# Patterned Laser Trabeculoplasty

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- BACKGROUND AND OBJECTIVE: A novel computer-guided laser treatment for open-angle glaucoma, called patterned laser trabeculoplasty, and its preliminary clinical evaluation is described.
- **PATIENTS AND METHODS:** Forty-seven eyes of 25 patients with open-angle glaucoma received 532-nm laser treatment with 100-μm spots. Power was titrated for trabecular meshwork blanching at 10 ms and subvisible treatment was applied with 5-ms pulses. The arc patterns of 66 spots rotated automatically after each laser application so that the new pattern was applied at an untreated position.
- **RESULTS:** Approximately 1,100 laser spots were placed

per eye in 16 steps, covering 360° of trabecular meshwork. The intraocular pressure decreased from the pretreatment level of  $21.9 \pm 4.1$  to  $16.0 \pm 2.3$  mm Hg at 1 month (n = 41) and remained stable around  $15.5 \pm 2.7$  mm Hg during 6 months of follow-up (n = 30).

■ **CONCLUSION:** Patterned laser trabeculoplasty provides rapid, precise, and minimally traumatic (subvisible) computer-guided treatment with exact abutment of the patterns, exhibiting a 24% reduction in intraocular pressure during 6 months of follow-up (*P* < .01).

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#### INTRODUCTION

The clinical management of glaucoma is evolving with a growing understanding of the pathophysiology, changes in population demographics, and advances in pharmaceutical, surgical, and laser technology. Medicare claims data show that the number of trabeculectomy procedures is decreasing despite an increase in the prevalence of glaucoma in the aging population.<sup>1</sup>

One of the major problems with pharmaceutical

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treatment is the patient's lack of compliance with reliably instilling eye drops. The most frequent reasons for noncompliance are difficulty with instilling the eye drops, cost, and side effects.<sup>2</sup> It has been reported that approximately half of glaucoma prescriptions are not refilled 6 months after initial prescription, despite awareness that the risk of glaucoma progression increases with failure to adhere to the prescribed regimen. This rate is typical for an asymptomatic disease.<sup>3</sup>

Argon laser trabeculoplasty was first introduced in the 1970s. <sup>4,5</sup> Its safety and efficacy in treatment-naïve subjects with newly diagnosed primary open-angle glaucoma was demonstrated in a large multicenter prospective clinical trial in 1995. <sup>6</sup> Argon laser trabeculoplasty provided longer control of intraocular pressure (IOP) without the need for additional therapy and greater stability of visual field and optic nerve status compared with timolol monotherapy. <sup>7</sup> With the argon laser (514-nm wavelength) or, more recently, with the equivalent 532-nm Nd:YAG laser, 50 spots of 50 µm in diameter are applied to the 180° on trabecular meshwork with pulses of 100 ms in duration. This procedure is now referred to as laser trabeculoplasty.

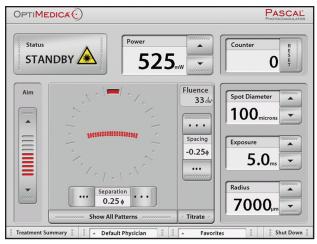
Selective laser trabeculoplasty was introduced in 1995.8,9 The commercially available selective laser trabeculoplasty laser systems (Lumenis Inc., Santa Clara, CA, and Ellex Inc., Adelaide, Australia) include a Qswitched, frequency-doubled, 532-nm Nd:YAG laser that delivers 3-ns pulses in a 400-µm diameter treatment spot. Typical selective laser trabeculoplasty pulse energy ranges from 0.4 to 1.2 mJ, approximately 100 times lower than laser trabeculoplasty. With a 400-µm beam diameter, 100 spots per 360° provide practically complete coverage of the trabecular meshwork. Selective laser trabeculoplasty has been shown to be an effective alternative to laser trabeculoplasty in the treatment of patients with open-angle glaucoma. 10,11 Selective laser trabeculoplasty leaves the trabecular meshwork intact with minimal damage to the endothelial cells lining the meshwork beams<sup>8</sup> in contrast to the laser trabeculoplasty, which results in extensive scarring of the meshwork.<sup>5</sup> This observation has led to significant speculation that selective laser trabeculoplasty may be more repeatable than laser trabeculoplasty. Selective laser trabeculoplasty is easier to perform than laser trabeculoplasty due to its larger spot size and it is better tolerated by patients due to reduced pulse energy. Similar to laser trabeculoplasty, the IOP-lowering effect of selective laser trabeculoplasty lasts for several years, but

tends to diminish over time. Selective laser trabeculoplasty is effective as primary therapy, can reduce the pharmaceutical burden in medically controlled eyes, and can prevent or delay the need for surgery in eyes poorly controlled but on maximally tolerated medical therapy. Both 180° and 360° treatments appear to be reasonable as initial therapy and there seems to be no contraindication to initial 360° treatment.

