness is observable and quantifiable on optical coherence tomography (OCT).

Biologic activities are thought to be the mechanisms by which laser photocoagulation works in sublethally injured RPE cells that surround areas of photocoagulation necrosis. Laser photocoagulation has the ability to upregulate various biochemical mediators with antiangiogenic activity, such as pigment epithelium-derived growth factor (PEDF). Additionally, laser stimulates the release of factors that increase angiotensin II and increase receptor activity, enabling inhibition of vascular endothelial growth factor (VEGF)-induced angiogenesis while decreasing VEGF inducers, such as transforming growth factor beta II. Evidence suggests that decreased serum VEGF levels following PRP in eyes with PDR is likely secondary to a reduction in the tissue’s hypoxic drive. The reduction in VEGF also reduces vascular permeability.

A typical PRP pattern of 1,200 to 1,500 burns of 0.5mm diameter may reduce the number of metabolically active photoreceptors as well as total oxygen consumption of the outer retina by approximately 20%. This reduction in the hypoxic state of the retina re-establishes a balance between retinal oxygen supply and demand. When the outer retinal oxygen consumption is dramatically decreased, oxygen from the choroid—which normally does not reach the inner retina—can now penetrate through the outer retina and compensate for the reduced retinal supply. Autoregulatory retinal arteriolar constriction follows the laser-induced reduction in inner retinal hypoxia, which likely induces a subsequent decrease in downstream capillary hydrostatic pressure and fluid leakage.

The predominant disadvantage to this modality is that it is destructive to viable tissue, which inevitably becomes a collateral casualty.

Retinal photocoagulation has a multitude of clinical applications, including the treatment of various ischemic, inflammatory and degenerative subretinal and intraretinal diseases. In clinical application, photocoagulation has been effective at treating extrafoveal choroidal neovascular membranes secondary to age-related macular degeneration (AMD) and retinal ischemia.

Micropulse Laser Technology

Eight-hundred ten (810nm) micropulse diode laser treatment is a low-intensity procedure that is administered via high-density distribution in both pathologically involved and uninvolved areas of the retina. This treatment was pioneered by Thomas R. Friberg, M.D., and associates in the late 1990s.

There are several commercially available 810nm micropulse lasers, including the OcuLight SLx (IRIDEX Corporation), IQ 810 (IRIDEX Corporation) and the FastPulse (Optos).

Micropulse photocoagulation technique divides the laser emission into a “train” of short, repetitive pulses that persist for 0.1 seconds to 0.5 seconds. The “on” time is the duration of each
MICROPULSE LASER THERAPY

micropulse (typically 100μs to 300μs) and the “off” time (1,700μs to 1,900μs) is the interval between successive micropulses. This “off” time allows for heat dissipation, which decreases collateral damage and confines treatment to the RPE. This is in stark contrast to conventional continuous wave laser, where the same magnitude of energy is delivered throughout the entire exposure cycle of 0.1 seconds to 0.5 seconds.

The duty cycle is calculated by taking the percentage of the period during which the laser is “on.” For example, with a duty cycle of 15% and a period of 1,000μs, the laser would be on for 150μs and off for 850μs (0.15=150/1,000). If the exposure time was set to 100,000μs, the laser would fire 100 repetitive pulses during that interval. The power and duty cycle are both adjustable, permitting the operator to vary the treatment intensity.

When a low duty cycle is used, less heat is generated, allowing the RPE to return to baseline temperature before the next pulse is initiated. This eliminates cumulative thermal build-up. Microscopic, isolated RPE photothermal damage can be achieved with laser powers as low as 10% to 25% of visible threshold powers.

Subthreshold micropulse diode laser photocoagulation (SMD) is designed to target the RPE melanocytes while avoiding photoreceptor damage. The term “subthreshold” refers to photocoagulation that does not produce visible preretinal damage or ophtalmically visible scarring either during or after treatment. In fact, burns are undetectable not only on clinical examination, but also on intravenous fluorescein angiography (IVFA) and fundus autofluorescence (FAF). Intensity of subthreshold treatment can vary from no lesion produced to microscopic destruction of the RPE and photoreceptor outer segment structures.

Such selective tissue photocoagulation is not possible with long, continuous wave exposure times (50ms to 400ms). Less collateral damage can be achieved by making the laser “on” time shorter than the thermal diffusion time. Due to the proximity of the RPE to the photoreceptors, very short laser exposures are required if the operator does not want the thermal wave to reach the neurosensory retina. This lower energy treatment only denatures a small fraction of proteins without causing coagulation necrosis.

When the threshold of sublethal cellular injury is reached via the cumulative addition of denatured proteins, transcriptional activation of cytokine expression, release of growth factors and upregulation of matrix metalloproteinases occurs. The same biologic activities that result from SMD treatment are induced indirectly by conventional threshold photocoagulation in sublethally injured RPE cells adjacent to the areas of the coagulation necrosis zone.

In addition to its advantage of decreased collateral damage over conventional argon laser photocoagulation, the absence of choriotneal scarring allows for an overlapping application of burns that may extend into noninvolved areas of the retina. Frequent retreatment of involved retinal areas is also possible without fear of creating confluent retinal scarring.

Also, because the transmission of near-infrared light through the cornea and lens is greater with an SMD laser than with the shorter-wavelength lasers (e.g., Argon, Krypton), there is less pre-target light scatter, which permits treatment through dense, nuclear sclerotic cataracts.

