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Trabeculectomy Can Improve Long-Term Visual Function in Glaucoma

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Purpose: To measure the magnitude and direction of visual field (VF) rates of change in glaucoma patients after intraocular pressure (IOP) reduction with trabeculectomy.

Design: Retrospective, comparative, longitudinal cohort study.

Participants: Patients with open-angle glaucoma.

Methods: Patients who underwent trabeculectomy (Trab) with mitomycin-C (74 eyes of 64 patients) with ≥4 reliable VF measurements before and after trabeculectomy and at least 4 years of follow-up before and after surgery were included. Decay or improvement exponential models were used to calculate pointwise rates of perimetric change before and after surgery. A separate comparison (Comp) group with unoperated glaucoma (71 eyes of 65 patients) with similar baseline damage, number of VF tests, and follow-up was used to address possible regression to the mean. Proportions of VF locations decaying or improving before and after surgery in the Trab group, and during the first and second halves of follow-up in the Comp group, were calculated. A multivariate analysis was used to explore variables associated with VF improvement.

Main Outcome Measures: The rate of pointwise VF change before and after surgery in the Trab group and Comp group.

Results: Patients in the Trab group were followed for 5.1±2.1 years (mean ± standard deviation) before and 5.4±2.3 years after surgery, with 8.9±4.7 VF tests before and 9.0±4.4 VF tests after surgery. The mean rate of change for all VF locations slowed from −2.5±9.3%/year before surgery to −0.10±13.1%/year after surgery ($P < 0.001$). In the Trab group, 70% of locations decayed and 30% improved preoperatively; postoperatively, 56% decayed and 44% improved. The differences between the Trab and Comp groups were significant ($P < 0.0001$, chi-square test). The magnitude of IOP reduction correlated with the excess number of VF locations that exhibited long-term improvement postoperatively ($P = 0.009$). In the Trab group, 57% of eyes had ≥10 improving VF locations postoperatively.

Conclusions: The results show that trabeculectomy slows the rate of perimetric decay and provide evidence of sustained, long-term improvement of visual function in glaucoma. These findings suggest the possibility of reversal of glaucomatous dysfunction of retinal ganglion cells and their central projections. *Ophthalmology 2016;123:117-128 © 2016 by the American Academy of Ophthalmology.*

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The importance of measuring the rate of visual field (VF) decay in glaucoma is well established.[1,2] Studies have documented reduction (13%−83%) in the rates of glaucoma VF decay after trabeculectomy.[3−15] Actual improvement of VF threshold sensitivity, however, has long and widely been thought not to occur. Conventional wisdom has dictated that vision loss from glaucoma is irreversible and that treatment can only preserve remaining vision, at best. Spaeth et al[16,17] previously presented the possibility of establishing new criteria for judging the benefit of reduced intraocular pressure (IOP) in glaucoma with improvements in visual function rather than its stability. Some studies examining VF threshold sensitivity changes after trabeculectomy show no significant change,[18−25] whereas others show some improvement.[26−31] There are reports of VF improvement after trabeculectomy with "reversal" of structural damage.[23,32−34] A recent study showed evidence of VF improvement over a 5-year period after initial glaucoma treatment (both surgical and medical).[35] Wright et al[36] recently reported short-term improvement of central and peripheral VF sensitivity after surgical reduction of IOP in glaucomatous eyes. Psychofunctional tests with contrast sensitivity,[37,38] electroretinography,[20,39−41] and color vision testing[42] have also demonstrated short-term improvement after glaucoma treatment, which supports the possibility of revitalization of retinal ganglion cell (RGC) function. No improvement of visual sensitivity was found in normal eyes, suggesting that the presence of glaucomatous damage is required for the enhancement of visual sensitivity.[25]

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Although the slowing of VF damage as a consequence of IOP reduction has been established by landmark glaucoma randomized clinical trials,[43–48] the measurement and quantification of real and sustained VF improvement have been investigated little, and at that, not beyond the global VF indices. The objective of this study is to investigate the frequency and distribution of VF improvement by analyzing the magnitude and direction of the rates of change after the IOP reduction afforded by trabeculectomy.

Methods

Patient Selection

This is a retrospective review of consecutive patients with open-angle glaucoma who underwent trabeculectomy at the Glaucoma Division of the Jules Stein Eye Institute, University of California, Los Angeles (UCLA), between December 2, 1993, and January 13, 2014, and who satisfied all inclusion and exclusion criteria for this study. Trabeculectomy was performed if (1) the patient showed convincing evidence of progressive structural or functional glaucomatous optic nerve damage that could not be adequately treated with more conservative measures or if (2) in the opinion of the surgeon, the IOP was at a level that would probably cause additional damage. Three experienced glaucoma specialists performed a previously described standardized trabeculectomy with intraoperative adjunctive mitomycin-C.[49] A separate comparison group of patients with glaucoma who did not have surgery but, with a similar amount of baseline VF damage, similar numbers of VF measurements, and similar durations of follow-up, were used to help address possible regression to the mean effects. This study was approved by the UCLA Human Research Protection Program, was performed in accordance with the tenets set forth in the Declaration of Helsinki, and complied with Health Insurance Portability and Accountability Act regulations.

Visual Field Inclusion Criteria

All VF examinations were performed with a Humphrey VF analyzer (Carl Zeiss Ophthalmic Systems, Inc., Dublin, CA) with a 24-2 test pattern, size III white stimulus, and with full threshold or Swedish Interactive Threshold Algorithm (SITA) standard strategies. Each eye's VF series contained all SITA or all full-threshold examinations; examinations were never mixed for any eye in the series. The VF tests with less than 30% fixation losses, false-positive rates, and false-negative rates were considered reliable, and all VFs belonging to each series that fulfilled these criteria were included in the study. The last preoperative and first postoperative VFs were required to be within 1 year of surgery. The VF tests performed <3 months after surgery were excluded. Eyes with ≥4 VF tests both before and after trabeculectomy that fulfilled these criteria were included. The minimum required VF follow-up both before and after surgery was 4 years. Eyes that had cataract surgery within the required follow-up period were excluded. Pseudophakic eyes were included if cataract surgery preceded enrollment. Eyes that had other major ocular surgeries or medical events within the follow-up period that may have affected visual function were excluded. Visual field locations were eliminated from the analysis if they were part of the physiologic blind spot or the initial 3 measurements at those locations before or after trabeculectomy had threshold sensitivities of 0 decibels (dBs). For test locations that included a threshold sensitivity of 0 dB, the 0 dB value was converted to 1 dB to allow for logarithmic transformation.

Determination of Improvement or Decay

The slope of a linear regression fit was first measured at each test location to determine whether that location had an improving or decaying trend. If the regression coefficient was positive, the series was tagged as "improving," and if negative, the series was tagged as "decaying."

