

Mechanism of Action of Selective Laser Trabeculoplasty and Predictors of Response

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Submitted: September 7, 2016

Accepted: February 8, 2017

Citation: Gulati V, Fan S, Gardner BJ, et al. Mechanism of action of selective laser trabeculoplasty and predictors of response. *Invest Ophthalmol Vis Sci*. 2017;58:1462-1468. DOI:10.1167/iov.16-20710

PURPOSE. This study was designed to evaluate the changes in aqueous humor dynamics (AHD) produced by selective laser trabeculoplasty (SLT) and to explore if baseline AHD parameters are predictive of IOP response to SLT.

METHODS. Thirty-one consecutive subjects diagnosed with ocular hypertension or primary open-angle glaucoma scheduled to undergo SLT as their primary IOP-lowering therapy were enrolled in this prospective observational study. Subjects underwent baseline assessment of AHD in both eyes. Variables assessed were IOPs at 9 AM and noon, aqueous humor flow rate (fluorophotometry), episcleral venous pressure (EVP, venomanometry), outflow facility (pneumatography and fluorophotometry) and uveoscleral outflow (calculated using modified Goldmann equation). All subjects underwent 360 degrees SLT and AHD measurements were repeated 3 months later.

RESULTS. Compared with baseline, IOPs after SLT were significantly lower at 9 AM (22.9 ± 5.1 vs. 19.7 ± 3.0 mm Hg; $P = 0.001$) and noon (23.4 ± 4.6 vs. 20.0 ± 3.5 mm Hg; $P < 0.001$). Outflow facility by fluorophotometry was significantly increased from 0.17 ± 0.11 $\mu\text{L}/\text{min}/\text{mm Hg}$ at baseline to 0.24 ± 0.14 $\mu\text{L}/\text{min}/\text{mm Hg}$ at 3 months ($P = 0.008$). Outflow facility by tonography (baseline: 0.16 ± 0.07 $\mu\text{L}/\text{min}/\text{mm Hg}$ vs. 3 months: 0.22 ± 0.16 $\mu\text{L}/\text{min}/\text{mm Hg}$; $P = 0.046$) was similarly increased. No change in aqueous flow or EVP was observed. There were no changes in IOP or AHD in the contralateral untreated eye. Using multiple linear regression models, higher baseline aqueous flow, lower baseline outflow facility, and possibly lower uveoscleral outflow were associated with more IOP lowering with SLT.

CONCLUSIONS. The IOP-lowering effect of SLT is mediated through an increase in outflow facility. There is no contralateral effect. Higher aqueous flow and lower outflow facility may be predictive of better response to SLT.

Keywords: laser trabeculoplasty, glaucoma laser, aqueous flow, trabecular meshwork, intraocular pressure

Lowering of IOP is currently the only well-established treatment strategy for management of ocular hypertension (OHT)¹ and glaucoma.²⁻⁴ Laser trabeculoplasty is extensively used as a primary or adjunctive therapy for lowering the IOP in OHT, glaucoma suspects, and patients with primary and several secondary open-angle glaucomas. Introduction of selective laser trabeculoplasty (SLT) in the late 1990s⁵ has resulted in a significant increase in the number of trabeculoplasties performed in the past decade.⁶⁻⁸ The IOP-lowering effect of argon laser trabeculoplasty (ALT) is mediated through an increase in conventional outflow facility,⁹ which in turn may be mechanically or biologically mediated after the delivery of laser to the anterior chamber angle structures.¹⁰⁻¹² As SLT delivers approximately 1% of total energy used by a typical ALT and does not have any thermal coagulative effects like ALT,¹³ it purportedly can have a mechanism of action different from ALT. Previous reports have shown an increase in conventional outflow facility at 1 and 3 months and no effect on aqueous humor inflow rate at 3 months after SLT.^{14,15} These are two important parameters of aqueous humor dynamics (AHD), changes in which alter IOP. Other parameters important in

regulating IOP but with unknown roles in the IOP responses to SLT treatment are episcleral venous pressure (EVP) and uveoscleral outflow. This is the first comprehensive study of the effects of SLT on all parameters of AHD in the same patients. Additionally, this study presents a multiple regression analysis of patient, treatment, and AHD variables to identify potential predictors of IOP response to SLT.