Recently, a micropulsed infrared (810-nm) laser has been used for laser trabeculoplasty, with a procedure termed micropulse diode laser trabeculoplasty.<sup>12</sup> In this approach, 200-ms long bursts composed of 100 micropulses were applied to 200-um spots on the trabecular meshwork. Micropulses were 0.3 ms in duration with 1.7-ms intervals in between. The micropulse structure was intended to allow for some cooling between them, resulting in improved heat confinement around the pigmented tissue, compared to a continuous laser. Approximately 70 spots were applied over 180° of trabecular meshwork. With a typical peak power setting of 2 W, 60 mJ of energy was delivered to each spot. This was a little higher than the typical laser trabeculoplasty pulse (approximately 33 mJ) (C. Engelman, personal communication, 2009). A 1-year follow-up in a clinical trial of micropulse diode laser trabeculoplasty demonstrated that 60% of eyes had an IOP reduction exceeding 20%.<sup>12</sup> With 100-ms exposures, the micropulse diode laser trabeculoplasty was found to be less efficient than argon laser trabeculoplasty and an IOP drop of 20% or greater was observed in 36% receiving micropulse laser trabeculoplasty versus 50% receiving argon laser trabeculoplasty. It has been also shown that, unlike laser trabeculoplasty, trabecular meshwork does not exhibit visible changes after micropulse diode laser trabeculoplasty. 13

The PASCAL Photocoagulator (OptiMedica Inc., Santa Clara, CA) was introduced in 2006 for semi-automated photocoagulation of the retina. The use of shorter pulse durations (10 to 20 ms) and predetermined patterns of spots resulted in reduced thermal diffusion and associated unintended tissue damage, and allowed for the achievement of greater control of the tissue effects, precise placement of the spots, faster treatment, and reduced patient discomfort. The semi-automated tissue effects are treatment, and reduced patient discomfort.

We present a computer-guided treatment method based on PASCAL technology called patterned laser trabeculoplasty and describe the rationale and the first clinical results with this system in patients with openangle glaucoma.



**Figure 1.** PASCAL (OptiMedica Inc., Santa Clara, CA) graphic user interface for patterned laser trabeculoplasty software allows for adjusting laser power, pulse duration, density of the pattern, and its length (radius), as well as starting position of the treatment on a circular diagram of an eye.

#### PATIENTS AND METHODS

## **Computer-Guided Pattern Scanning System**

The PASCAL photocoagulator provides aiming (633 nm) and therapeutic (532 nm) continuous wave light. Laser beams are directed onto the trabecular meshwork using a Latina gonioscopic contact lens (Ocular Instruments, Bellevue, WA). The clinician titrates laser power using a single spot to achieve light trabecular meshwork blanching with 10-ms laser pulses in the inferior segment of the eye, because it typically has the highest pigmentation. After titration, the power is maintained but the pulse duration is reduced to 5 ms. This reduces the pulse energy by half, which makes the treatment outcome ophthalmoscopically invisible. The use of the inferior segment for titration helps to ensure that the 5-ms treatment pulses will be invisible in all of the segments of the trabecular meshwork.

To achieve tissue blanching within 10 ms at power levels below 1 W, the spot size is limited to 100  $\mu$ m. The trabecular meshwork is a strip of tissue approximately 44 mm long and 0.3 mm wide, and its uniform coverage with 100- $\mu$ m spots requires more than 1,000 pulses. To simplify and speed up the procedure and provide accurate alignment of the invisible treatment spots, we developed a computer-guided pattern scanning algorithm.

