Is Effective Photocoagulation Without Laser-Induced Damage Possible?

Is subthreshold diode micropulse photocoagulation the "Emperor's new laser" or a paradigm shift for retinal vascular disease?

BY JEFFREY K. LUTTRULL, MD

Visible endpoint retinal photocoagulation has been the mainstay of treatment for diabetic retinopathy and other retinal vascular disorders for many years.[1,2] Grey-to-white retinal burns testify to the thermal retinal destruction inherent in conventional threshold and suprathreshold photocoagulation.

This thermal tissue damage is the sole source of the many potential complications of conventional photocoagulation that may lead to immediate and late visual loss.[3] Such complications include inadvertent foveal burns, pre- and subretinal fibrosis, choroidal neovascularization and progressive expansion of laser scars. Inflammation resulting from this same tissue destruction may cause or exacerbate macular edema, induce precipitous contraction of fibrovascular proliferation with retinal detachment and vitreous hemorrhage, and cause uveitis, serous choroidal detachment, angle closure or hypotony.[4]

Conventional photocoagulation is often painful. Local anesthesia, with its own attendant risks, may be required. Alternatively, treatment may be divided into stages over an extended time to minimize treatment pain and postoperative inflammation. Transient reduction in visual acuity is common following conventional photocoagulation. Such factors may increase patient anxiety and reduce compliance with the prescribed treatment regimen compromising effective treatment. Some of these complications are rare. Others, including treatment pain, progressive scar expansion, visual field loss, transient visual loss and decreased night vision, are so common as to be accepted as inevitable side-effects of conventional

Figure 1. Preop fundus photo of the left eye (A) demonstrating clinically significant macular edema (CSME) with heavy hard exudate deposition. Postoperative fundus photo of left eye (B) following subthreshold diode micropulse (SDM). Note resolution of macular edema and exudates; also note absence of clinically visible laser lesions.

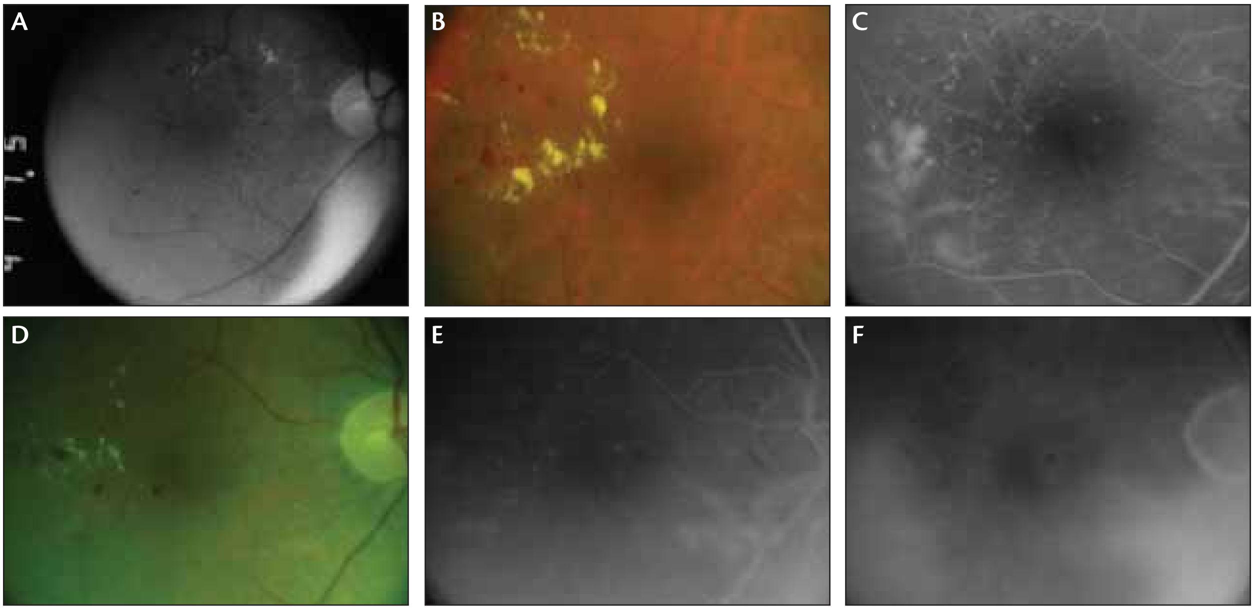

Figure 2. Preoperative fundus photograph of diffuse CSME in right eye January 2001 (A). Severe proliferative diabetic retinopathy with retinal neovascularization was also present. Preoperative visual acuity 20/30. Macular and panretinal SDM was performed. Fundus photo of right eye (B), August 2004. Note resolution of previous CSME super nasally with new CSME in temporal macula. Note absence of clinically visible laser lesions from prior SDM. Early phase IV fundus fluorescein angiogram (FA) of right eye (C), August 2004. Note absence of angiographically visible laser lesions from prior SDM in super nasal macula. Note temporal capillary nonperfusion and leakage from regressed retinal neovascularization. Additional macular SDM was performed for new CSME followed by additional panretinal SDM. Fundus photograph of right eye (D), December 2005. Note resolution of CSME, involution of retinal neovascularization and absence of visible laser lesions despite total of 2,665 macular and 7,486 spots of panretinal SDM applied since 2001. Visual acuity of right eye = 20/25. Early phase FA (E), December 2005. Note absence of visible laser lesions. Late phase FA (F), December 2005. Note persistent angiographic leakage from clinically involutional (regressed and fibrotic) retinal neovascularization.