METHODS

This prospective study, conducted at a tertiary care academic practice, enrolled consecutive patients undergoing primary SLT with a clinical diagnosis of OHT, glaucoma suspect, or primary open-angle glaucoma. The study followed the tenets of the Declaration of Helsinki and was approved by the institutional review board of the University of Nebraska Medical Center. Primary therapy for the purpose of the study was defined as SLT being considered as the only IOP-lowering modality whether or not patients have used IOP-lowering medications in the past. Subjects considered for the study were those interested in SLT

as primary first-line therapy, those with a preference to discontinue current medication(s) for concerns such as side effects and medication cost, and those who were recommended SLT due to past poor compliance with medication use. After the patient agreed to proceed with SLT, he or she was approached for participation in this study. A total of 31 of 35 consecutive subjects agreed to participate in the study and gave informed consent.

Participating subjects underwent a screening visit composed of a detailed anterior segment examination, including dynamic gonioscopy, and a dilated fundus examination. A subjective assessment was made of angle pigmentation on a scale of 0 to 4. Inclusion criteria consisted of subjects with a clinical diagnosis of OHT, glaucoma suspect, or primary open-angle glaucoma undergoing primary SLT (as defined above) who were either not on any medications or could be safely washed out of a single topical medication. Subjects were excluded if they had a history of prior ocular incisional surgical procedures, known history of past laser trabeculoplasty, corneal opacity precluding fluorophotometry, use of topical or systemic steroids within 3 months of the study, narrow angle (scleral spur not visible for greater than 180 degrees without pressure on dynamic gonioscopy), secondary open-angle glaucoma (exfoliation, pigment dispersion, or angle recession glaucoma), and known allergy to fluorescein, proparacaine, or sulfa medications. Subjects with a diagnosis associated with potential retinal ischemia (diabetic retinopathy or retinal arterial or vein occlusion) also were excluded from the study.

Of the 31 enrolled subjects, none were excluded from participation at the screening visit.

Enrolled subjects on a topical medication at the time of screening started a washout in both eyes, after approving the safety of the washout with the treating physician. For subjects who had stopped the topical medication before the screening visit, washout was deemed to start at the reported time point of stopping the medication. Of the eight subjects who underwent washout before baseline measurements were made, seven were using a prostaglandin analog in both eyes and one was using a carbonic anhydrase inhibitor in both eyes. Washout for a prostaglandin analog was a minimum of 4 weeks and that for the carbonic anhydrase inhibitor was 1 week. During the washout period, IOP was monitored every 2 weeks. The actual median washout in the study was 7 weeks (range, 4–11 weeks).

Subsequent to the screening visit and any required washout, subjects underwent a baseline assessment of AHD. Standard techniques for AHD measurement and the underlying assumptions have been reported previously.¹⁶ For the purpose of fluorophotometry, subjects self-instilled 8 drops of sodium fluorescein at 10 PM the night before each scheduled visit. On the study day, central cornea thickness and anterior chamber depth were measured by ultrasound pachymetry and A-scan, respectively. Seated IOP was measured by pneumatonometer (performed by SE, CBT, or DGN, masked to treatment plan) at 9 AM, followed by hourly fluorophotometry scans until noon. Intraocular pressure measurement was repeated at noon. Episcleral venous pressure was measured at 10 AM using an episcleral venomanometer.¹⁷ For both EVP and IOP, two measurements were obtained for each eye. A third measurement was obtained if the first two differed by more than 2 mm Hg. The median value for each eye was used for analysis. The rate of fluorescein decay in the cornea and anterior chamber was used to calculate the aqueous humor flow rate.¹⁶ Subjects were given 500 mg acetazolamide at noon. Three additional hourly fluorescein scans and IOP measurements were obtained after acetazolamide administration. Outflow facility was calculated as the ratio of change in flow to change in IOP

accomplished by acetazolamide. Two-minute pneumatonography was performed at 3 PM after all other measurements were completed. Intraocular pressure data during tonography was captured digitally at 40 Hz using Powerlab (ADInstruments, Colorado Springs, CO, USA) and Lab Chart 7 (ADInstruments) software. The starting and ending IOP were deduced using regression techniques previously described.^{18,19} Pressure volume relationship data for the human eye were thereby used to calculate the outflow facility by tonography.²⁰ Uveoscleral outflow was calculated with the modified Goldmann equation, by using the outflow facility obtained by fluorophotometry and tonography, respectively. Data were obtained from all study eyes and the contralateral untreated eyes that met the inclusion and exclusion criteria.