Micropulse laser therapy is not free of disadvantages, however. The possibility of under-treatment is always a concern. SMD treatment also seems to take longer to reach the same clinical endpoint as conventional continuous laser, particularly when low-density application is used. For example, subthreshold micropulse panretinal photocoagulation (SMD PRP) induces a response that develops gradually, but without marked contraction of neovascular tissue. Another limitation of SMD is that treatment protocols are not well established and there are no standards or dose-response clinical studies that outline specific combinations of pulse energy, duration and treatment density for ideal clinical responses.

Documentation of treated areas and inadvertent re-treatment of areas during a single session continue to be a problem. Because the modality delivers energy without leaving an observable fingerprint, it is incumbent on the surgeon to keep track of what has been treated. One solution to this dilemma is indocyanine green angiography-assisted SMD photocoagulation. SMD laser-treated areas appear dark from the resultant quenching of indocyanine green fluorescence. Micropulse treatment can be angiographically documented to prevent inadvertent re-treatment as well as to aid in the planning of future therapy.

Diabetic Macular Edema

Perhaps the most widely used application of retinal laser therapy is focal and grid photocoagulation for the treatment of DME, which results when inner retinal hypoxia catalyzes the production of VEGF. When the pathologically produced VEGF overcomes the naturally produced inhibitor PEDF from the RPE, increased vascular permeability ensues, which causes the leakage of osmotically active molecules (retinal exudates) into the retinal...
tissues. These exudates siphon water from the capillaries, resulting in intraretinal edema. Additionally, hypoxic autoregulatory dilatation of the arterioles decreases resistance inside the vessels, indirectly increasing downstream capillary hydrostatic pressure. The result is fluid movement into the retinal tissues between the photoreceptors and the horizontal, bipolar and amacrines, yielding disorganization of the retina’s architecture and reduction of its ability to efficiently function as a light-gathering instrument. The outcome is variably reduced visual function.

The therapeutic effect of photocoagulation for DME was first documented in the Early Treatment of Diabetic Retinopathy Study (ETDRS) in 1979. This landmark, randomized control trial included 754 eyes with macular edema and mild to moderate diabetic retinopathy. Patients were randomly assigned to receive focal argon laser photocoagulation or deferral of photocoagulation. Results showed that the combination of focal and grid laser photocoagulation yielded a reduction in the occurrence of moderate visual acuity loss by approximately 50% to 70% in eyes with retinal thickening or associated hard exudate formation that involved or threatened the center of the macula.

The treatment effect was most pronounced in eyes with clinically significant macular edema (CSME). CSME was defined as a thickening of the retina at or within 500 μm of the center of the foveola; hard exudates at or within 500 μm of the center of the foveola; or a zone or zones of retinal thickening measuring one disc area or larger located within one disc diameter of the center of the foveola.

In the ETDRS, a pretreatment fluorescein angiogram was used to identify treatable lesions that were located between 500 μm and two disc diameters of the center of the foveola. “Treatable lesions” included: discrete points of retinal hyperfluorescence or leakage (microaneurysms); areas of diffuse leakage within the retina (microaneurysms, intraretinal microvascular abnormalities or diffusely leaking retinal capillary beds); or large areas of hypofluorescence that were indicative of significant retinal avascular zones.

Focal leakage sites received 50-μm to 100-μm argon blue-green (70% blue 488nm, 30% green 514.5nm) or green-only (514.5nm) burns of 0.1 seconds duration or less with enough power to achieve observable whitening. For all microaneurysms greater than 40 μm in diameter, the researchers attempted to obtain retinal whitening or darkening of the microaneurysm itself—even if repeated burns were necessary. Treatment of lesions within 500 μm of the foveola was recommended only if the visual acuity measured 20/40 and an intact perifoveal capillary network was present. In these cases, the researchers recommended treatment of lesions up to 300 μm from the center of the foveola.

The ETDRS researchers treated areas of diffuse leakage or non-perfusion in a grid pattern using moderate-intensity burns of 50 μm to 200 μm in size, spaced one burn-width apart. They concluded that, for all eyes with CSME, focal photocoagulation should be considered to reduce the risk of additional visual loss; increase the chance of visual improvement; and decrease the possibility for chronic, persistent macular edema.

SMD photocoagulation of DME has gained momentum because of its association with an increase in central retinal sensitivity, as detected by microperimetry. This is in comparison to a decrease within the central 12° of visual field in eyes treated with standard lasers as indicated in the modified ETDRS photocoagulation parameters. The poor absorption of near infrared radiation by the yellow xanthophyll pigment of the macula may also allow for safer treatment administration closer to the center of the fovea.

Three prospective, randomized clinical trials compared the results of the ETDRS or modified ETDRS protocols for conventional argon laser photocoagulation to SMD photocoagulation in eyes with CSME.

The first trial, conducted by João P. Figueira, M.D., and associates, included 84 previously untreated eyes with CSME secondary to type 2 diabetes mellitus that exhibited a best-corrected visual acuity of 20/80 or better. The patients were randomized to receive 810nm SMD photocoagulation or conventional argon laser treatment.

Results showed no statistical difference in visual acuity at one-year follow-up; however, there was a trend for better vision in the SMD group. Additionally, there was no significant difference in contrast sensitivity or central retinal thickness between the two groups at any point during follow-up.

The second trial, lead by Stela Vujosevic, M.D., compared 810nm SMD photocoagulation with the modified ETDRS argon laser treatment protocol. The study included 62 previously untreated eyes with CSME in patients with type 2 diabetes mellitus who exhibited foveal thinning of at least 250 μm and a best-corrected visual acuity of at least 20/200.