panretinal photocoagulation.[5]

It is problematic, then, that thermal retinal destruction has never been demonstrated to be necessary to achieve the benefits of photocoagulation treatment. Indeed, the history of photocoagulation for retinal vascular disease suggests the contrary. Since the Diabetic Retinopathy Study almost 30 years ago, one may observe an orderly progression from Xenon arc to suprathreshold argon blue-green, argon green, krypton red and diode lasers; and from dense grey-white retinal burns to *light, minimally intensive* and subthreshold treatment protocols each reporting effective photocoagulation despite progressive reductions in retinal destruction and treatment complications.[1,6-8] Recently, Luttrull, Musch and Mainster reported a new laser technique which can effectively treat retinal vascular disease without causing any laser-induced retinal damage.[9] How is this possible?

SDM PHOTOCOAGULATION: THE THEORY

To paraphrase Samuel Johnson, the wonder of SDM is not that it works well, but that it works at all.[10] SDM exploits three key principals to achieve clinically effective yet atraumatic photocoagulation.

• **Selectivity**. SDM targets the retinal pigment epithelium (RPE). The diode 810-µm (infrared) laser is maximally absorbed by the melanosomes of the RPE and underlying choroid while sparing neurosensory retina. Evidence increasingly suggests that cellular factors produced and mediated by the RPE such as vascular endothelial growth factor (VEGF), pigment epithelium derived factor (PEDF) and others may play essential roles in the development of complications of retinal vascular disease such as macular edema and neovascularization and are apt targets for treatment.[11]

• ***Cold* photocoagulation.** In micropulsing, diode laser applications are delivered in millisecond envelopes similar to conventional continuous wave lasers. Within each delivery envelope, however, the laser energy is divided into a train of microsecond packets. If the time interval between these microsecond laser bursts exceeds the thermal relaxation time of the target molecule (melanin), there is no clinically significant thermal effect or injury at the cellular level despite achieving intracellular photocoagulation effects.[12] Such *low-duty cycle* (5% to 15% on and 95% to 85% off) SDM increases the safety margin in being able to

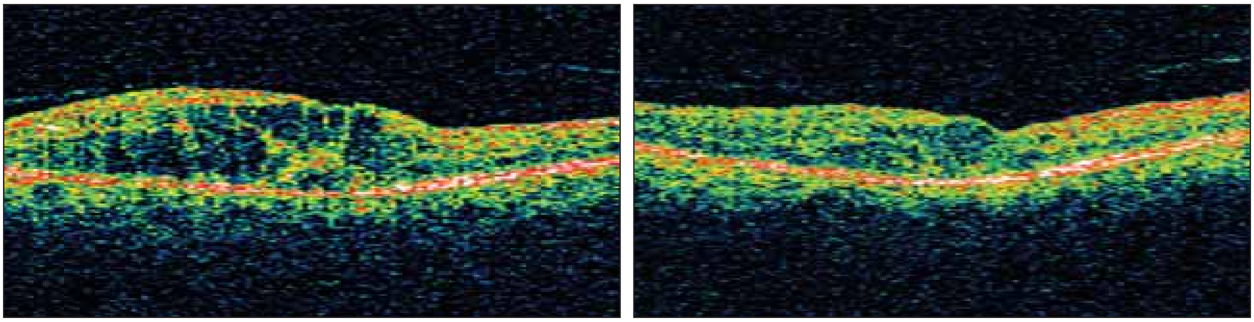

Figure 3. Optical coherence tomography (OCT) of CSME in right eye preoperatively (A). OCT 3 months following macular SDM. Note marked resolution of macular edema (B).

avoid creating inadvertent threshold lesions by 10-fold over continuous wave lasers.[9] Thus, while typical subthreshold continuous-wave or even high-duty cycle micropulse photocoagulation treatment protocols (which behave clinically much like a continuous-wave laser) are difficult to titrate, reducing rather than eliminating retinal damage, low-duty cycle SDM can reliably perform truly atraumatic subthreshold retinal photocoagulation.[13]

> Because of the lack of any laser-induced retinal damage, SDM can be repeated as necessary over time until the desired clinical effect is achieved.