The study eye underwent SLT within 1 week of obtaining baseline measurements. Preoperatively, all subjects received one drop each of pilocarpine 2% and brimonidine 0.2%. Goldmann lens was used to perform all trabeculoplasties. A total of 80 spots were placed over 360 degrees of the anterior chamber angle. Laser power was titrated starting at 0.8 mJ (with the exception of one case with excessive angle pigment) to 0.1 mJ below the minimum required to generate “champagne bubbles” at the application site. A subjective estimate of the percentage of applied laser spots associated with champagne bubbles was recorded by the treating physician (VG) in the patient chart. Intraocular pressure was checked 1 hour after the laser treatment and the patients were provided with a nonsteroidal anti-inflammatory drop to use if needed for relief of ocular pain and discomfort.

Following SLT, two subjects required topical IOP-lowering medications in the study eye (one prostaglandin analog, one carbonic anhydrase inhibitor), and four subjects required IOP-lowering medications in the fellow control eye (three prostaglandin analogs, one carbonic anhydrase inhibitor) in the postoperative period. All medications were washed out using the protocol described above before obtaining the 3-month follow-up study measurements.

Three months after the SLT, the subjects underwent repeat assessment of all AHD variables obtained at the baseline visit.

Descriptive statistics were calculated for all data. Data are presented as mean \pm SD unless indicated otherwise. The primary comparison was made for the IOP and AHD data obtained in the study eye between baseline and 3 months after the laser treatment using paired *t*-tests. Sample size was calculated based on changes in outflow facility, which was the leading hypothesis before the conduct of the study. With an expected change in outflow facility of 0.05 $\mu\text{L}/\text{min}/\text{mm Hg}$ and presumed SD of 0.09 $\mu\text{L}/\text{min}/\text{mm Hg}$ for the change,⁹ a sample of 27 subjects would have 80% power to detect such a difference at an α of 0.05. Multiple linear regression was used to study the association between baseline AHD, demographic, and treatment parameters and IOP response. Three separate regression models were constructed: one based on parameters of AHD (aqueous flow, EVP, outflow facility, and uveoscleral outflow), the second based on patient demographic variables (age, sex, race, and central corneal thickness), and the third based on variables relevant to laser-tissue interaction (angle pigmentation, total laser energy used, and percentage of spots with bubble formation). A stepwise backward elimination approach was used to develop the model, discarding associations with a *P* value less than 0.05 until all remaining covariates in the model had a *P* value less than 0.05. Interactions were not included in the model to limit the covariates given the small sample size. The outcome variable for both models was mean change (mean for 9 AM and 12 noon) in IOP. Multiple regression analysis also was performed using the percentage change in IOP as the outcome variable

TABLE 1. Aqueous Humor Dynamics Parameters at Baseline and 3 Months After Selective Laser Trabeculoplasty in the Treated Eye and Contralateral Control Eye

Variable	Treated Eye, <i>n</i> = 29			Control Eye, <i>n</i> = 25			Treated vs. Control, <i>n</i> = 25	
	Baseline	3 mo	<i>P</i>	Baseline	3 mo	<i>P</i>	Baseline	3 mo
IOP, 9 AM, mm Hg	22.91 ± 5.12	19.67 ± 3.00	0.001	21.60 ± 4.80	21.83 ± 3.20	0.79	0.01	0.001
IOP, Noon, mm Hg	23.43 ± 4.60	20.00 ± 3.45	<0.001	21.53 ± 4.61	21.42 ± 3.49	0.87	0.01	0.01
Aqueous flow, μL/min	2.51 ± 1.11	2.27 ± 0.84	0.16	2.60 ± 1.45	2.33 ± 1.00	0.28	0.47	0.51
EVP, mm Hg	9.74 ± 1.46	9.61 ± 1.12	0.64	9.89 ± 1.09	9.35 ± 1.30	0.07	0.62	0.54
Outflow facility, fluorophotometry, μL/min/mm Hg	0.17 ± 0.11	0.24 ± 0.14	0.008	0.24 ± 0.16	0.22 ± 0.20	0.74*	0.01*	0.85
Outflow facility, tonography, μL/min/mm Hg	0.16 ± 0.07	0.22 ± 0.16	0.046	0.18 ± 0.07	0.20 ± 0.12	0.53	0.18	0.73

P values obtained using paired *t*-test.

* *n* = 24 (subject excluded because of undetectable change in IOP with acetazolamide precluding outflow facility calculation).