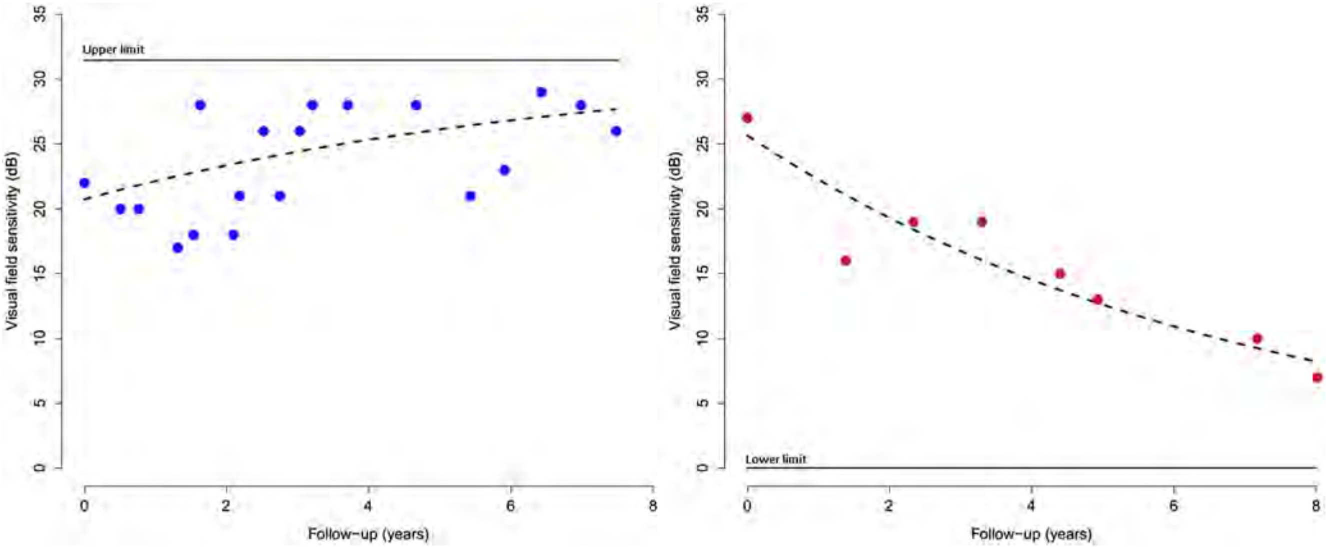

Figure 1. Observed decibel (dB) values and the improvement model fit based on the exponential decay curve bounded by an upper limit based on the age- and location-matched normal sensitivity (*left*). Observed dB values and the decay model fit based on the exponential decay curve bounded by a perimetric lower limit of 0 dB (*right*).

Decay and Improvement Models with Pointwise Exponential Regression

For VF locations tagged as "decaying," the pointwise exponential regression model was used, expressed as $y = e^{\alpha + \beta x}$ or, equivalently, the logarithmically transformed linear model $\ln y = \alpha + \beta x$, where y = sensitivity (dBs), α = constant, β = regression coefficient, and x = time in years. For VF locations tagged as "improving," an exponential function with an asymptote as a ceiling instead of a floor was used (Fig 1). The improvement model was similar to the decay model with an additional step of subtracting the observed threshold sensitivities from the age-adjusted normal threshold sensitivities (denoted by Y). The age- and location-matched normal dB served as the "ceiling" asymptote. Thus, the function used to model improvement was effectively a mirror image of the one used to model decay. Its equation is $Y - y = e^{\alpha + \beta x}$ or, equivalently, $y = Y - e^{\alpha + \beta x}$ where y = sensitivity at time x, and α and β are constants. The percentage rate of change for improvement or decay was calculated preoperatively and postoperatively as $[(y(t) - y(0))/y(0)]/t$, where t is the final follow-up time in years, and y(t) and y(0) are the final and initial sensitivities, preoperatively and postoperatively, respectively, as estimated from the pointwise exponential regression equation. The rates of progression are expressed as percentage per year.

To help examine the effect of trabeculectomy on VF rates and to address the possibility of regression to the mean with this approach, a matched glaucomatous, nonoperated comparison group (with a simulated surgical date inserted in the middle of follow-up) from the same UCLA glaucoma database served as a comparison group (Comp) with the operated group (Trab). The Comp eyes had ≥4 VF measurements before and after the middle follow-up time, ≥8 years' total follow-up, and no inter-current eye surgery; all were medically treated for open-angle glaucoma. This group was not intended for or used as a control group for the treatment effects of surgery versus medicine.

Removal of Outliers

In an effort to reduce random noise and outliers that unduly influence model fits, such points were removed on the basis of Cook's[50] distance estimates. All threshold values in a series for a test location with a Cook's distance >1 were removed from the series, and the best fit was recalculated. This was performed separately for the preoperative and postoperative series, and was applied likewise to the Trab group and the nonoperated Comp group.

Analysis of Factors Associated with Visual Field Improvement

Multiple linear regression analysis was performed with the difference between the number of improving points postoperatively and preoperatively regressed against baseline age, baseline mean deviation (MD), and change in IOP, where change in IOP was the difference between the average of the last 3 IOPs before surgery and the first 3 IOPs starting 3 months after surgery. Univariate analysis was performed with the difference between the numbers of improving points postoperatively and preoperatively regressed against change in IOP. These analyses were performed with the results obtained with the Cook's corrected exponential model.

Statistical Analysis

All statistical analyses were performed in (R Core Team, Vienna, Austria).[51] The assumption of normality for each variable was tested with the Kolmogorov–Smirnov method. The differences in variables before and after trabeculectomy were assessed with 2-tailed paired t tests (for variables approximating a normal distribution) or Wilcoxon signed-rank tests (for variables not normally distributed). A McNemar's test was used to determine whether the frequencies of preoperative decay and improvement were different than the frequencies of postoperative decay and improvement. Chi-square testing was used to compare the numbers of test locations that exhibited decay or improvement in the Trab and Comp groups. Pearson's correlation was used to compare changes in IOP parameters with changes in the rate parameters. The rates of change for MD and the visual field index (VFI) were calculated with a linear regression model ($y = \alpha + \beta x$) and expressed in dB/year for MD and percentage/year for VFI.

Additional Analyses

The entire rate and frequency analysis was performed 3 additional times with different approaches to examine the sensitivity of regression results to outliers based on various model assumptions and to test the robustness of the results. These additional analyses were used: (1) the raw data without removal of influential measurements based on Cook's distance; (2) a set of test locations that excluded those with an exponential fit for which the P value for testing the correlation significance was >0.10; and (3) an entirely linear model (pointwise linear regression) instead of an exponential model. These additional analyses were applied to both the Trab and Comp groups.