There was no significant difference in either visual acuity or central retinal thickness at one-year follow-up between the two treatment groups.
number of treatments was also similar (2.03 treatments in the SMD group vs. 2.1 treatments in the argon laser group). However, mean central 12° retinal sensitivity—as measured by microperimetry—increased significantly at one-year follow-up in the SMD group. In contrast, retinal sensitivity decreased significantly in the argon laser group. Another measurement of general posterior segment health, FAF, remained unchanged in SMD-treated eyes, even after re-treatment. Conversely, all argon laser-treated eyes showed an increased number of FAF changes at one-month follow-up.

The third randomized clinical trial, conducted by Daniel Lavinsky, M.D., and associates, included 125 previously untreated eyes with CSME and retinal thickening within 500μm of the center of the foveola, a central retinal thickness of 250μm or greater and a best-corrected visual acuity that ranged between 20/40 and 20/400.46 Eyes were randomized to one of three treatment groups: Modified ETDRS protocol argon laser photocoagulation; normal-density 810nm SMD photocoagulation; or high-density 810nm SMD photocoagulation.

In both the normal-density and high-density subthreshold groups, the majority of the posterior pole including involved and uninvolved retinal areas was treated. In the normal-density SMD group, a grid of 125μm spots (300ms exposure duration and 15% duty cycle) spaced two burn-widths apart was applied.46 In the high-density group, the researchers confluent applied 125μm burns, with no attempt to specifically target or avoid microaneurysms.

Results showed that high-density SMD photocoagulation was superior to the modified ETDRS treatment recommendation at one-year follow-up, while normal-density SMD eyes fared the worst.46 There was no difference in postoperative central retinal thickness between the high-density SMD group and the modified ETDRS group at one-year follow-up.46 Approximately twice as many eyes experienced a gain of three or more lines in visual acuity at one year in the high-density SMD group (48%) compared to the modified ETDRS group (23%).46

A non-comparative case series of 25 eyes utilized the longest documented follow-up period: three years.44 The researchers indicated that SMD photocoagulation had a beneficial, long-term effect on visual acuity improvement and resolution of CSME.31 At three years, just 8% of the patients experienced a three-line or greater loss in visual acuity.31 By the second year, CSME had completely resolved in 92% of eyes.31 Recurrent CSME was noted in 28% of patients by the third year. Accordingly, 24% of eyes received three sessions of SMD photocoagulation over the three-year period.31 Nevertheless, no detrimental side effects or scarring were associated with repeated treatment.

Proliferative Diabetic Retinopathy
Panretinal photocoagulation, or scatter laser photocoagulation, is used for regressing cases of PDR as well as for treating intraretinal neovascularization secondary to any causative retinal pathology.20 The Diabetic Retinopathy Study (DRS) indicated that PRP reduced the risk of severe visual loss (SVL), which was defined as visual acuity worse than 5/200.28 SVL secondary to vitreo-proliferative retinopathy of any kind typically is the result of either vitreous hemorrhage or tractional retinal detachment.20

In the DRS, treatment reduced the risk of SVL by approximately 50% for eyes with proliferative or severe nonproliferative diabetic retinopathy and visual acuity of 20/100 or better.20 In particular, the DRS showed that the risk of developing SVL outweighed the risks of treatment side effects for eyes with PDR exhibiting high risk characteristics (HRC).20 The HRC were defined as: eyes that exhibited intraretinal neovascularization on or within one disc diameter of the optic disc that equaled or exceeded 1/4 to 1/3 of a disc area in extent with or without vitreous hemorrhage or preretinal hemorrhage; or eyes with neovascularization and preretinal or vitreous hemorrhage with either neovascularization that measured less than 1/4 to 1/3 the size of the optic disc or neovascularization elsewhere that measured at least of a disc area.20 Comparing only eyes with HRC, the rate of SVL was 49% in control eyes and 22% in treated eyes at five-year follow-up.20

The DRS argon treatment technique specified 800 to 1,600, 500μm burns of 0.1 seconds duration that extended to or beyond the vortex vein ampulace.20 Focal treatment was recommended for neovascularization of the disc and retinal surface or elevated neovascularization elsewhere.20 The researchers also recommended focal treatment for any microaneurysms or lesions thought to be causing macular edema before undergoing treatment for PDR.20

Today, patients rarely receive focal treatment for neovascularization of the disc and elevated neovascularization elsewhere. In most cases, only scatter photocoagulation is completed, and treatment frequently is accomplished over two or more sessions.20 Two major studies have investigated the benefits of SMD PRP. The first was a retrospective noncomparative review of 99 eyes with severe non-proliferative retinopathy or any degree of PDR
that were treated with subthreshold 810nm micropulse PRP. These subjects were followed for a mean duration of one year. Treatment was performed using a 500μm aerial spot size, 0.20 second exposure duration, and a 15% duty cycle with an initial power setting of 2,000mW. All visible areas outside the major vascular arcades ranging to the retinal periphery were treated with a tight grid pattern. The mean number of laser applications per session was 1,218. No patient complained of postoperative pain or loss of visual acuity, accommodation, night vision or visual field.

The researchers found that the overall visual acuity of treated subjects was unchanged compared to controls; however, eyes with a visual acuity of 20/30 or better increased from 39% to 48% during the course of the study. The probability of vitreous hemorrhage at one year was 12.5% and the likelihood of vitrectomy was 14.6%.

