To date, all of the noninvasive procedures that increase aqueous outflow involve the use of a laser to mediate the desired effects. Although these treatment modalities are relatively effective, they all have several limitations. For one, laser trabeculoplasty (LTP) requires a slit lamp for viewing the angle and for the application of laser energy. Another drawback is that these systems are designed such that the patient must sit upright at a slit lamp with his or her head carefully positioned in the headrest. This positioning can sometimes be challenging, particularly for patients with debilitating neck and back pathology. Finally, successful LTP requires that the surgeon have an excellent view of the trabecular meshwork (TM), yet visualization is sometimes limited by the iris configuration, corneal opacities, or patients’ lack of cooperation.

The aforementioned obstacles have motivated innovators to seek therapeutic alternatives that will maintain the safety and efficacy of LTP while minimizing its weaknesses. Based on the observation that IOP tends to increase after intra- or extracapsular cataract surgery but typically decreases after phacoemulsification surgery, researchers began investigating sonic energy as a cause of the ocular hypotensive effect. Wang et al reported that a phacoemulsification ultrasound stressor activates the IL-1/NF-κB/ELAM-1 pathway in TM cells.¹ This response initiates a complex and incompletely understood cascade that culminates in an improved outflow facility. The objective finding that sonic energy can mediate IOP lowering has inspired several researchers to pursue this medium and transform it into a clinically meaningful instrument. This article focuses on two procedures: therapeutic ultrasound for glaucoma (TUG) and deep wave trabeculoplasty (DWT). The sidebars by Iqbal Ike Ahmed, MD, FRCSC, and Miho Nozaki, MD, PhD, discuss micropulse laser trabeculoplasty and pattern scanning laser trabeculoplasty, respectively.

**THERAPEUTIC ULTRASOUND FOR GLAUCOMA**

Donald Schwartz, MD, has been an active proponent of transforming sonic energy into an IOP-lowering...
By Iqbal Ike K. Ahmed, MD, FRCSC

The popularity of selective laser trabeculoplasty has risen in recent years owing to its significantly lower laser fluency and enhanced predictability compared to argon laser trabeculoplasty (ALT). Selective laser trabeculoplasty (SLT) has also been found to be equal in efficacy to topical prostaglandin monotherapy at lowering IOP.\(^1\) One of the advantages of SLT compared to ALT has been minimal thermal and collateral tissue damage, with the theoretical benefit of repeatability.

SLT still rarely may cause pressure spikes after treatment, however, in addition to mild and transient inflammation and pain. Growing knowledge about heat stress proteins and cellular response emphasizes that lethal damage to cells is not necessary to provide a therapeutic benefit in retinovascular applications,\(^2,3\) and the same is likely true with glaucoma.

Micropulse technology (Iridex) breaks a continuous-wave laser beam into short, repetitive pulses that allow cooling between laser applications, thereby reducing or preventing thermal damage,\(^4\) as is true for SLT. After setting a level for laser power and a spot size, the surgeon controls thermal exposure with the duration and duty cycle. Duration refers to the total length of time that laser energy is delivered, including the rest periods, and duty cycle denotes the percentage of time that the laser is delivering energy versus resting. For example, for a pulse duration of 2 milliseconds with a duty cycle of 15%, laser energy would be applied for 0.3 milliseconds followed by a 1.7-millisecond rest period. This pattern would be repeated for the indicated duration.

By using short bursts of laser energy, micropulse laser trabeculoplasty (MLT) has been shown to cause no anatomical effects compared to ALT burns on the trabecular meshwork when evaluated by electron microscopy. Essentially, MLT-treated tissue was similar in appearance to control tissue.\(^5\) MLT seems to be a very gentle treatment for glaucoma, and I look forward to more high-quality peer-reviewed research.

MLT lowered IOP in a phase 2 clinical study,\(^5\) and over the past year, my colleagues and my early results with modified laser settings have been promising. I have been performing the procedure for a year. My current technique is to use a 532-nm wavelength, 1,000 mW of power, a spot size of 300 μm, a total exposure duration of 300 milliseconds, and a duty cycle of 15%. After a 360º pulse laser therapy appears to offer additional safety. This may be particularly important for patients who are at risk of an IOP spike or for whom inflammation could be problematic. I look forward to gaining more experience and seeing more data.