Results

Demographics

Of 1290 consecutive eyes of 952 patients with open-angle glaucoma from the UCLA glaucoma database who underwent trabeculectomy during the study period, 74 eyes fulfilled the inclusion and exclusion criteria for this study. The following were excluded from the database of 1290 eyes: 25 eyes that underwent combined phacoemulsification-trabeculectomy, 57 eyes with missing VF data, and 1134 eyes with an inadequate number VFs measurements or duration of follow-up. Demographic characteristics of the Trab

Table 1. Demographics for the Trabeculectomy and Comparison Groups

	Trabeculectomy Group	Comparison Group
No. of eyes	74	71
No. of patients	65	55
No. of patients with both eyes as study eyes	9	16
Right eyes, n (%)	36/74 (48.6%)	33/71 (46.5%)
Left eyes, n (%)	38/74 (51.4%)	38/71 (53.5%)
Age (yrs), mean ± SD	61.4±12.6 (20.5–82.0)	62.5±10.0 (39.65–79.1)
Gender, n (%)		
Male	30/65 (46.2%)	29/55 (52.7%)
Female	35/65 (53.8%)	26/55 (47.3%)
Race, n (%)		
White	40/65 (61.5%)	38/55 (69.1%)
Black	4/65 (6.2%)	3/55 (5.5%)
Other	21/65 (32.3%)	14/55 (25.5%)

SD = standard deviation.

Table 2. Visual Field Characteristics

	Trabeculectomy Group (n = 74 eyes)		Comparison Group (n = 71 eyes)	
	Preoperative	*Postoperative*	*First Half Follow-up*	*Second Half Follow-up*
VF follow-up duration, mean yrs ± SD (range)	5.1±2.1 (2.1–10.8)	5.4±2.3 (2.1–10.5)	4.9±2.0 (1.4–11.2)	5.0±1.9 (2.5–9.2)
No. of VF, mean ± SD (range)	8.9±4.7 (4.0–31.0)	9.0±4.4 (4.0–22.0)	5.7±4.3 (4.0 to 13.0)	6.2±4.1 (5.0–14.0)
Initial MD, mean ± SD (range)	−7.2±5.3 (−21.8 to 0.8)		−5.6±4.3 (−21.5 to 1.5)	
Final MD, mean ± SD (range)	−10.7±6.4 (−21.8 to −0.7)		−8.2±5.1 (−21.0 to 1.2)	
Total VF	1316		913	
Total VF locations included, n	3064*		2897*	

MD = mean deviation; SD = standard deviation; VF = visual field.
*For the exponential regression excluding physiologic blind spot or if the initial 3 locations of the VF series had threshold sensitivities of 0 decibels.

and Comp groups are presented in Table 1. The specific diagnoses of the patients included were primary open-angle glaucoma (n=65), pigmentary glaucoma (n=2), angle-recession glaucoma (n=1), chronic angle-closure glaucoma (n=4), and secondary open-angle glaucoma (n=2).

The Trab eyes were followed for 5.1±2.1 years (mean ± standard deviation) before and 5.4±2.3 years after surgery, with 8.9±4.7 VF tests before and 9.0±4.4 VF tests after surgery (Table 2). The mean time from the last VF test before surgery to surgery was 3.4±3.7 months, and the mean time from surgery to the first VF test after surgery was 7.7±3.1 months. A total of 71 eyes were used in the Comp group. The eyes were followed for 4.9±2.0 years for the first half of follow-up and 5.0±1.9 years for the second half of follow-up, with 5.7±4.3 VF tests during the first half and 8.2±4.1 VF tests during the second half of the follow-up period (Table 2). Counts for the total number of VF locations included for the additional analysis are shown in Table 3 (available at www.aaojournal.org).

The frequency distributions of the mean IOP before and after surgery for each eye are shown in Figure 2. The overall mean IOP before surgery was 14.7±3.3 and 10.0±3.2 after surgery, which represents a mean decrease of 32% ($P < 0.0001$). The peak IOP before surgery was 18.8±5.3 and 13.6±4.5 after surgery ($P < 0.0001$). The IOP standard deviation was 2.4±1.7 before surgery and 2.2±1.0 after surgery ($P = 0.4$).

Cook's Distance Correction

With the application of Cook's distance criteria, a total of 1313 points (3.7%) preoperatively and 1209 points (3.4%) postoperatively were removed from the raw data of the Trab group. A total of 2440 points (11.2%) for the first half of follow-up and 1394

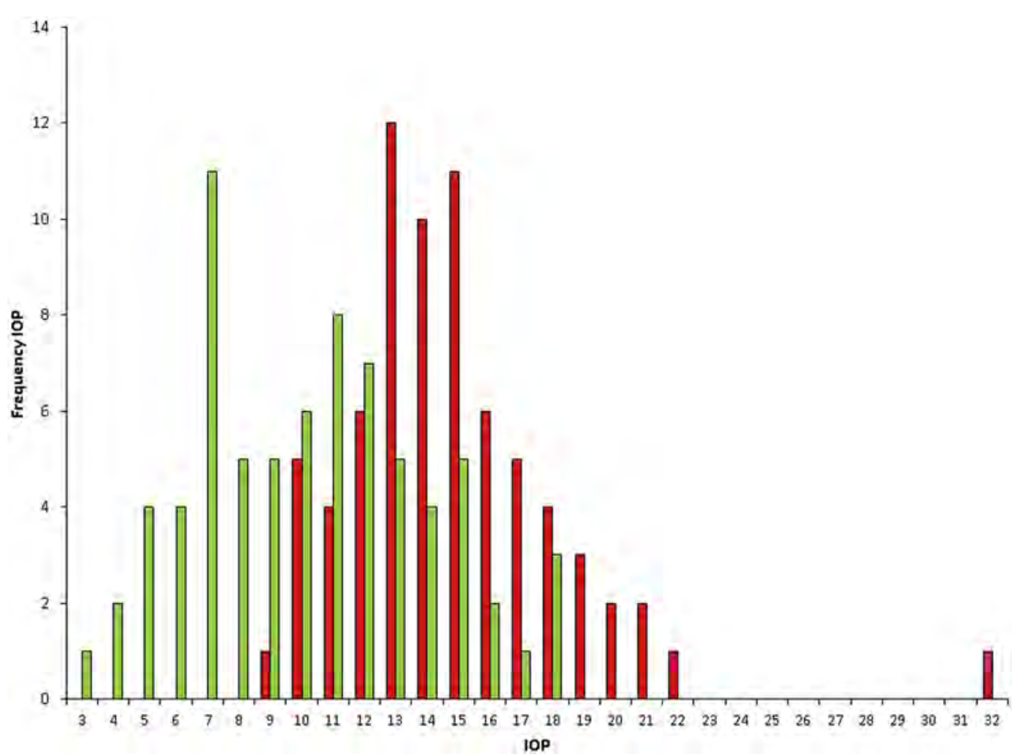

Figure 2. The frequency distribution of the mean preoperative (*red bars*) and postoperative (*green bars*) intraocular pressures (IOPs) in the trabeculectomy group. The last 3 IOPs before trabeculectomy and the final 3 IOPs at the end of follow-up were used for this calculation.