• **Cumulative effect.** The same biologic effect can be achieved by many low-energy or few high-energy laser applications. SDM operates at energy levels sufficient to produce biologic photocoagulation effects without causing cell damage or destruction.[14] By increasing the density of this low-intensity treatment, clinically effective photocoagulation can be achieved by SDM without tissue injury. For example, I treat diabetic macular edema with confluent SDM over all areas of retinal thickening up to the edge of the fovea. With a 125-µm spot size, an average macular SDM treatment employs 1,000 SDM applications — a marked departure from standard Early Treatment of Diabetic Retinopathy Study (ETDRS) techniques. Because of the lack of any laser-induced retinal damage SDM can also be repeated as necessary over time until the desired clinical effect is achieved.

SDM IN PRACTICE

Until recently most clinical studies describing use of micropulse diode laser photocoagulation for treatment of retinal vascular disease have described performance of classical subthreshold photocoagulation for diabetic macular edema aimed at reducing retinal damage.[15] Recently, a new subvisible endpoint high-density low-intensity SDM photocoagulation technique designed to avoid any clinically or angiographically detectable laser treatment lesions was reported.

In a pilot study of SDM, CSME was effectively treated without the creation of any laser lesions detectable by clinical examination or fluorescein angiography postoperatively.[9] These findings were corroborated by a smaller nonrandomized prospective study of eyes treated with SDM for CSME and followed with fluorescein angiography and serial OCT[16,17] (Figures 1 through 3). Once again, despite effective treatment documented by OCT there were no clinically or angiographically detectable laser lesions postoperatively. Consistent with the absence of laser-induced thermal retinal damage, neither study noted any complication of SDM.

Effective treatment of proliferative diabetic retinopathy and retinal vein occlusions has been noted as well and first reported at the Cannes Retina Festival 24th Annual Meeting of the American Society of Retina Specialists (ASRS) & 6th Annual Meeting of the European Vitreoretinal Society (EVRS).[18] More recently, in a prospective randomized clinical pilot trial in eyes with macular edema complicating branch retinal vein occlusion, SDM demonstrated comparable therapeutic results to conventional visible endpoint grid photocoagulation with regard to visual acuity and resolution of macular edema, but without any of the biomicroscopic and angiographic signs of laser-induced damage associated with the conventional treatment.[19]

SDM: MECHANISTIC IMPLICATIONS

Traditional theories proposed to explain the therapeutic effects of conventional photocoagulation not surprisingly focus on thermal retinal destruction as the source, either direct or indirect, of the treatment benefit. Such theories include improved transretinal oxygen transmission, reduced retinal oxygen demand, alterations in retinal and choroidal blood flow and debridement of dysfunctional RPE.[20] Yet SDM appears to be effective without causing any clinically apparent retinal, RPE or choroidal injury. The atraumatic nature of SDM would thus seem to preclude these proposed mechanisms of laser action.

Mounting evidence indicates that the primary mediators of the complications of retinal vascular disease may be cytokines, such as VEGF and PEDF, derived from the RPE.[21-25] We are currently in the midst of a revolution in the pharmacologic treatment of retinal disease responding with great success to these very observations. In the absence of thermal retinal destruction, could it be that SDM may somehow influence the RPE to alter its production of such potent cellular factors?[24] Such a mechanism of action could explain the effectiveness of SDM. If so, might this also be a mechanism of action of even conventional photocoagulation? Could the benefits of even conventional threshold and suprathreshold photocoagulation actually stem from photocoagulative effects on seemingly unaffected RPE cells outside the margins of the (possibly unnecessarily) thermally destroyed retinal tissue?

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CONCLUSION

Is there a future for photocoagulation for retinal vascular disease in the era of drug therapy? While drug effects are often rapid, they are also often transient. Our lengthy experience with photocoagulation indicates, however, that while laser effects may manifest more slowly, the effect is lasting. Complementary rather than exclusionary roles are suggested. If it remains a useful tool, will photocoagulation for retinal vascular disease continue to look like it did three decades ago?

When using high-density/low-intensity SDM protocols to treat the complications of retinal vascular disease there is no visible laser lesion (endpoint) at the time of treatment or at any point postoperatively.[9,13] This lack of a visible treatment marker is often disconcerting to retinal surgeons accustomed to a clear indicator of what they have done and where they have been. With SDM, the only indicator of treatment is the clinical effect. Certainly, this at least approaches a therapeutic ideal. Implicit in the dictum "First, do no harm" is the philosophy that there must be compelling reason to cause injury in order to bring healing. Given the choice between two courses of treatment with equivalent outcomes, the least destructive is always to be preferred. Is it possible to perform effective photocoagulation for retinal vascular disease without any laser-induced retinal damage or associated complication? Evidence, albeit limited, suggests that it may be. There is compelling reason to find out. ■

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