The system applied a sequence of patterns onto the trabecular meshwork, where alignment of each pattern

ensured that consecutive treatment steps were pieced together around the trabecular meshwork without overlap or excessive gaps. The pattern parameters were controlled by a touch-screen graphic user interface (Fig. 1). The pattern consisted of several arcs composed of multiple laser spots. In the example shown in Figure 1, there were three adjacent arcs with spots separated by 0.25 diameter along the arc. The pattern corresponded to 22.5° of arc on the trabecular meshwork, and its starting position on the left in Figure 1 is highlighted in red. The graphic user interface allowed adjusting of the laser spot size, pulse duration, laser power, and pattern parameters including the number of arcs (1 to 3), separation of spots along the arc, spacing between the arcs, curvature, and starting angular position. The pattern is scanned along the length of the arcs (Fig. 2A). This way the delay between applications of the adjacent spots in two arcs was increased, allowing for cooling between the pulses and thus improving localization of the thermal effects in tissue.

Figure 2 illustrates the application of a pattern to the trabecular meshwork as viewed from above (left frame in each figure), and from the physician's perspective as seen through the lens assembly (right frames). The pattern in this example includes 12 columns of 2 spots adjacent to each other. The pattern has a slight arc shape to match the shape of the trabecular meshwork as viewed through the contact lens assembly. Initially, the pattern was projected using alignment light (633 nm) so that the physician could see where the pattern would be applied on the trabecular meshwork. The physician could rotate the gonioscopic lens assembly (ie, rotate the mirror) so that the pattern was aligned to the length of the trabecular meshwork (dark band in the image). Once the pattern was properly aligned to the trabecular meshwork, the physician pressed a foot pedal activating the therapeutic laser and the scanning system rapidly applied a pattern with predetermined laser power and pulse duration. The pattern consists of 24 spots and is applied during 120 ms (Fig. 2). This duration, similar to the duration of a single pulse in laser trabeculoplasty, is short enough to avoid eye movements during the application.

After application of a treatment pattern, the scanning system automatically rotated it by 22.5° and projected a new pattern with the aiming beam. The pattern was now misaligned with respect to the trabecular meshwork (Fig. 2B). The contact lens was then rotated

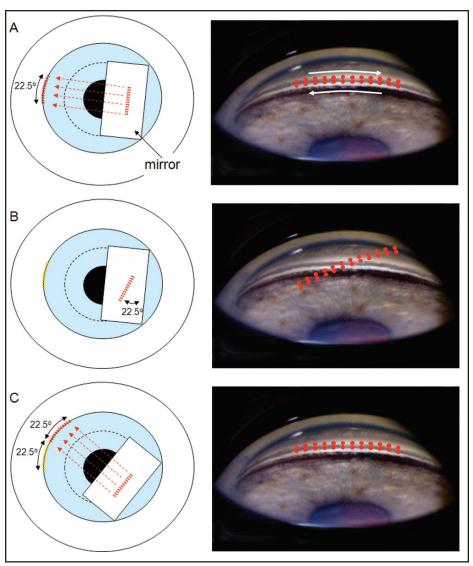


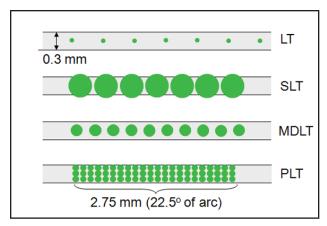
Figure 2. Computer-guided procedure of pattern application. Left panels show diagrammatic frontal view of the gonioscopic mirror and the trabecular meshwork. Right panels demonstrate a view of the anterior chamber angle via gonioscopic lens. Spot sizes and spacing are exaggerated for better visibility. (A) Pattern is projected with a red aiming beam (633 nm). After alignment onto trabecular meshwork, the physician presses the foot pedal to administer the treatment laser. (B) After laser application, the pattern is automatically advanced (rotated) by 22.5°, which makes it misaligned with respect to the trabecular meshwork. (C) The clinician rotates the gonioscopic lens to align the pattern onto the trabecular meshwork, which shifts it by 22.5°, bringing into a position adjacent to the previously treated zone.

by 22.5° to bring it into alignment along the trabecular meshwork. The clinician rotated the mirror (clockwise in this example) until the outline of the pattern became aligned again to the outline of the trabecular meshwork (Fig. 2C). Due to rotation of the mirror, the new pattern was now shifted clockwise by 22.5°, and was therefore adjacent to the previous pattern of treatment spots on the trabecular meshwork. A record of the treated segments was displayed on the graphic user interface so that if the treatment was interrupted, the clinician and the system knew where to resume. Once the overlap of the pattern and the trabecular meshwork was established, new treatment spots aligned with no overlap and no gap with respect to the previously formed treatment spots (Fig. 2C). This procedure was repeated 8 or 16 times to cover 180° or 360° of the trabecular meshwork.