(rather than absolute change in IOP). A *P* value of less than 0.05 was considered statistically significant.

RESULTS

A total of 31 subjects who consented for the study underwent a screening visit. Eleven subjects had opted for SLT as first-line therapy, 12 had used medications in the past but were pursuing SLT because of issues with medications such as cost and side effects, and 8 were recommended to undergo SLT because of poor compliance with recommended medications. In terms of the clinical profiles, enrolled subjects included 5 subjects with two or more IOPs above 24 with no glaucomatous cupping or visual field defect, 16 with glaucomatous cupping (as determined by the treating physician) without any visual field defect, and 10 with repeatable (two or more occasions) visual field defects with supportive optic nerve head appearance. The IOP targets set by the treating physician for the subjects consented for the study were mid-teens (*n* = 1), high teens (*n* = 7), low 20s (*n* = 10), and mid-20s (*n* = 13).

Of the 31 subjects enrolled, 29 completed all study-related measurements, 1 was lost to follow-up after the SLT, and 1 was unable to adequately administer fluorescein for fluorophotometry on scheduled baseline visits on two different days. The latter subject was withdrawn from the study and underwent SLT as planned. Four contralateral eyes also were excluded from analysis. Three of these were pseudophakic and one had previously undergone laser trabeculoplasty. Data were analyzed for 29 subjects, comprising 29 study eyes and 25 contralateral eyes.

Mean age of the study population was 64.0 ± 9.3 years (range, 48–79 years). Eleven subjects were females. Based on self-reported race, 15 subjects were Caucasian, 12 were African American, and 1 each were Hispanic and Asian.

Baseline and 3-month AHD data are summarized in Table 1. Post SLT, there was a significant decrease in both the 9 AM and 12 noon IOP in the SLT-treated eye, with no change in IOP in the contralateral control eye. There was no change in aqueous flow or EVP in either the treated or contralateral eye 3 months after treatment. Outflow facility (by fluorophotometry) was significantly increased from 0.17 ± 0.11 μL/min/mm Hg at baseline to 0.24 ± 0.14 μL/min/mm Hg at 3 months after treatment (*P* = 0.008). The outflow facility in the contralateral eye was unchanged. The change in outflow facility was reproducible on tonography, increasing from 0.16 ± 0.07 μL/

min/mm Hg at baseline to 0.22 ± 0.16 μL/min/mm Hg at 3 months (*P* = 0.046).

Three months after SLT treatment, uveoscleral outflow in the treated eye was lower by 0.36 ± 0.94 μL/min when calculated using fluorophotometry data (*P* = 0.05), but not when using tonography data (Δ = -0.26 ± 2.15 μL/min, *P* = 0.52). At the same time, no change in uveoscleral outflow was detected in the contralateral untreated eye. These results are summarized in Figure 1.

Responder Analysis

To further validate the “cause-effect” hypothesis of change in fluorophotometric outflow facility being the mediator of IOP lowering seen with SLT, secondary analysis of the variable was conducted by using a binary categorization of subjects as responders and nonresponders (Fig. 2). When IOP response was defined as 10% or more IOP lowering at either 9 AM or noon, a statistically significant increase in outflow facility was reproducible with greater confidence (*P* = 0.004) in IOP responders (*n* = 20). The outflow facility in IOP nonresponders was unchanged (*n* = 9, *P* = 0.90). If the definition of response was changed to 10% or greater IOP lowering for both the 9 AM and noon IOP, the confidence in increase in outflow facility increased further in IOP responders (*P* = 0.0003, *n* = 15). The outflow facility was unchanged in IOP nonresponders by this definition as well (*P* = 0.84). Scatter plot of change in IOP plotted against change in outflow facility for the lasered and contralateral eye (Fig. 3) was suggestive of a linear relationship in the lasered eye and no correlation in the contralateral eye. The Spearman correlation coefficient was statistically significant for lasered eyes (σ = -0.41, *P* = 0.03) but not for control eyes (σ = 0.21, *P* = 0.34).

Predictors of Response

Using change in IOP as the outcome variable, baseline demographic, treatment, and AHD variables were analyzed as covariates by using multiple linear regression models (Table 2).