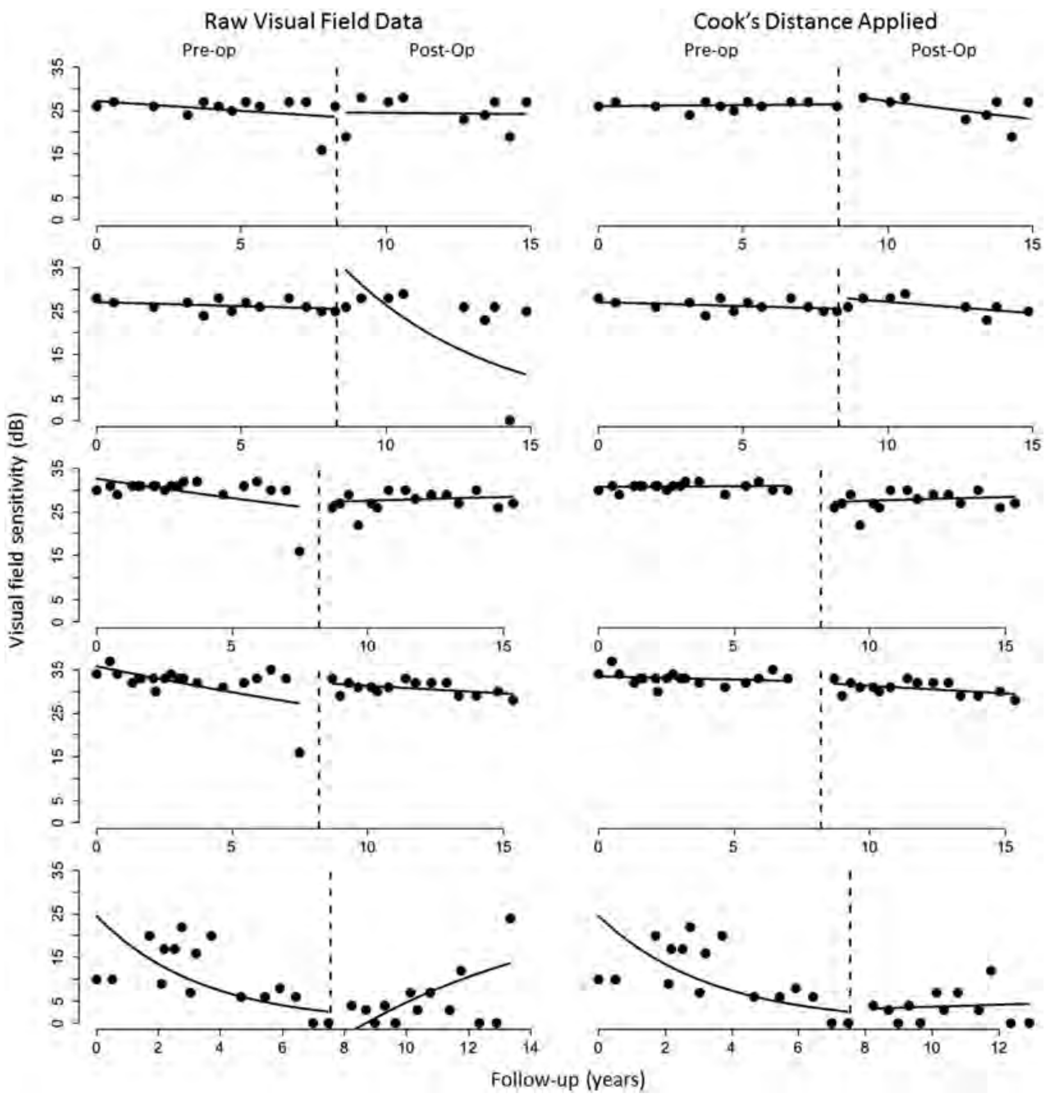

Figure 3. Examples from the trabeculectomy group of exponential fits of rates before (*left*) and after (*right*) removing influential observations based on Cook's distance >1. Shown are individual test locations pre- and postoperatively for the trabeculectomy group of the raw data (*left 2 columns*), and after removal of outliers (*right 2 columns*), along with the fitted pointwise exponential regression. dB = decibel.

points (5.1%) for the second half of follow-up were removed from the raw data of the Comp group. The maximum number of points removed for a single test location series in the Trab group or Comp group was 2. The mean number of points removed was 0.3 preoperatively and 0.3 postoperatively for the Trab group, and 0.6 for the first half of follow-up and 0.4 for the second half in the Comp group. Typical examples of the raw data exponential fits and the fits after Cook's correction are shown in Figure 3.

Rates

The mean decay rate of the Trab group slowed from −2.4±9.3%/year before surgery to −0.6±13.1%/year after surgery ($P < 0.001$). The mean decay rate of the Comp group was −1.4±9.5%/year during the first half of follow-up and −1.7±8.0%/year during the second half of follow-up ($P = 0.14$) (Table 3, Fig 4). The change in rate in the Trab group (pre- vs. postoperatively) was significantly greater than the change in rate in the Comp group (first half vs. second half; $P < 0.001$).

The mean MD rate of the Trab group improved from −0.7±1.1 dB/year before surgery to −0.1±0.8 dB/year after surgery ($P < 0.001$). The mean rate of change in MD of the Comp group was −0.2±0.6 dB/year during the first half of follow-up and −0.3±0.6 dB/year during the second half of follow-up ($P = 0.20$). Change in MD rate (postoperative MD rate − preoperative MD rate) as a function of change in IOP after trabeculectomy (r=0.1; $P = 0.005$) is shown in Figure 5 (available at www.aaojournal.org). The rate of change of MD slowed after surgery.

The spatial distributions of the mean rate of change (improvement or decay) for each location preoperatively and postoperatively for the Trab group and for the first half and second half of follow-up for the Comp group are shown in Figure 6.