The authors concluded that, compared to conventional PRP, the response to SMD PRP developed more gradually and without marked contraction of the neovascularization. They also determined that SMD PRP was useful in the management of eyes with extensive, active neovascularization that is more prone to retinal detachment following conventional PRP.

The second study was a prospective non-comparative case series of 13 eyes with PDR that were treated with 810nm SMD PRP. Initially, eyes were treated with 1,500 burns. Retreatment was performed as necessary at six-week intervals thereafter. Laser “on” time was 100μs to 300μs and “off” time was 1,700μs to 1,900μs within an exposure duration of 0.1s to 0.3s. Power was initially adjusted upward until a burn was barely visible and then adjusted to half that value for treatment. The overall number of burns required was approximately 5,250 over three to four treatment sessions, with an average response time of 13 weeks. At six months, 62% of eyes showed complete regression of new vessels, 15% showed some regression and 23% showed no regression.

The authors concluded that satisfactory regression of new vessels was achieved using SMD PRP, although the technique required more burns than would be expected using the argon laser. The numerous advantages of SMD PRP included absence of clinically visible laser scars, sparing of the neurosensory retina and photoreceptors in most cases, and the ability to treat larger areas of involved and uninvolved retina.

Having a decreased hemoglobin absorption profile, treatment is also more successful than conventional laser through preretinal fibrosis, vitreous hemorrhage and thin preretinal blood. SMD PRP allowed for earlier treatment of neovascular retinal diseases given its lack of common side effects compared to conventional focal or pan retinal laser treatment.

Venous Occlusion

The Branch Retinal Vein Occlusion Study (BRVOS) indicated that grid argon laser photocoagulation improves the visual outcome of patients with 20/40 vision or worse who experienced debilitating macular edema three to eighteen months following the retinal venous occlusive event.

Of the treated eyes, 65% gained two or more lines from baseline and maintained that acuity for at least two consecutive visits, compared to 37% of control eyes.

One study compared the effect of SMD grid photocoagulation to conventional threshold krypton grid photocoagulation in 36 eyes with macular edema secondary to BRVO. SMD treatment was performed using a 125μm spot size and a 0.2s exposure duration at 10% duty cycle. Power was determined by means of a continuous-wave test burn, which yielded a medium-white endpoint. In both treatment arms, treatment sites were spaced one burn-width apart and covered the entire area affected by macular edema. The mean number of laser spots was greater in the SMD group (101 vs. 65), because the technique dictated high-density deployment.

Both groups demonstrated a reduced mean foveal thickness of half the original value. The result was achieved at six months in the standard laser group compared to one year for the SMD group.

After one year, there was no difference in mean foveal thickness or total macular volume between the two groups. At 24-month follow-up, the researchers documented a visual acuity gain of three lines or more in 59% of patients in the SMD group compared to 26% of patients in the threshold group. Visual acuity loss (three lines or more) at 24 months was similar between the two groups (12% in the SMD group and 10% in the threshold group).

Similar to the diabetic retinopathy experiments, these results confirm that while SMD treatment may take longer to achieve a similar reduction in edema compared to threshold treatment, long-term visual acuity gain is approximately two times more likely in treated eyes, where photoreceptors are spared.

An additional study showed that treatment with SMD grid photocoagulation, in combination with intravitreal triamcinolone injection, resulted in even better visual outcomes—91% of patients gained at least two lines of visual acuity at one-year follow-up. To date, no clinical trials have documented the head-to-head effi-
MICROPULSE LASER THERAPY

Photoocoagulation is an effective technique in the treatment of neovascularization secondary to BRVO. However, there is no gross pathophysiologic reason to assume that results for venous occlusive disease—or any other retinal vascular diseases that produce neovascularization—would be any different than those found in the PDR trials. Nevertheless, to ensure accuracy, the work needs to be completed.

Idiopathic Central Serous Chorioretinopathy

Idiopathic central serous chorioretinopathy (ICSC) is distinguished by a flat serous detachment of the neurosensory retina secondary to single or multiple serous RPE detachments, with or without areas of RPE atrophy. 

Conventional laser photoocoagulation is not normally indicated for ICSC, because it typically regresses spontaneously within several months. It is only considered in specific cases, including persistent (four to six months) or progressive detachment (with or without inferior guttering); risk of permanent ICSC changes in the fellow eye; following multiple recurrences; or when an individual requires rapid visual recovery. The treatment for these specific cases of ICSC is derived from multiple, randomized, controlled clinical trials, which have indicated that direct argon laser treatment to sites of leakage on IVFA has the potential to reduce disease duration without altering the final visual outcome. Additionally, treatment offers the potential to reduce the recurrence rate, particularly at the specific treatment site.

It is thought that the benefit of photoocoagulation in ICSC is accomplished through occlusion of leaking defects in Bruch’s membrane and the adjacent RPE. Photoocoagulation induces stress on the contacted RPE cells, which promotes the proliferation and remodeling of RPE cells with new, healthy tight junctions, restoring the integrity of the outer blood-retinal barrier. As photoocoagulation destroys the defective RPE barrier, non-proteinaceous subretinal fluid is drawn out rapidly by the oncotic pressure of the choroid. This process reduces fluid accumulation and promotes homeostasis.