Outflow facility and uveoscleral outflow were assessed in this study by using two different methods: fluorophotometry and tonography. Therefore, the multiple regression model using AHD parameters was run separately for the fluorophotometry and tonography data for these variables (models 1a and 1b, respectively). The same values for aqueous flow and EVP were used for the two models. In the model with fluorophotometry data, the change in IOP was significantly

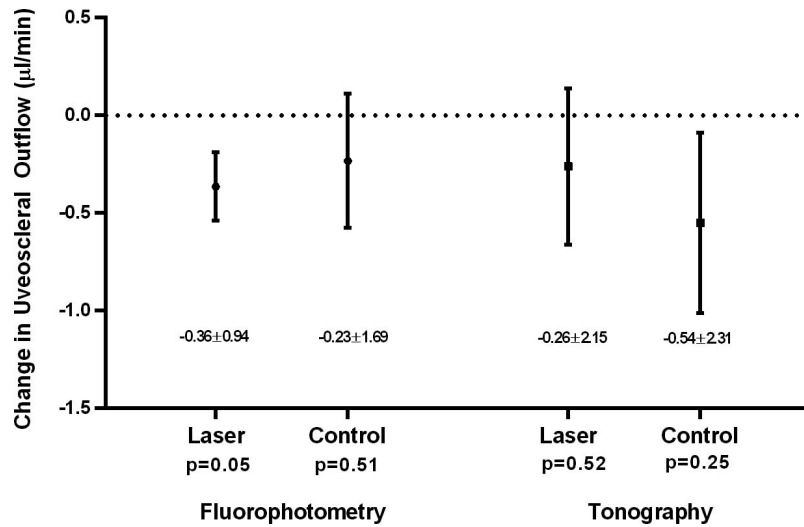


FIGURE 1. Change in uveoscleral outflow at 3 months after selective laser trabeculoplasty in the treated ($n = 29$) and contralateral control eyes ($n = 24$ for fluorophotometry, 25 for tonography). Values on the plot indicate mean \pm SD. Error bars: 1 SE. P values calculated using paired *t*-test.

associated with aqueous flow and outflow facility. Specifically, higher baseline aqueous flow was associated with a greater reduction in IOP ($P = 0.004$). Lower baseline outflow facility also was associated with greater reduction in IOP ($P = 0.002$).

Similarly, in the model with tonographic data, both higher aqueous flow and lower outflow facility were associated with a greater reduction in IOP. In addition, a lower baseline uveoscleral outflow also was associated with a greater IOP reduction ($P < 0.001$). When percentage IOP reduction was used as the outcome variable, there was no change in substantive conclusions (data not presented).

In the patient demographics-based model (model 2), none of the variables were found to be significantly associated with IOP response at an α of 0.05. However, a weak association was seen between IOP response and age ($P = 0.052$) and IOP response and central corneal thickness ($P = 0.076$). Specifically, the regression analysis approached significance for a greater IOP response being associated with younger age and thinner corneas. None of the treatment variables, angle pigmentation, percentage spots with visible bubbles, or total laser power, were associated with IOP response (model 3, data not presented).

DISCUSSION

Similar to ALT, the IOP-lowering effect of SLT appears to be mediated through an increase in outflow facility with no substantial effects on any of the other parameters of AHD. Using Schiøtz tonometry-based tonographic assessment, other authors^{14,15} have reported an increase in outflow facility after SLT. This study has an expanded design as compared with any prior similar study. Both techniques used to assess outflow facility in our study are different from the ones reported in the past. Episcleral venous pressure and uveoscleral outflow calculations were included in the design to address all parameters in the modified Goldmann equation. Contralateral eyes were also studied for the first time and the negative results are important considering past speculations on the contralateral effects of SLT. The primarily Caucasian composition of our study was different from any of the prior publications. The follow-up measurement was done at a consistent time after the laser, allowing 3 months for laser effects to be established before making repeat measurements. Given the fairly low baseline outflow facility in the two prior reports (0.08 $\mu\text{L}/\text{min}/\text{mm Hg}$ and 0.09 $\mu\text{L}/\text{min}/\text{mm Hg}$),^{14,15} our study perhaps