Improvement and Decay Counts

A total of 3064 locations for the Trab group and a total of 2897 locations for the Comp group were analyzed. In the Trab group,

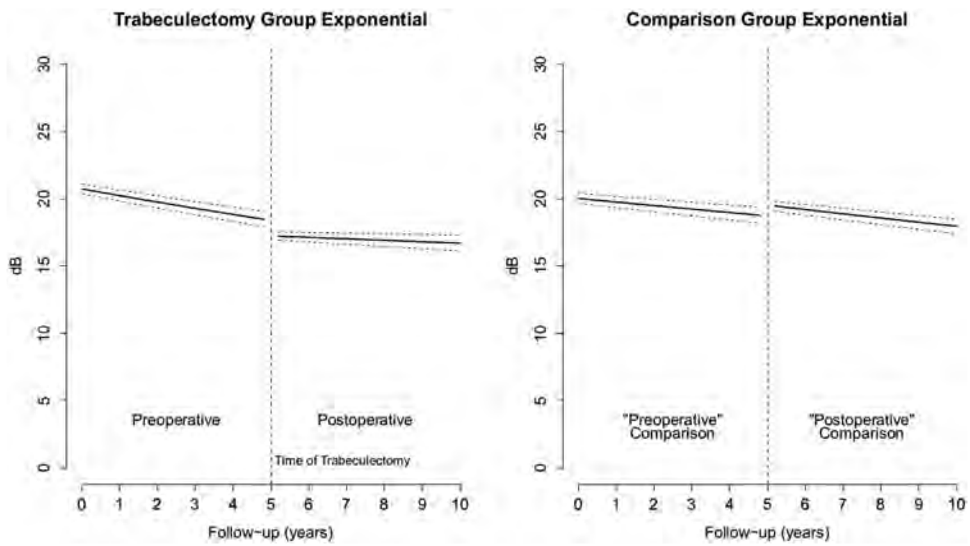

Figure 4. Overall fits of locations pre- and postoperatively for the trabeculectomy group and the first and second halves of follow-up for the comparison group, with 95% confidence intervals. Cook's distance is applied in each case. dB = decibels.

909 locations (30%) improved preoperatively and 1339 locations (44%) improved postoperatively (Table 3). In the Comp group, 972 locations (34%) improved during the first half of follow-up and 1010 improved (35%) during the second half of follow-up; the chi-square comparison of the proportions of improving points in these 2 groups was significant ($P < 0.0001$). Typical examples of test locations that decayed preoperatively and improved post-operatively in the trabeculectomy group are shown in Figure 7. The

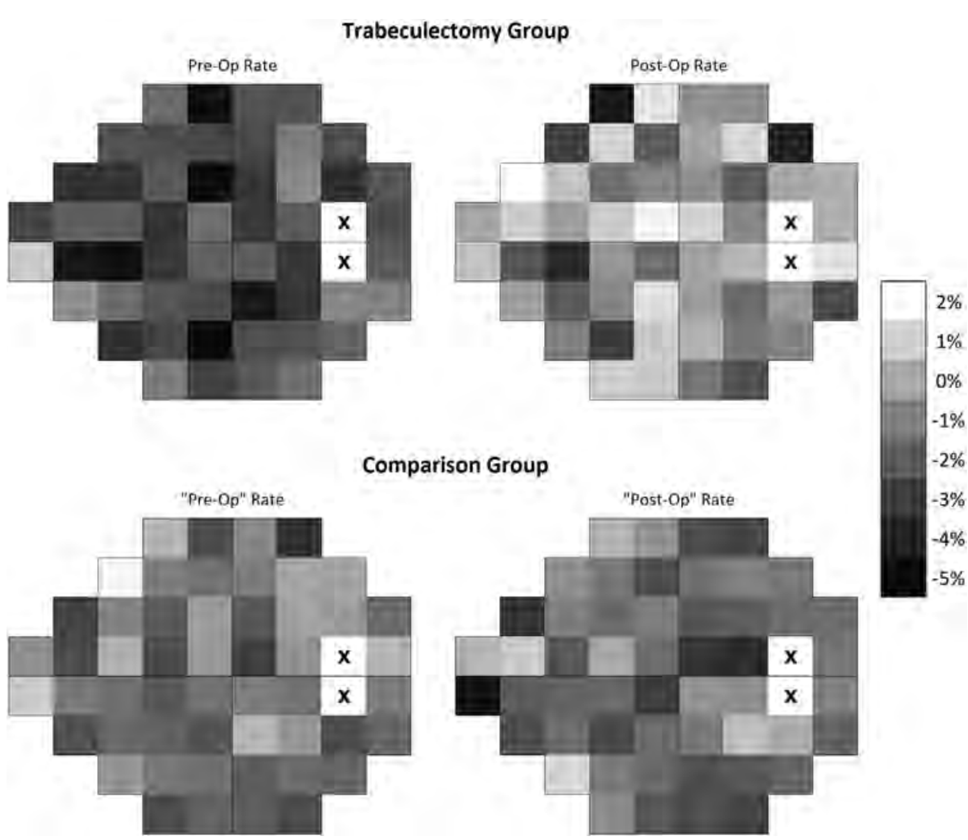

Figure 6. The spatial distribution of the average rate for each location for the trabeculectomy group pre- and postoperatively, and for the comparison group for the first half of follow-up ("pre-op") and the second half of follow-up ("post-op"). The scale indicates change in percentage/year; positive change indicates improvement. The difference in rates pre- and postoperatively (in the trabeculectomy group) was significantly different from the difference in rates between the first half and second half of follow-up (in the Comp group) ($P < 0.001$). Cook's distance is applied.