One limitation of argon laser therapy for ICSC is that only extrafoveal sites are considered for treatment. Treating affected juxtafoveal or subfoveal areas has the capability of enlarging existing central and paracentral scotomas created by the evolving pathologies. Another side effect that has been reported is the development of CNV. This phenomenon is more common when treatment is applied in closer proximity to the fovea. Here, CNV is generated through a cytochemical response caused by laser-induced ruptures in Bruch’s membrane. The vulnerable tissues are particularly susceptible in the foveal region, where laser energy is absorbed in greater concentrations.

Subthreshold micropulse photoocoagulation has been implemented in cases of ICSC with chronic or persistent leakage. In a prospective, non-comparative case series, researchers evaluated seven patients with chronic ICSC (unresolved after six months), persistent serous neuro-epithelial detachment, metamorphopsia, decreased visual acuity, and one or more active RPE leakage sites identified via IVFA. Photocoagulation using an SMD was initiated 15 minutes after the injection of indocyanine green dye, when staining of the RPE/Bruch’s membrane complex was visible. Leakage sites were treated with a series of 50, 500ms exposures that were separated by 500ms pauses. Each 500ms exposure delivered a train of 250 micropulses at 10% duty cycle, with a 112.5μm retinal spot size at 500mW of power.

Results suggested that, within two weeks following treatment, visual acuity and serous detachment improved in all seven patients. Complete resolution of the serous neuro-epithelial detachment occurred within a median of six weeks in five patients, while the remaining two exhibited only a marked reduction. At one year, the researchers noted no recurrence or worsening of the serous neuro-epithelial detachments or a decrease in visual acuity.

Another prospective consecutive case series included 26 eyes with ICSC juxtafoveal leakage that persisted for longer than four months. Eyes were divided into three groups based on IVFA findings: Point source leakage without associated RPE atrophy; point source leakage and associated RPE atrophy; and diffuse RPE decompensation without definite point source leakage. SMD was applied, dispensing approximately 100 exposures to each leaking site using an 810nm micropulse diode laser with 125μm spot size, 2ms exposure duration of 15% duty cycle and a mean power of 535mW.

In the first group, 83.3% of eyes experienced an improvement in visual acuity of three lines or greater, and all patients exhibited total reabsorption of subretinal fluid without recurrence after eight months of follow-up. In the second group, 89% of eyes had total subretinal fluid reabsorption after one to three photoocoagulation sessions, and 77.8% had an improvement in visual acuity of three lines or greater. In the third group, 45% of eyes exhibited subretinal fluid reabsorption, with just 27% of those eyes gaining three or more lines.
of visual acuity at the end of the follow-up.60 The remaining 55% of eyes required photodynamic therapy for final subretinal fluid reabsorption.34,40 No eyes in any group developed laser-related scotoma, even after repeat treatment.40

The authors concluded that SMD photocoagulation is effective in treating ICSC exhibiting point source leakage as identified by IVFA.40 The authors noted that, in eyes with associated RPE atrophy or diffuse RPE decompensation, rapid recurrence is common and supplemental photodynamic therapy may be necessary.40

SMD photocoagulation seems to offer a superior safety profile and appears to be as effective at treating numerous retinal conditions as conventional continuous wave argon laser photocoagulation.9,12,43 The combination of budding micropulse delivery with radiation of various wavelengths is also groundbreaking, offering exciting new options in photocoagulation therapy for retinal disease.

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**MICROPULSE LASER THERAPY**

**Questions**

1. Subthreshold micropulse diode laser photocoagulation has been used to treat which retinal condition?
   a. Diabetic macular edema (DME).
   b. Proliferative diabetic retinopathy.
   c. Central serous chorioretinopathy.
   d. All of the above.

2. Which item is NOT an essential laser component?
   a. Lasing material.
   b. Amplification diode.
   c. Pump source.
   d. Optical cavity with reflectors.

3. Which property of laser application can be modified to create specific target effects?
   a. Spot size.
   b. Exposure duration.
   c. Power.
   d. All of the above.

4. What is NOT a potential side effect of focal photocoagulation treatment of DME?
   a. Progressive enlargement of retinal scars.
   b. Generalized peripheral visual field constriction.
   c. Subretinal fibrosis.
   d. Decreased paraxial retinal sensitivity.

5. What is the LEAST likely mechanism of action for conventional argon laser treatment?
   a. Direct closure of retinal microaneurysms.
   b. Autoregulatory retinal arteriolar constriction.
   c. Upregulation of pigment-derived growth factor (PEDF).
   d. Reduced retinal oxygen consumption.

6. What is a defining characteristic of subthreshold micropulse diode laser photocoagulation treatment?
   a. It divides laser emission into a train of short repetitive pulses.
   b. It uses a near-infrared wavelength laser of 810nm.
   c. Laser burns are not detectable ophthalmically, either during or after treatment.
   d. All of the above.

7. Which statement best defines subthreshold photocoagulation treatment?
   a. It divides laser emission into a train of short repetitive pulses.
   b. It uses of a near-infrared wavelength laser of 810nm.
   c. Laser burns are not detectable ophthalmically, either during or after treatment.
   d. All of the above.

8. Which statement is true?
   a. Direct closure of retinal microaneurysms.
   b. Autoregulatory retinal arteriolar constriction.
   c. Upregulation of pigment-derived growth factor (PEDF).
   d. Reduced retinal oxygen consumption.

9. What is NOT an advantage of subthreshold micropulse diode laser photocoagulation over conventional argon laser photocoagulation?
   a. Decreased burn collateral heat damage.
   b. Simple and easy documentation of treated areas.
   c. Increased pre-target laser light scatter.
   d. None of the above.