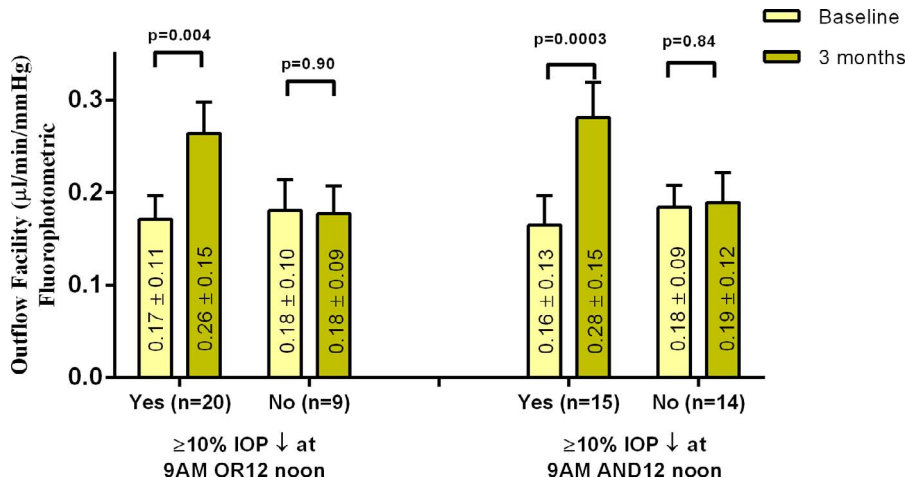


FIGURE 2. Change in outflow facility at 3 months in lasered and contralateral control eyes categorized based on percentage IOP lowering from baseline with selective laser trabeculoplasty. Values on the bars are mean \pm SD. Error bars: 1 SE. P values calculated using paired *t*-test.

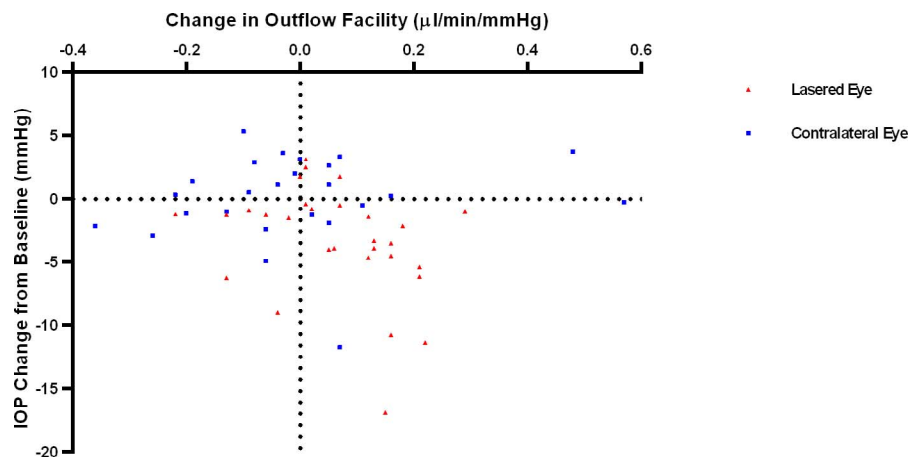


FIGURE 3. Scatter plot of change in IOP against change in fluorophotometric outflow facility in lasered and contralateral eyes. Intraocular pressure change is the average of change at 9 AM and noon for each subject. The Spearman σ for the correlation in lasered eyes was -0.41 ($P = 0.03$) and that in contralateral untreated eyes was 0.21 ($P = 0.34$).

represents a more moderate degree of trabecular pathology, more representative and generalizable to what is likely to be encountered in clinics.

In our study, as the criteria for IOP response was made more robust, the statistical significance of increase in outflow facility became greater. Even though this is not a true dose-response relationship, it does imply that for subjects with more IOP lowering, increase in outflow facility was more obvious. At the same time, there was no change in outflow facility in subjects who did not have a good IOP response to SLT, adding credence to the hypothesis that IOP changes after SLT are mediated through an increase in outflow facility.

The overall magnitude of IOP response in our study subjects (approximately 15%) can be considered to be modest compared with the expectation from SLT for primary therapy. The mean clinic IOP at which a decision was made to proceed with SLT was 26.05 ± 4.40 mm Hg. This was considerably higher than the baseline visit's IOP of 22.91 ± 5.12 mm Hg at 9AM and 23.43 ± 4.60 mm Hg at 12 noon in the treated eye. The difference is reflective of the regression to the mean that affects clinical glaucoma management, in which treatment decisions are typically made at IOP values on the higher end of the tonometry measurement error or inherent diurnal IOP