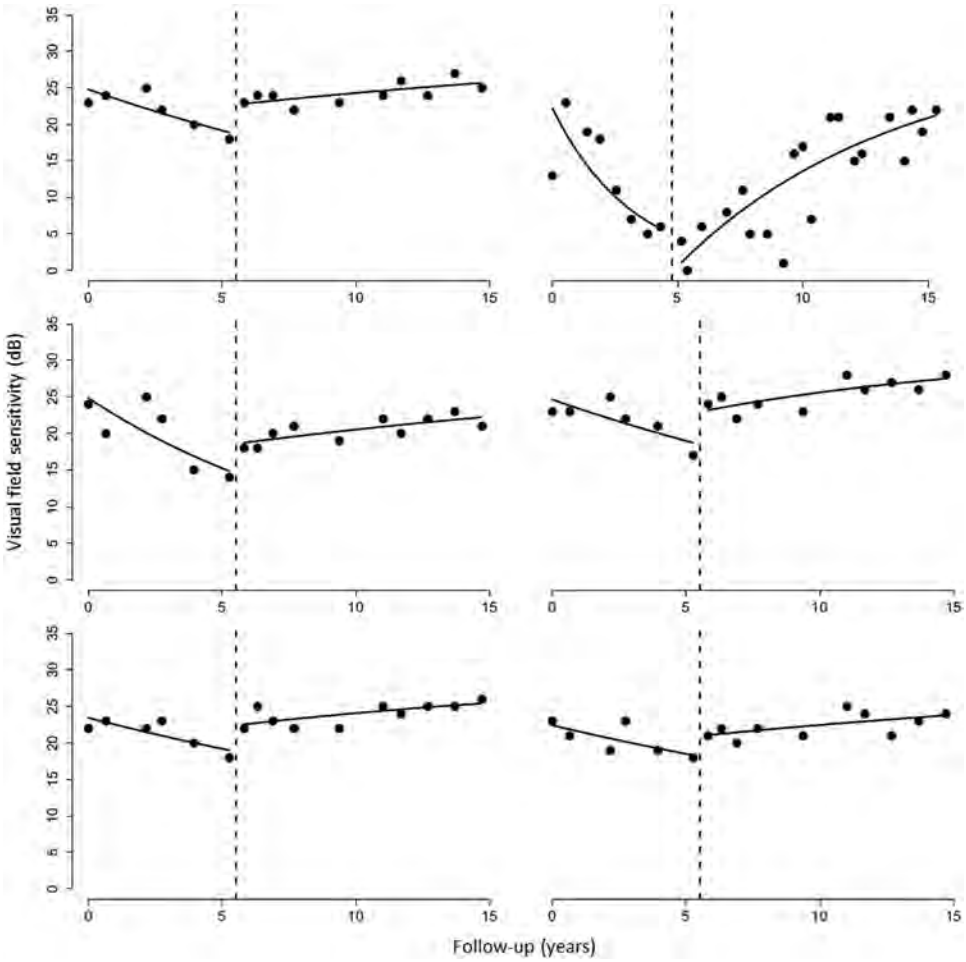

Figure 7. Typical examples of test locations that decayed preoperatively and improved postoperatively in the trabeculectomy group. dB = decibels.

number of locations decaying preoperatively for the Trab group and Comp group are presented in Table 4. A spatial gray scale of the percentage of points per location that changed from decay to improvement and from improvement to decay is shown separately for both groups in Figure 8. The proportion of eyes in the Trab group with 5 or more test locations improving postoperatively was 80%, and the proportion of eyes with 10 or more locations improving postoperatively was 57%; these were significantly greater than in the Comp group ($P = 0.007$).

Table 4. Exponential Regression Rates and Counts for the Trabeculectomy and Comparison Groups

	Trabeculectomy Group*		Comparison Group*	
Rate Pre†	−2.4±9.3%		−1.4±9.5%	
Rate Post†	−0.6±13.1%		−1.7±8.0%	
Total, n (%)	3064	(100)	2897	(100)
Before decay, n (%)	2149	(70)	1916	(66)
After decay, n (%)	1724	(56)	1886	(65)
Before improvement, n (%)	909	(30)	972	(34)
After improvement, n (%)	1339	(44)	1010	(35)

*Data with removal of influential observations based on Cook's distance.
†Pre and post are defined as preoperative and postoperative for the trabeculectomy group and first half follow-up and second half follow-up for the comparison group.

Multivariable Analysis

The difference between the number of improving points postoperatively and preoperatively in the Trab group was regressed against baseline age ($P = 0.67$), baseline MD ($P = 0.77$), and change in IOP ($P < 0.01$; R^2=0.28), where change in IOP was the difference of the average of the last 3 IOPs postoperatively and the first 3 IOPs preoperatively (starting 3 months after surgery). The corresponding scatterplot is shown in Figure 9.

Additional Analyses

Raw Data (All Points Included). The analysis of the pointwise exponential regression of the raw data (without the Cook's distance applied) provided results similar to those obtained after removal of data with Cook's distance >1. Preoperative rates improved for the Trab group and worsened for the Comp group. The number of locations improving postoperatively increased for the Trab group and decreased for the Comp group ($P < 0.001$). The results are summarized in Table 5 (available at www.aaojournal.org).

Models Constrained to Tighter Fits ($P < 0.10$). The results for the subset of points with regression fits when P for testing the

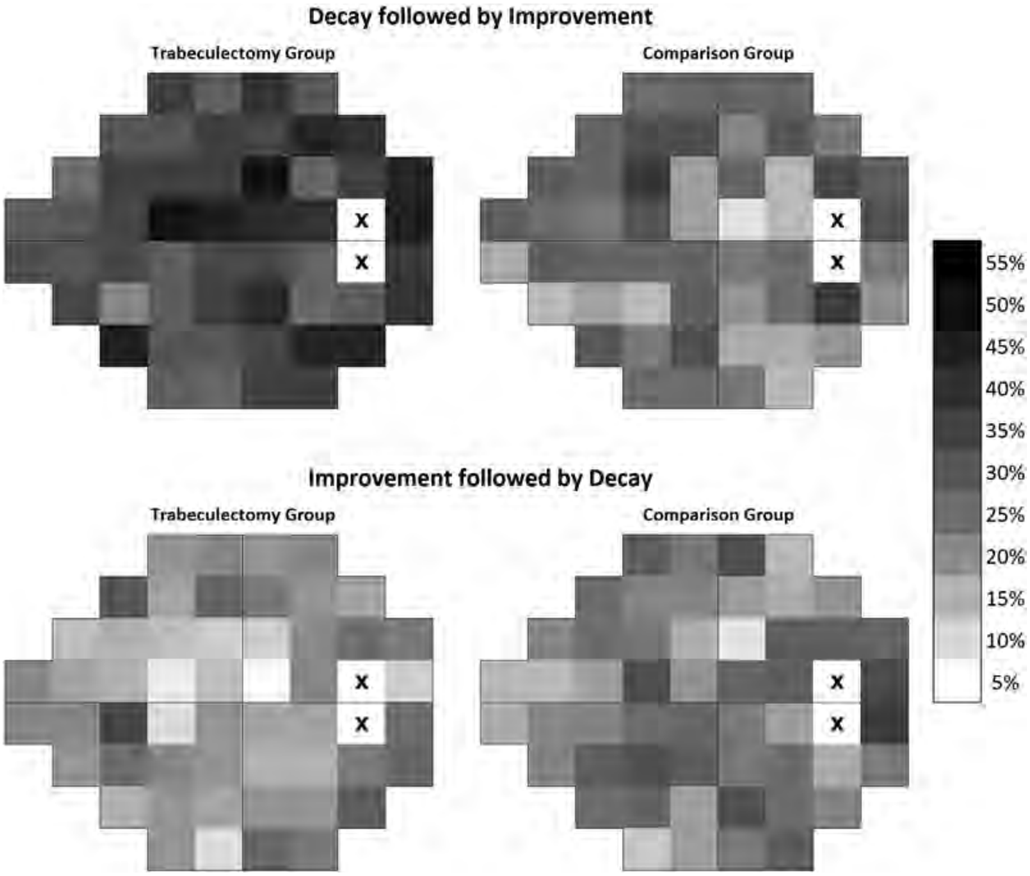

Figure 8. The percentage of eyes that converted from decay to improvement and from improvement to decay for the trabeculectomy and comparison groups. There were substantially higher rates of conversion from decay to improvement in the trabeculectomy group (chi-square = 72; $P < 0.001$). Cook's distance correction is applied.