10. What is NOT a contributing cause of DME?
    a. Increased levels of vascular endothelial growth factor (VEGF).
    b. Osmotically active intraretinal deposits.
    c. Increased capillary hydrostatic pressure.
    d. Increased levels of PEDF.

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**Examination Answer Sheet**

Valid for credit through December 1, 2014

A Review of Micropulse Laser Photocoagulation

Directions: Select one answer for each question in the exam and completely darken the appropriate circle. A minimum score of 70% is required to earn credit. There is a $20 fee to take this course

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There is an eight-to-ten week processing time for this exam.

1. __________
   a. Diabetic macular edema (DME).
   b. Proliferative diabetic retinopathy.
   c. Central serous chorioretinopathy.
   d. All of the above.

2. __________
   a. Lasing material.
   b. Amplification diode.
   c. Pump source.
   d. Optical cavity with reflectors.

3. __________
   a. Spot size.
   b. Exposure duration.
   c. Power.
   d. All of the above.

4. __________
   a. Progressive enlargement of retinal scars.
   b. Generalized peripheral visual field constriction.
   c. Subretinal fibrosis.
   d. Decreased paraxial retinal sensitivity.

5. __________
   a. Direct closure of retinal microaneurysms.
   b. Autoregulatory retinal arteriolar constriction.
   c. Upregulation of pigment-derived growth factor (PEDF).
   d. Reduced retinal oxygen consumption.

6. __________
   a. It divides laser emission into a train of short repetitive pulses.
   b. It uses a near-infrared wavelength laser of 810nm.
   c. Laser burns are not detectable ophthalmically, either during or after treatment.
   d. All of the above.

7. __________
   a. Direct closure of retinal microaneurysms.
   b. Autoregulatory retinal arteriolar constriction.
   c. Upregulation of pigment-derived growth factor (PEDF).
   d. Reduced retinal oxygen consumption.

8. __________
   a. Subthreshold micropulse diode laser photocoagulation burns are visible on clinical examination, intravenous fluorescein angiography and fundus autofluorescence.
   b. Subthreshold micropulse diode laser photocoagulation burns typically are not detectable by clinical examination, intravenous fluorescein angiography and fundus autofluorescence.
   c. Subthreshold micropulse diode laser photocoagulation burns are visible only on intravenous fluorescein angiography.
   d. Subthreshold micropulse diode laser photocoagulation burns are visible only on fundus autofluorescence.

9. __________
   a. Decreased burn collateral heat damage.
   b. Simple and easy documentation of treated areas.
   c. Increased pre-target laser light scatter.
   d. None of the above.

10. __________
    a. Increased levels of vascular endothelial growth factor (VEGF).
    b. Osmotically active intraretinal deposits.
    c. Increased capillary hydrostatic pressure.
    d. Increased levels of PEDF.
The Clinical Applications of Multispectral Imaging

By Richard Maharaj, O.D., B.Sc.

DIAGNOSTIC IMAGING OF THE POSTERIOR SEGMENT is one of the most interesting and dynamic topic areas in eye care. With several advanced diagnostic technologies on the market, including confocal laser scanning microscopy, spectral-domain optical coherence tomography (SD-OCT) and fundus autofluorescence (FAF), it is virtually impossible for eye care professionals to exhaustively upgrade their practices with the latest and greatest devices.

Often, it is the simplest ideas that yield the best results. It is this practical approach to retinal imaging that has propelled a Canadian company, Annidis Health Systems, to develop the RHA. The RHA, a digital imaging device that employs multispectral imaging (MSI) as a fundamental method of visualizing the retina, received 510(k) clearance from the FDA in July 2011. The device uses multiple monochromatic LED-sourced wavelengths—ranging from 550nm to 780nm—to dissect and visualize the retina in spectral slices, from the inner limiting membrane all the way to the choroid.

Fundus imaging allows the clinician to visualize different retinal structures based on their absorption spectra. Within an image, structures with relatively large absorption spectra appear dark, while features with relatively weak absorption spectra appear bright. Image processing can further highlight differences between the absorption spectra of retinal features.

Of particular clinical value, the RHA includes a feature that highlights the difference in the absorption spectra between oxygenated hemoglobin (arterial blood) and deoxygenated hemoglobin (venous blood). Within this oxy/deoxy Hb map, areas with a relatively higher percentage of oxygenated blood will appear brighter than regions with a lower percentage of oxygenated Hb (figure 1).1,2

Similar to the visualization of lipofuscin on FAF, RHA’s unique mapping feature generates an accurate representation of metabolic activity. Oxy/deoxy Hb mapping of the posterior segment can be used not only to approximate areas oxygenated Hb saturation in the retina, but also to enhance choroidal vascular species.

This article reviews applications of MSI as well as compares the ability of various imaging devices to help facilitate an early diagnosis of rare and occult retinal pathologies.

The Use of MSI in Primary Eye Care

Retinal angiomatous proliferation (RAP) is a particular subset of exudative macular degeneration that was first characterized in 1992. RAP is a specific type of occult lesion that originates in the neurosensory retina as opposed to the choroidal space.3 What makes this type of occult lesion difficult to manage is the atypical natural course of the disease.

In a primary care setting, AMD progression typically is monitored based on the ophthalmological changes of drusen—both with and without retinal pigment epithelial (RPE) changes. Once in the exudative stage, angiography and OCT help to further classify neovascularization into its appropriate category.