variability. This also highlights the potential overestimation of IOP response with the typical design of a retrospective analysis in which the most recent pretreatment IOP is considered the baseline IOP. The modest IOP response seen in the study theoretically could be related to lower total energy used for treatment as compared with some other studies of primary SLT.^{14,21} It can be speculated that higher total energy levels could have affected additional parameters of AHD besides outflow facility or may have shown greater changes in outflow facility. However, we feel that the magnitude and particularly the range of responses seen in the study served the purpose of the study well. We had a fair number of “nonresponders” with either of the two criteria used to make such comparisons and multiple regression analysis meaningful. Additionally, within the range of laser energy used in this study, a correlation between the total laser energy used and IOP response was not detectable. This study did not find any IOP or AHD effects in the contralateral untreated eye. However, one prior study has raised the possibility of a crossover effect of laser trabeculoplasty on the contralateral untreated eye.²²

A direct comparison of baseline parameters between responders and nonresponders based on more robust criterion 2 (at least 10% IOP lowering at both measurement time points) is presented in Table 3. Subjects with a greater response had a higher IOP at baseline. Other than IOP, the difference between the parameters of AHD between the two groups was not significant. In other words, in such an arbitrary binary comparison, the parameters of AHD were not evidently predictive of treatment response. Intraocular pressure can be considered to be an outcome of the complex interplay between parameters of AHD. Therefore, examining and contrasting these parameters between groups as covariates, without controlling for others, is likely to yield limited information. Multiple linear regression facilitates such evaluation of a covariate while controlling for others in the model. Use of multiple regression revealed the significant influence of baseline AHD parameters on IOP outcomes (Table 2).

To the best of our knowledge, this is the first report using regression modeling identifying what does and does not matter for laser response. This is perhaps the first report to identify any pretreatment AHD predictors of response to any IOP-lowering treatment. Our study found a significant association between IOP response and AHD parameters of aqueous flow rate and outflow facility. This association seen between aqueous humor flow rate and IOP response for a fixed change

TABLE 2. Results of Multiple Linear Regression Analysis With IOP Response (Baseline IOP-IOP at 3 Months) as Outcome Variable

Model	Coefficient (SE)	P	ANOVA P
Model 1a fluorophotometry data			0.003
Aqueous flow	2.377 (0.749)	0.004	
Outflow facility	-26.822 (7.684)	0.002	
Model 1b tonography data			<0.001
Aqueous flow	4.170 (0.966)	<0.001	
Outflow facility	-51.509 (11.383)	<0.001	
Uveoscleral outflow	-3.003 (0.735)	<0.001	
Model 2 patient variables			0.08
Age	-0.182 (0.090)	0.052	
Central corneal thickness	-0.044 (0.024)	0.076	

Intraocular pressure response (outcome) was the average of the response at 9 AM and 12 noon. Model 1a included EVP ($P = 0.64$) and uveoscleral outflow (fluorophotometric) ($P = 0.48$) in the initial model. Model 1b included EVP ($P = 0.06$) in the initial model. Model 2 included sex ($P = 0.41$) and race ($P = 0.69$) in the initial model.

TABLE 3. Comparison of Baseline AHD Parameters in Lasered Eyes With at Least 10% IOP Lowering at Both 9 AM and 12 Noon With Those That Did Not Have Such a Response

Baseline Parameters	≥10% IOP Lowering, <i>n</i> = 15	<10% IOP Lowering, <i>n</i> = 14	<i>P</i> *
IOP, 9 AM, mm Hg	25.38 ± 5.63	20.25 ± 2.77	0.005
IOP, 12 noon, mm Hg	25.61 ± 4.91	21.08 ± 2.85	0.006
Aqueous flow, μL/min	2.82 ± 1.20	2.17 ± 0.92	0.11
Outflow facility, fluorophotometry, μL/min/mm Hg	0.16 ± 0.13	0.19 ± 0.09	0.60
Outflow facility, tonography, μL/min/mm Hg	0.15 ± 0.09	0.17 ± 0.07	0.52
EVP, mm Hg	9.91 ± 1.82	9.55 ± 0.98	0.53
Uveoscleral outflow, tonography, μL/min	0.55 ± 1.64	0.18 ± 1.08	0.29
Uveoscleral outflow, fluorophotometry, μL/min	0.61 ± 1.02	0.15 ± 0.85	0.46

* *P* value using paired *t*-test. Values are mean ± SD.