significance of the correlation was <0.10 were similar to those of the entire group of points. Preoperative rates for the Trab group improved, and they worsened for the Comp group. The mean rate in the Trab group slowed from −6.2±9.9%/year before surgery to 0.9±19.1%/year after surgery ($P < 0.001$). In the Comp group, the rate was 2.5±11%/year for the first half of follow-up and −3.7±10.0%/year for the second half of follow-up ($P = 0.28$) (Table 5, Fig 10, both available at www.aaojournal.org). The number of locations improving postoperatively increased for the Trab group and decreased for the Comp group ($P < 0.001$). A summary of results is given in Table 5 (available at www.aaojournal.org).

Linear Model. Use of the linear regression model (with Cook's correction) provided similar results as the exponential regression. Rates of decay for the Trab group improved postoperatively and were unchanged for the analogous periods in the Comp group ($P < 0.001$). Multivariate analysis also showed that the change in IOP was statistically significantly correlated with the proportion of test locations improving postoperatively in the Trab group. The results were similar when linear regression was applied to the raw data (without Cook's correction) or to the subset of points constrained to a linear fit with $P < 0.1$. A summary of these results is given in Table 6 (available at www.aaojournal.org).

Repeat Analysis after Last Preoperative VF Omitted. As an additional check for effects caused by regression to the mean, the entire analysis was repeated with the last preoperative observation excluded. The treatment effects we saw with the entire VF series remain undiminished in this additional analysis. The results of this analysis are supplied in Tables 7 and 8 (available at www.aaojournal.org).

Relationship between Baseline Sensitivity and Postoperative Improvement. The relationship between baseline sensitivity (average of the last 2 preoperative measurements) and the excess number of locations with improvement postoperatively was investigated. There does not seem to be any significant correlation for the entire VF where the eye is the unit of analysis (Fig 11, available at www.aaojournal.org). However, logistic regression analysis of the likelihood of improvement is a function of terciles preoperatively and postoperatively for all points across all eyes. The highest tercile of preoperative sensitivities is less likely to improve postoperatively than the lowest tercile, although the associated correlation coefficient is low (pseudo r^2=0.03).

The mean baseline sensitivities (average of the last 2 preoperative values) were 21.2±7.9 dB for those points improving postoperatively and 22.3±7.3 dB for those points decaying postoperatively; although the absolute difference is only approximately 1 dB, the difference in the means is statistically significant because the number is large (n = 1384 and 1738, respectively; $P < 0.001$).

Discussion

Long-term improvement of visual function after IOP reduction for glaucoma has traditionally been thought not to

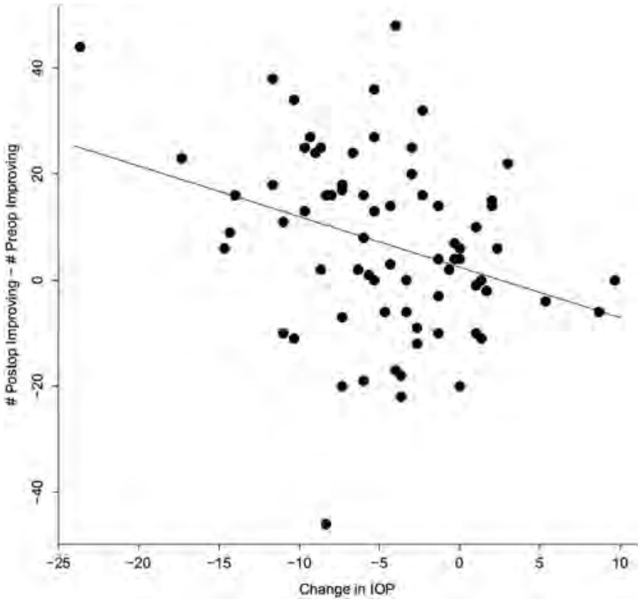

Figure 9. Scatterplot of the change in intraocular pressure (IOP) versus the change in the number of improving points in the trabeculectomy group after surgery compared with before. The last 3 IOPs before trabeculectomy and the first 3 IOPs postoperatively (at least 3 months after surgery) were used for the calculation of IOP reduction ($r = 0.32$; $P = 0.005$).

occur commonly. We offer evidence to the contrary. The sensitivities of individual test locations of the VF frequently show improvement after IOP reduction with trabeculectomy; this improvement is sustained and continues over time. We postulate that RGCs that are damaged but not yet dead remain dysfunctional for some time and contribute to areas of reduced perimetric sensitivity. Their functionality can sometimes be restored by the reduction of stress related to IOP. Robust IOP reduction can thereby improve visual sensitivities, and this improvement can continue over a period of years.

Eighty percent of eyes after trabeculectomy had 5 or more point locations on the VF improve postoperatively, whereas 57% had 10 or more point locations improve. The rate of VF decay slowed overall, and a substantial proportion of VF test locations exhibited sustained and long-term improvement over years. The mean rate of visual sensitivity decline in the Trab group slowed from −2.4±9.3%/year before surgery to −0.6±13.1%/year after surgery ($P < 0.001$), compared with the mean rate of the Comp group, which was −1.4±9.5%/year during the first half of follow-up and changed to −1.7±8.0%/year during the second half of follow-up ($P = 0.14$). Similar results were found with a subset of test locations constrained to regression fits with $P < 0.1$, or the raw data were used for both exponential and linear regression models. There was little difference in results between the exponential and linear models. In general, efforts to "clean up" the data with Cook's correction or with constraints to tighter fits increased the strength of the effects we observed.

The original exponential decay model could not be used to fit improving trends because this model would call for an exponential increase in sensitivities over time: clearly, this is not physiologically possible.[52-54] To solve this problem for locations classified as "improving," a ceiling was defined as the normal age- and location-matched threshold sensitivity that became the model's asymptote for that location. The baseline sensitivities were subtracted from the observed "improving" sensitivities, and the difference provided an inverted decay pattern; this was a mirror-image of a VF exponential decay pattern (Fig 1).