In RAP, a vasogenic sequence stimulates intraretinal neovascularization (IRN). This occult lesion extends posteriorly toward the subretinal space and proliferates, forming retinal-retinal anastomosis and an accompanying pigmented epithelial detachment (PED). This process further stimulates the growth of a choroidal neovascular membrane (CNVM), which communicates with the vascularized PED. Unlike classic CNVM development that precedes retinal choroidal anastomosis (RCA) and subsequent PED noted with classic and occult lesions, RAP has an insidious initiation.4
Clinical Examples

Here are four brief case reports that showcase the clinical utility of MSI imaging:

**Case 1.** A 64-year-old white female presented with a family history that was significant for AMD, but no history of smoking. Entering corrected visual acuity measured 20/30 O.D. and 20/20 O.S. The patient exhibited discrete areas of RPE atrophy in her right eye that were only visible with long-wave-length near infrared (NIR) MSI (figure 2).

At this stage in the pathogenesis, this finding was the only indicator of an underlying problem. Given the presence of confluent drusen with mild RPE atrophy, we performed no further testing. We placed her on oral antioxidant therapy and carotenoid supplementation, and recommended annual follow-up as well as home Amsler grid monitoring.

Within the year, the patient developed an RAP lesion in the affected eye. A comparison between IVFA and oxy/deoxy Hb map on RHA depicted an area of leakage (figure 3). The intraretinal leakage was evident in the late stages, which correlated well with the increased foveal hypersaturation on oxy/deoxy Hb on RHA. The pathology was confirmed by both tertiary tests, and we referred the patient for anti-VEGF therapy with intravitreal ranibizumab (Lucentis, Genentech).

Following anti-VEGF therapy, visual recovery was remarkable. Additionally, both the intraretinal fluid and subretinal fluid resolved completely. However, the five-year prognosis for this patient remained guarded, given the natural course of this type of exudation.

**Case 2.** An 81-year-old white female presented with clinical findings that were suggestive of exudative AMD in her left eye. She received a prosthetic right eye following significant trauma 10 years earlier. Her ocular history was significant for dry AMD. Her current medications included AREDS-formulated multivitamins and carotenoid supplements.

Her best-corrected visual acuity measured 20/30 O.S. Digital fundus imaging revealed a confluent patch of drusen larger than 125μm; however, the obvious atrophic RPE was apparent using NIR imaging of the RPE choroid complex (figures 4 and 5). Stratus OCT (Carl Zeiss Meditec) imaging of this patient confirmed a PED with associated intraretinal cysts and fluid.

The comparison of late-stage IVFA to the oxy/deoxy Hb map on RHA revealed a distinct area of hypersaturation, which was congruent to the late leakage observed on angiography.

Retrospectively analyzing this case, the entity’s pathogenesis initially appeared in the form of RPE disruption. Color fundus photography, which is similar to that of the visible spectrum of the human eye using white light ophthalmoscopy, failed to show the focal area of atrophy. Here, the use of MSI completely illustrated the natural history of this type of exudative AMD—from a focal area of RPE disruption and atrophy to a full-blown occult lesion.

The first observable finding using NIR imaging of the RPE suggests that this diagnostic examination should be part of every macular assessment on at-risk patients. NIR
imaging is particularly useful on the fellow eyes of patients with existing lesions, because current evidence indicates that virtually all unilateral cases will convert to bilateral cases in due course.\(^5\)

Fortunately this patient received anti-VEGF therapy monthly in a treat-and-extend approach, which adequately resolved the lesion and has been maintained since that time.

- **Case 3.** A 45-year-old white male presented with intraretinal hemorrhaging that was visualized on both SD-OCT for in vivo dissection and RHA for topographical spectral slices. The RHA image set showed slices from the nerve fiber layer to the RPE-choroid complex.

  In vivo dissection offered a clear depiction of a PED as well as the intraretinal hemorrhage and associated edema. In the SD-OCT image, we saw that the bleed spanned posteriorly; however, the RHA spectral slicing revealed an underlying macular hole. The intraretinal blood was confined to the anterior layers, masking the hole. It was likely that this hole was caused by retinal traction in the area secondary to the sudden collection of blood and fluid. Note that the splinter hemorrhages in the anterior retina located nasally to the main area of leakage did not travel deeper than the nerve fiber layer and were absent on the bottom row of longer wavelength MSI images.

  Oxy/deoxy Hb mapping with RHA demonstrated hypersaturation surrounding the hole, which was highlighting the presence of blood (figure 6). As in the previous cases, these hypersaturated areas tended to agree with the late-phase IVFA.

  In this patient, intraretinal blood eventually was reabsorbed and the hole was assessed for repair. However, given the longstanding nature of the condition and the associated scarring, we deferred surgical intervention.

- **Case 4.** A 50-year-old white male presented with chronic, recurrent central serous chorioretinopathy (CSCR) that persisted for the last five years. We evaluated a color composite image from the RHA, topographical spectral slices and a oxy/deoxy Hb map of this longstanding case of CSCR (figure 7). Interestingly, visual acuity measured 20/20-in this right eye; however, the oxy/deoxy Hb map showed the choroidal glow showing though Bruch’s membrane and also highlighted the hypersaturated region, which categorized this atrophic macula as high risk for exudative development.

  For this patient, we considered a diagnosis of polypoidal choroidal vasculopathy (PCV), which has been shown to masquerade as chronic CSCR.\(^6\) On closer analysis of the monochromatic images, the macula seemed to be fed from the nearby arterial supply and may have been a source for this atrophy. In fact, with a red-free equivalent wavelength, the atrophy is almost completely invisible.