## Patient Selection and Follow-up

Forty-seven eyes of 25 patients were treated during this study, including 10 men and 15 women, with an average age of 57 years (range: 29 to 74 years). The study had the following inclusion criteria: diagnosis of open-angle glaucoma; older than 18 years of age with two sighted eyes; willingness to undergo a washout period of 3 weeks prior to the treatment if receiving medical treatment (12 patients, 1.5 prostaglandin analogue medications on average); ability and willingness to comply with the treatment and follow-up schedule and requirements; and ability to provide written informed consent.

If in need of treatment, both eyes received laser treatment to avoid crossover effects. Any of the following excluded the subject from the study: pregnancy or



**Figure 3.** Diagram illustrating relative sizes of the laser spots and their placement on the trabecular meshwork in various approaches to trabeculoplasty: laser trabeculoplasty (LT), selective laser trabeculoplasty (SLT), micropulse diode laser trabeculoplasty (MDLT), and patterned laser trabeculoplasty (PLT).

intention to become pregnant during the course of the study, less than 3 months postpartum, or less than 6 weeks after completion of breastfeeding; advanced visual field defect within 10° of fixation; previous glaucoma surgery; corneal disease obviating the use of corneal applanation for a reliable IOP measurement or that would cause difficulty in viewing the trabecular meshwork by means of gonioscopic lens; use of systemic steroids; participation in a study of another device or drug within 3 months prior to study enrollment or during this study, and as per the investigator's careful discretion, as long as not contradictory to any of the above criteria; any condition that, in the investigator's opinion, would make it unsafe (for the subject or for the study personnel) to treat the subject as part of this research study; no concomitant use of IOP-lowering medicine; and no coexisting ocular pathology with the exception of cataract.

We included the results collected up to 6 months posttreatment and continued to observe the patients for 1 year. Special attention was paid to all adverse events including, but not limited to, the following: anterior chamber hemorrhage; posttreatment pressure spiking; anterior chamber inflammation (> 2+ cell and flare); pain; status of the optic nerve; and development of peripheral anterior synechiae.

Success of the laser treatment was defined as an IOP reduction of 20% or greater, relative to the patient's pretreatment baseline. The clinical protocol was approved by the local ethics committee and all patients signed informed consent documents.

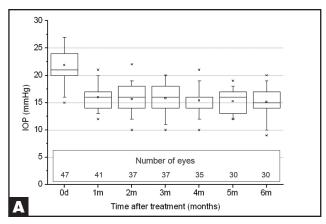
Patients received patterned laser treatment using the following pattern parameters: 3 arcs (ie, forming columns of 3 spots across the trabecular meshwork), with adjacent spots overlapping by 25 µm. Each arc was composed of 22 spots along the trabecular meshwork separated by a 0.25-spot diameter (ie, by 25 µm edge-to-edge), as shown in the last line on Figure 3. Thus, the total number of spots in each pattern was 66, and the 360° of trabecular meshwork were treated in 16 steps. The laser was first titrated for trabecular meshwork blanching at 10 ms and, using the same power, sub-visible treatment was applied with 5-ms pulses.

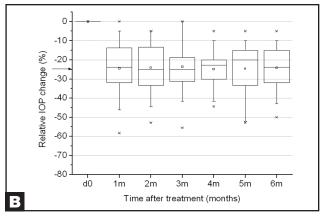
## Measurements and Statistical Analysis

IOP was measured with Goldmann applanation tonometry at approximately the same time of day to minimize errors of interpretation due to diurnal variation. All IOP measurements were taken by the same masked observer to eliminate measurement bias. On average, three IOP measurements were averaged per study time point to minimize measurement variations. IOP was measured before treatment and then monthly at approximately the same time of the day. The data were collected and plotted as box-plots using Origin (Version 7.0; OriginLab, Northampton, MA). Boxplots represent the distribution of the data by displaying the mean as center point, median as center line, 25th and 75th percentiles as a box, and 5th and 95th percentiles as whiskers, assuming a normal distribution curve. The maximum and minimum numbers are displayed as stars. The significance of the data was tested by using the Student t test (Microsoft Excel 2003; Microsoft Corp., Redmond, WA) assuming a two-tailed distribution and paired samples. Data points of patients who received any additional therapy (re-treatment or IOP-lowering medicine) were removed from further statistical analysis starting at the time point of intervention.