Earlier studies[26–29] that investigated improvement after trabeculectomy had limitations, and most[26–28] had a small number of VFs in the series. Salim et al[26] observed VF improvement 3 to 8 months postoperatively, which was enhanced by focusing on location subgroups with lower baseline VF sensitivities. They concluded that the most glaucoma-damaged VF areas had the most functional recovery postoperatively, but they acknowledged the confounding possibility of increased test−retest variability for patients with more advanced glaucoma.[26] However, these results were probably influenced by regression to the mean because deeply depressed points are more likely to improve than to decay. In a study by Vuori et al,[27] who used VF clusters, there was a tendency toward local improvement in the VF after trabeculectomy. From a total of 35 VF clusters, there was an average of 3.9 clusters where retinal sensitivity had improved at least 5 dB in 1 VF after trabeculectomy. In their study, regression to the mean was acknowledged to influence the results because a majority of the improved clusters had returned to the lower baseline level in the second postoperative VF test.[27]

In a recent analysis of VF data from the Collaborative Initial Glaucoma Treatment Study, substantial VF improvement was observed in open-angle glaucoma eyes after medical or surgical glaucoma treatment.[35,36] The authors reported that the rates of VF loss and improvement were similar after 5 years of treatment initiation, and they believed approximately half of the observed change reflected "real" loss or "real" improvement. As in other studies, clinically substantial change (loss or improvement) was defined with MD, with no ability to measure regional rates or to conserve spatial information. Wright et al[36] recently reported short-term improvement of central and peripheral VF sensitivities after surgical reduction of IOP in glaucomatous eyes.

Electrophysiologic studies have shown improvement with IOP reduction, suggesting reversibility of RGC function. Sehi et al[39] showed that although neither the MD nor the pattern standard deviation significantly changed 3 months after trabeculectomy, in the central 16 VF locations (matched to the area subtended by the pattern electroretinogram [ERG]) there was a significant direct association between the percentage improvement in pattern ERG amplitude optimized for glaucoma screening and the percentage improvement in VF sensitivity observed in patients younger than 70 years of age.[39] The photopic negative response is the negative response of the photopic ERG that follows the b-wave, and its amplitude is associated with cone-related RGC function. A recent study showed that the photopic negative response amplitude increased after IOP reduction in eyes with glaucoma and ocular hypertension.[41]

The method for determination of rates in our study allowed for the possibility of detecting VF improvement. For those locations classified as decaying, we used a "decay model," and for locations classified as improving, an "improvement model" was used. Possible regression to the mean effects were investigated by including a comparative, nonoperated group (Comp): A group of 63 nonoperated glaucoma eyes with similar amounts of baseline glaucomatous damage, number of VF tests, and duration of follow-up was compared with the operated (Trab) eyes. The first half of follow-up in the Comp group corresponded to the preoperative portion of the Trab group, and the second half of follow-up corresponded to the postoperative series in the Trab group. The finding that there were significantly more locations that both decayed preoperatively and improved postoperatively ($P < 0.001$) in the Trab group compared with the Comp group supports the conclusion that there was real, sustained VF improvement in the Trab group.

To mitigate fluctuation or noise effects in our study, we used an average of 9 VFs before and 10 VFs after trabeculectomy. Repeating the analysis by excluding outliers (Cook's method), by requiring tighter fits to the model ($P < 0.10$), or by repeating the entire analysis with a linear model, provided similar results and the same conclusions. In fact, methods used to reduce noise (Cook's correction and tighter fit constraints) strengthened the relationships we found; that is, these methods demonstrated a larger reduction in rates of decay and a greater proportion of VF points with long-term improvement (Tables 5 and 6, available at www.aaojournal.org). We chose the exponential model as our primary analysis because our previous work demonstrated more accurate fits and better predictions with the exponential model compared with the linear model.[52,53] We also used Cook's correction of the exponential model in our primary analysis because it effectively removed outliers that unduly influenced the slope fits; careful examination of the raw results compared with the results obtained after Cook's correction made clinical and statistical sense (Fig 3). However, all of the approaches presented in this article are in agreement, and all point to a robust long-term reduction of VF decay rates and in many cases continued long-term improvement of VF sensitivities.

Study Limitations

The limitations of the study must be considered. No statistical model of VF behavior is perfect; models provide simplified approximations of actual, complex, and noisy VF behavior. The majority of patients (63%) in the study population were white, and it is possible that the effects of surgery on VF rates may be different in other patient populations. Overall, our study population consisted of patients with mild to moderate glaucoma severity based on the average initial and final MD values. Therefore, the behavior of severely damaged VFs after trabeculectomy is yet to be determined. Regression to the mean effects were carefully considered because we were examining the change of the behavior of a noisy variable before and after a time point (surgery). To help address this possibility, we similarly examined VF behavior after a middle time point in a separate nonoperated comparison group. This group is expected to have the same type of noisy perimetric behavior and evidence of slow decline overall. This group did not exhibit the improvement effects that we detected in the Trab group. Although there was a statistically significant difference in baseline MD between the Trab group and the Comp group ($P < 0.001$), the magnitude of the difference is relatively small (1.5 dB), and we believe that the match is close enough to serve its purpose: to mitigate effects caused by regression to the mean. To further mitigate possible effects caused by regression to the mean, the entire analysis was repeated with the last VF observation omitted. The treatment effects that were observed with the entire data series remain undiminished, and our conclusions remain the same. This, together with the results from the Comp group, argues against regression to the mean playing a significant role in the treatment effects that we report.

The IOP reduction will remain an important aspect of glaucoma treatment because it is demonstratively effective in decreasing the rate of visual worsening. To date, it remains the most potent neuroprotective treatment for glaucoma available. An effective method for reducing IOP to low levels is trabeculectomy, although it is certainly not without attendant risks and complications. The pressure reduction attendant to trabeculectomy in this study was more than 30%, although the mean preoperative IOP was only 15 mmHg; this represents a substantial reduction of IOP. Although it is not known whether a similar reduction achieved medically would provide the same results, we suspect that they would.

In summary, trabeculectomy significantly slows the rate of perimetric decay from glaucoma. The results presented provide evidence of sustained, long-term improvement of RGC function in glaucoma; these findings suggest the possibility of the reversal of RGC dysfunction from glaucoma. These findings also give credence to the concept that the traditional goal of treating patients with glaucoma to maintain stability should be challenged, and that long-term improvement of visual function may be a reasonable and attainable goal in some patients.[16,52]

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Abbreviations and Acronyms:
Comp = comparison (unoperated group); **dB** = decibels; **ERG** = electroretinogram; **IOP** = intraocular pressure; **MD** = mean deviation; **RGC** = retinal ganglion cell; **Trab** = trabeculectomy (group undergoing surgery); **UCLA** = University of California, Los Angeles; **VF** = visual field.

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