in outflow facility is to be expected based on the Goldmann equation. Similarly, lower baseline outflow facility also can be expected to be more amenable to improvement after laser trabeculoplasty. The results of multiple linear regression of the AHD data from this study experimentally confirm these intuitive expectations. Based on the estimated coefficients in our regression models, we can speculate that for every 1 μL/min higher baseline aqueous flow rate (approximately 40% higher than the study mean), the predicted IOP reduction from SLT treatment was more by 2.38 ± 0.75 mm Hg (fluorophotometry-based model) to 4.17 ± 0.97 mm Hg (tonography-based model). For every 0.1 μL/min/mm Hg lower baseline outflow facility, the predicted IOP reduction from SLT treatment was more by 2.68 ± 0.77 mm Hg (fluorophotometry-based model) to 5.15 ± 1.14 mm Hg (tonography-based model). The application of this information to clinical care of patients currently is limited by the techniques used to measure these variables. Aqueous flow determination is a fairly time-consuming exercise and difficult to incorporate into clinical practice. Tonography has better potential as a clinical tool to predict treatment response before laser treatment. However, the technique has substantial measurement noise, whereby the repeatability at the individual level is low despite a very good reproducibility for large sample means. Further advances in these techniques may allow for better estimation of likelihood of individual treatment response and aid in patient selection based on these baseline variables.

This study did not find any statistically significant association between IOP response and patient demographic variables or treatment variables possibly relevant to laser-tissue interactions, such as total laser energy, angle pigmentation, or percentage of laser spots with visible response. The association between younger age and greater IOP response did approach statistical significance ($\beta = -0.18$, $P = 0.052$). This translates into a possible 1.8 mm Hg (95% confidence interval of 0.0–3.6 mm Hg) additional IOP response being associated with a 10-year younger age of patient.¹² The association with central corneal thickness also approached statistical significance ($\beta = 0.04$, $P = 0.076$), implying a possible additional 1.0 mm Hg (95% CI 0.0–2.0) IOP response associated with 25-μm thinner cornea. Thinner corneas have previously been shown to be associated with better IOP-lowering efficacy of topical medications.²³ Even though the association between these variables and IOP response did not reach statistical significance in this study, the authors recommend controlling for these variables in future studies exploring the predictors of response to laser trabeculoplasty.

Our study limitations are largely related to the limitations of the techniques available for the assessment of AHD. Both fluorophotometry and tonography have several assumptions that need to be taken into account when interpreting the data. The select population required for the study, such as exclusion

of pseudophakic patients, and those that could not be washed off medications safely, limits the generalizability of the results to such subjects, who form a large part of any glaucoma practice.

Currently, the only way to assess uveoscleral outflow noninvasively is by mathematical calculation. The result shows a fair amount of variability depending on the EVP value used in the calculation.²⁴ However, change in uveoscleral outflow is more robust to errors in EVP estimation.¹⁸ Therefore, we have reported the changes in uveoscleral outflow in this study, which is more meaningful than absolute values. A statistically significant decrease in uveoscleral outflow was noted after SLT by the fluorophotometric method, but was not replicable with tonographic method. Therefore, the strength of evidence to support any changes in uveoscleral outflow is weak. We speculate that any small decrease in uveoscleral outflow after SLT may merely reflect more aqueous flowing through the trabecular than uveoscleral pathway. Proparacaine drops were administered to measure the IOP and EVP in the same 7-hour period when the fluorophotometry scans were obtained. These measurements can potentially dislodge additional fluorescein and thereby result in an underestimation of the aqueous flow rate. With the assumption that any systematic error will affect the two measurement time points equally and thereby have negligible effect on the calculated change in flow, we proceeded to obtain all IOP and EVP measurements on the same day, to allow for chronologic proximity of all variables entered in the Goldmann equation.

In summary, this comprehensive study of changes in AHD 3 months after SLT found the IOP-lowering effects of SLT to be mediated through an increase in outflow facility. No meaningful effects on any of the other parameters of AHD or the contralateral eye were detected. A higher baseline aqueous flow and a lower baseline outflow facility were found to be predictive of IOP response to SLT. Future advances in techniques for the assessment of AHD may make these parameters useful for patient selection for trabeculoplasty.

Acknowledgments

Supported by American Glaucoma Society Clinician Scientist Award (VG) NEI K23EY023266, Research to Prevent Blindness

Disclosure: **V. Gulati**, Allergan, Inc. (R); **S. Fan**, None; **B.J. Gardner**, None; **S.J. Havens**, None; **M.T. Schaaf**, None; **D.G. Neely**, None; **C.B. Toris**, None

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