## **RESULTS**

Earlier studies of retinal photocoagulation<sup>16,18</sup> have shown that when power is titrated to produce light burns with 10-ms pulses, the 5-ms lesions are ophthalmoscopically invisible. However, fluorescein angiography, live-dead staining, and histological analysis demonstrate detectable damage to the retinal pigment epithelium and some photoreceptors.<sup>16</sup> We used





**Figure 4.** Intraocular pressure (IOP) follow-up during the first 6 months. (A) Average absolute pressure over time with the corresponding current number of the eyes after the exclusions. (B) Average relative changes in the intraocular pressure over time. Box-plots display the mean as center point, median as center line, 25th and 75th percentiles as a box, and 5th and 95th percentiles as whiskers. The maximum and minimum are displayed as stars.

Time Period (Mo)	Mean IOP (mm Hg)	SD IOP (mm Hg)		Mean IOP Drop (%)	No. of Eyes <sup>b</sup>	Virus/ Re-treated <sup>c</sup>
			Pa			
Pretreatment	21.9	4.1	_	_	47	_
1	16.0	2.3	2.6 E-10	-24.5	41	2/2
2	15.7	2.8	9.3 E-11	-24.1	37	2/2
3	15.8	2.9	2.7 E-10	-23.6	37	2/2
4	15.4	2.3	1.3 E-13	-24.9	35	2/4
5	15.2	2.2	4.4 E-8	-24.4	30	4/4
6	15.2	2.7	1.5 E-11	-24.2	30	4/4

SD = standard deviation.

a similar protocol to minimize structural tissue damage in the trabecular meshwork and to affect only pigmented epithelial cells. The laser power was titrated to light blanching of trabecular meshwork at 10 ms and then the exposure duration was set to 5 ms at the same power for the actual treatment.

Patients experienced mild or no discomfort during the treatment and no discomfort posttreatment. There were no IOP spikes, no inflammation detected, and no steroids given posttreatment.

The threshold laser power required for light trabecular meshwork blanching at 10-ms exposures was 0.68 W (0.26 standard deviation [SD]), and the corresponding pulse energy with 5-ms duration was 3.4 mJ. A 100-µm spot diameter corresponds to irradiance

of 43 J/cm<sup>2</sup>. On average, 1,097 (373 SD) spots were applied per eye, corresponding to the total energy of 3.7 J.

The average IOP decreased from the pretreatment level of 21.9 mm Hg (4.1 SD) to 16.0 mm Hg (2.3 SD) at 1 month (n = 41) and remained stable at approximately 15.5 mm Hg (2.7 SD) during 6 months of follow-up (n = 30) (Fig. 4A; Table). This represents a 24% reduction of average IOP, which is statistically significant at all time points, with all *P* values less than .01 using the Student's *t* test (Fig. 3B; Table). The average initial IOP in the 30 eyes that reached the 6-month follow-up was 20.0 mm Hg.

Eight of the 47 treated eyes were excluded during the study time frame. Two patients (4 eyes) developed

<sup>&</sup>lt;sup>a</sup>Student's t test.

<sup>&</sup>lt;sup>b</sup>Number of eyes counted in the statistics of IOP.

cNumber of excluded eyes due to viral conjunctivitis (left) and due to elevated pressure that required re-treatment or medications (right).

a viral conjunctivitis and were treated with steroid eye drops (fluorometholone every 4 hours and oxymetazoline every 6 hours). Four eyes from the other 2 patients returned to their original IOP levels (one at 1 month and one at 4 months), and these eyes were re-treated with a laser (same protocol, 2 eyes, 1 patient) or transferred to IOP-lowering medications (2 eyes, 1 patient). The re-treated eyes exhibited robust IOP lowering (44% and 48% drop at 1 month), but IOP returned to the original levels 5 months after the re-treatment. After the moment of re-treatment or transfer to medications, these eyes were excluded from further follow-up statistics reflected in the table and in Figure 4. Sixteen patients (30 eyes) came for the follow-up measurements up to 6 months. At 6 months, 20 of 30 eyes (67%) had a pressure drop of 20% or greater (defined as a success), with an average drop of 24%. The success rate at 6 months was 60%, including the 4 eyes that were re-treated or transferred to medication. No changes in visual acuity were observed.