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device. In 2006, he was impressed by the data implicating ultrasound energy as the mediator of a reduction in IOP after phacoemulsification. While reviewing the literature, Dr. Schwartz identified three possible mechanisms through which ultrasound energy could exert its influence: (1) a thermal effect, (2) a sonomechanical (vibratory) effect, and/or (3) an integrin-induced inflammatory response. Although it is quite possible that the true mechanism is a combination of the three pathways, he focused his attention on the thermal effects of ultrasound.

Dr. Schwartz noted that cytokine release occurred at 42.5ºC and that cellular necrosis occurred at 45ºC. Given these parameters, he designed an ultrasound unit that created a localized, controlled, limited hyperthermia that produced a sustained temperature of 43ºC. To perform TUG, the physician places an ultrasound probe circumferentially around the limbus at all 12 clock hours (Figures 1 and 2). The tip of the ultrasound probe is positioned on the limbus, 0.5 mm from the cornea, and oriented such that the focal point of the ultrasound is within the TM. The focused ultrasound energy (20,000-100,000 Hz) generates enough heat to reach 43ºC without going any higher, thus triggering the cytokine cascade that mediates improved outflow facility.

Although the results of the clinical studies have not been released, Dr. Schwartz provided a glimpse of the data at the 2014 Ophthalmology Innovation Summit. The TUG-3 clinical trial is a prospective study with two groups, both of which were treated with TUG: (1) those who either were naïve to pharmaceutical treatment or had not used any glaucoma medications for 6 months and (2) those who had been actively using glaucoma medications and subsequently underwent a washout. Dr. Schwartz reported that 80% of the treatment-naïve patients experienced a decrease in IOP of 20% or more compared with baseline after 1 year of follow-up. In the group of patients who had previously been treated and completed a washout, 80% had IOPs that were less than or equal to their IOP while on glaucoma drops. Moreover, he stated that the side effect profile of TUG was quite favorable, with no pain and very mild hyperemia.

**DEEP WAVE TRABECULOPLASTY**

Malik Kahook, MD, was also impressed by the intrinsic potential of sonic energy to elicit an IOP reduction. Like Dr. Schwartz, Dr. Kahook was inspired by the observation that IOP often decreases after
uncomplicated phacoemulsification-assisted cataract extraction.9 His clinical interest peaked when it was reported that this drop in IOP was mediated by ultrasonic activation of a stress response within TM cells that culminated in cytokine release and the modification of outflow channels.

Whereas TUG relies on ultrasound energy, Dr. Kahook favors the use of a lower frequency to exert a therapeutic effect. His research resulted in the development of a new procedure that he named deep wave trabeculoplasty (DWT) (Figure 3). This technology is designed to enhance aqueous outflow through the TM without damaging tissue.
operates in the sonic range and, when applied over the limbus, generates enough mechanical oscillation to cause focal stretching and relaxation of the TM cells (Figure 4). A resultant stress response within the TM presumably stimulates a cytokine cascade that positively influences aqueous outflow.\(^\text{10}\)

To date, two human trials have studied the safety and efficacy of DWT. The first recruited a cohort of patients with primary open-angle glaucoma whose IOPs were higher than 23 mm Hg after a washout of their medications. The 30 patients who met the inclusion and exclusion criteria underwent DWT in one eye, while the fellow eye served as the control. The researchers noted a significant (26%) decrease in IOP in the treated group over the 3-month follow-up period (Figure 5). Moreover, they reported that only 30% of the patients in the DWT group required rescue medications to achieve the target IOP, whereas 100% of the controls restarted IOP-lowering medications. No significant side effects were reported. Nor was there any evidence of anterior chamber inflammation in the patients treated with DWT.

The second clinical trial is a prospective, randomized study in which glaucoma patients are assigned to one of three groups: DWT, selective laser trabeculoplasty, or sham treatment. The primary endpoints and other secondary efficacy parameters will be monitored over a 2-year period. This study is currently being completed in the Philippines, and results are expected later this year.

**CONCLUSION**

Although laser energy has been the dominant medium for noninvasive glaucoma surgery, nascent evidence suggests that sonic energy can provide comparably efficacious IOP lowering. Moreover, this new technology offers the potential advantages of being cost-effective, portable, and ergonomic with fewer potential side effects. The results of the prospective, randomized clinical studies will help define the potential impact that these new treatments will have on future clinical practice.

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