  Over a long period of time, chronic CSCR will result in a disruption to the photoreceptor outer segments as well as cause a honeycomb pattern of RPE disruption. The RPE pattern demonstrates the atrophic areas of leakage through Bruch’s membrane, which allows access to the intraretinal space.

  Repetitive insult to the RPE—originally allowing leakage from the choriocapillaris to the intraretinal space—may permit the development of a potential portal for new anastomosis.\(^7\)
With this topographical view, the potential pathology became evident. The hypersaturated “pods” were noticeable immediately surrounding the atrophic macula on the oxy/deoxy Hb map. The atrophic RPE obscured the underlying choroid; however, the questionable RPE integrity and chronic course suggested a risk of PCV. Indocyanine green (ICG) angiography was not warranted at this point, and we recommended close follow-up every six months as well as antioxidant and carotenoid supplementation although this may have very little impact on long-term prognosis.

Discussion

Due to its ubiquity and occult nature, RAP gave the practitioners limited diagnostic tools to identify these pathologies early enough to permit meaningful intervention in cases 1 and 2. RPE atrophy in both of the cases was, in fact, the first physical representation of the pathology’s progression, and identification of this atrophy may be an early marker for IRN.

Physiologically, the atrophy is a result of local inflammatory insult, which is now known to play a key role in AMD development. The resulting inflammatory cascade that stimulates atrophy might be concomitantly stimulating IRN.

We are still uncertain about the chronology of IRN and CNVM development, but evidence is clear that RPE atrophy is a local inflammatory marker. Therefore, identifying key changes to the integrity of the RPE should be a point of focus for patients who are at risk for RAP and exudative AMD in general. In both cases, the relatively swift progression of the pathology, as well as the lack of objective findings, is both obvious and troubling.

From the AREDS findings, we can identify the initial risk of patients developing advanced AMD over five years with the singular presence of confluent drusen coupled with the focal area of RPE atrophy. Each factor carries a 3% risk in isolation, but the combined occurrence increases the five-year risk to 12%. Consequently, a reduced risk assessment yielded just a 3% risk of advanced progression.

To accurately assess risk and determine management protocols, you must identify all associated factors. Detecting and monitoring RPE disruption and atrophy is a clear area that we, as eye care providers, can improve upon. And in these cases, for example, MSI permitted the identification of the atrophic changes to the overlying RPE; these findings were not visible on ophthalmoscopy or digital fundus photography.

Finally, angiography studies—particularly ICG—have great potential in describing the extent of choroidal involvement compared to IVFA. ICG uses a near-infrared absorption of 770nm to 805nm and emits between 770nm and 880nm, with a peak of 835nm. Early technology limited the usefulness of ICG due to poor film processing and low-resolution imaging; however, with current ICG modules and systems, this is no longer a problem.

ICG fluoresces through naturally occurring macular pigments, such as xanthophyll and melanin. The invasive nature of ICG does, however, put the patient at risk for diverse events, including mortality. Fortunately, OCT is completely non-invasive and is useful in revealing intraretinal cysts, edema, highly refractive intraretinal masses and PED development in suspected RAP patients.

MSI vs. Other Imaging Devices

SD-OCT permits visualization of a cross-sectional slice of the retina. Combining multiple slices allows for a seamless review of an entire area. Digital fundus photography has been a proven tool that adds diagnostic value to the practitioner. In the OHTS, fundus imaging identified four times more nerve fiber hemorrhages than the human counterpart.

Today, the RHA takes digital imaging to a new diagnostic level and adds the intuitive topographic/layered view of the area. Eye care providers now have a comprehensive repertoire of diagnostic tools to choose from. Access to both in vivo dissections on SD-OCT and topographic spectral slices on RHA generates a wealth of information that can help a managing clinician more accurately diagnose an occult pathology like RAP and exudative AMD.

The differentiating factors between MSI and digital fundus imaging are multifaceted—one of which being monochromatic spectral slicing. Digital fundus cameras
are designed to view only the visible spectrum. This is why red-free images from a digital source are similar to what the clinician sees during ophthalmoscopy with a red-free filter. Similarly, there is no infrared filter on a slit-lamp, because our macula cannot resolve that wavelength of light.

Considering that most of the metabolic activity occurs in the deeper aspects of the retina, it is imperative to be able to visualize its anatomy without the "noise" of the anterior layers. MSI has the ability to utilize a single color at a time, which optimizes the contrast and brightness of each spectral slice. MSI is an emerging technology that is being developed in a solitary device that will continue to evolve as new metabolic diagnostics are required for enhanced patient care.

With multiple wavelength sources, ranging from the visible to NIR, eye care practitioners are able to examine the x-, y- and z-axis of complex neurovascular tissue. Clinicians can use MSI to image several devastating posterior segment conditions including vitreo-macular traction syndrome, diabetic retinopathy, glaucoma and vascular occlusive disease.

The cases reviewed above show how visualization of oxygenated Hb in the posterior segment could change how clinicians diagnose pathologies that have vascular components. Reducing the reliance on invasive testing will not only decrease the incidence of adverse events, but also increase compliance with management strategies and yield better outcomes.

Technology is constantly yielding novel methods of examining known structures within the posterior segment. These advances permit the eye care practitioner to see the eye in a completely new way, and potentially identify pathologies with more ease than ever before.

Cutting-edge diagnostic strategies, such as MSI imaging, ultimately will have a profound impact on the way we currently understand pathologi-cal development.

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