#### **DISCUSSION**

The average laser power in standard laser trabeculoplasty protocol with 50-µm spots and a 100-ms pulse duration is 0.33 W. This corresponds to a pulse energy of 33 mJ and an irradiance of 1,680 J/cm², which is 10 times higher energy and 40 times higher irradiance than in patterned laser trabeculoplasty. Fifty spots of 50 µm in diameter applied in laser trabeculoplasty cover 0.1 mm², corresponding to only 0.7% of the trabecular meshwork area (Fig. 3, top line).

Because patterned laser trabeculoplasty involves approximately 10 times more spots per same area of the trabecular meshwork, the average energy per unit length of the trabecular meshwork was similar in both procedures (approximately 3.5 J for 360° treatment). A total of 1,056 spots of 100 µm in diameter applied in patterned laser trabeculoplasty cover 8.3 mm², corresponding to 63% of the trabecular meshwork area (Fig. 3, bottom line).

Micropulse diode laser trabeculoplasty has higher energy per pulse (60 mJ), higher irradiance (191 J/cm²), and higher average energy per same segment of the trabecular meshwork (approximately 4.2 J per 180°) than patterned laser trabeculoplasty. Seventy spots of 200 µm in diameter applied in micropulse diode laser tra-

beculoplasty cover 2.2 mm<sup>2</sup>, corresponding to 33% of the treated trabecular meshwork area.

On the other hand, selective laser trabeculoplasty has much lower energy per pulse (approximately 1 mJ) with a corresponding irradiance of 0.8 J/cm², and a total energy of 0.1 J per 360° of the trabecular meshwork. One hundred spots of 400 µm in diameter applied in selective laser trabeculoplasty cover 82% of the trabecular meshwork area (Fig. 3, second line).

Much lower energy requirements in selective laser trabeculoplasty compared to all other modalities are due to different mechanisms of cellular damage produced by nanosecond and millisecond pulses. Millisecond hyperthermia of pigmented cells leads to cellular damage due to the denaturation of proteins and other cellular macromolecules.<sup>19</sup> However, nanosecond exposures are too short to produce thermal denaturation below the vaporization threshold and cells are damaged by cavitation bubbles forming around melanosomes.<sup>19</sup> With sub-microsecond pulses, the heat does not diffuse beyond one micrometer; thus, the damage can be confined within a cell. With pulses of 5 ms in duration, heat can diffuse to distances of approximately 50 µm and can affect, to some extent, cells surrounding the pigmented structures. With 100-ms exposures in standard laser trabeculoplasty, the heat diffusion zone can reach 220 µm, covering practically the whole width of the trabecular meshwork. Future studies should determine the actual extent of cellular and structural damage to the trabecular meshwork produced by sub-visible 5-ms exposures of patterned laser trabeculoplasty.

The application time of a pattern including 66 spots (3 rows of 22) with 5-ms exposures is 330 ms (plus the transitions time of the scanner). The length of a pattern can be decreased to avoid distortions of the pattern due to eye movements, with a corresponding increase in the number of segments. For example, with 32 segments per eye, each pattern will include only 33 spots and will be applied under 200 ms (ie, within the eye fixation time). This makes the segments shorter (11.2° rather than 22.5° of arc) and will also simplify alignment of the pattern along the trabecular meshwork.

It is important to emphasize that this is a pilot study with a short follow-up and a relatively small group. A larger study with a control group will be required to verify the extent and the long-term stability of the pressure reduction.

### CONCLUSION

Patterned laser trabeculoplasty is an efficient method for treatment of open-angle glaucoma, providing nearly uniform coverage of the trabecular meshwork with more than 1,000 spots of 100 µm in diameter. This large number of exposures is efficiently delivered in 16 steps using the pattern scanning system of PASCAL with novel software. Because the treatment outcome is sub-visible, a computer-guided procedure provides automatic alignment of the patterns with no need for visible marks.

The pressure decrease of 24% is comparable to the results from selective laser trabeculoplasty studies. <sup>9-11</sup> The reduced amount of tissue damage in sub-visible lesions may provide benefits similar to selective laser trabeculoplasty, including reduced scarring and possibility of re-treatment. These potential benefits, as well as the long-term stability of the pressure reduction, should be verified in additional studies.

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