The Effects of Intraocular Pressure Reduction on Perimetric Variability in Glaucomatous Eyes

Paolo Fogagnolo,1 Andrew McNaught,2 Marco Centofanti,1,3 Luca Rossetti,4 and Nicola Orzalesi4

PURPOSE. To investigate changes in the variability of white-on-white perimetry in patients with glaucoma who are undergoing surgical or medical reduction of intraocular pressure (IOP).

METHODS. This retrospective study included 67 eyes of 50 patients who underwent trabeculectomy (25 eyes) or medical IOP reduction (25 eyes) about midway through the follow-up; 17 fellow eyes of the surgical group were the control group. Their pre- and postinterventional visual fields were analyzed (full-threshold, 24-2 program, Humphrey Field Analyzer; Carl Zeiss Meditec, Inc., Oberkochen, Germany) to evaluate changes in short-term fluctuation (SF) and test-retest variability (TRV). The longest follow-up periods possible were considered, provided that glaucoma was stable (as confirmed by intraocular pressure, optic nerve appearance and visual field). For each patient and in each period, TRV was defined as the mean of the square roots of the mean variances in each of the 54 locations.

RESULTS. Trabeculectomy reduced mean IOP (5.7 ± 4.7 mm Hg; P < 0.0001), IOP fluctuations (−2.9 ± 4.4 mm Hg; P = 0.003), and eye drop use (−1.3 ± 1.4; P = 0.0001). Pre- and postsurgical SF was 3.0 ± 1.1 and 2.7 ± 1.0, respectively (P = 0.34), and pre- and postsurgical TRV was 2.90 ± 0.97 and 2.53 ± 0.86, with a decrease of 0.37 dB (P = 0.006). In the medical group, mean IOP decreased (−4.0 ± 2.0 mm Hg; P < 0.0001) as did IOP fluctuation (−3.7 ± 4.1 mm Hg; P = 0.0008), but eye drop use increased by 1.0 ± 0.6 (P < 0.0001). TRV (2.58 ± 0.53 vs. 2.72 ± 0.67 dB; P = 0.37) and SF (2.3 ± 0.8 vs. 23.8 ± 0.8 dB; P = 0.89) remained stable during the study. There was no change in perimetric variability throughout the study in the control group. The individual reductions in TRV were higher in the surgical group than in the medical (P = 0.004) or control (P = 0.015) groups. No differences were found between the control and medical groups (P = 0.55).

CONCLUSIONS. After trabeculectomy, there was a small but statistically significant reduction in long-term perimetric variability compared with the medical and control groups. There were no significant changes in short-term variability in any of the groups during the study. (Invest Ophthalmol Vis Sci. 2007;48: 4557–4563) DOI:10.1167/iovs.06-1496

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Evaluating visual field over time is a key element in the management of glaucoma and is the gold standard for detecting progression, although it is limited by the “noise” of perimetric variability, which can mask or even mimic glaucomatous deterioration.1 Variability can affect any single visual field test as a result of changes in the nature of the visual system and the testing situation (random variability2) and the patients’ conditions (e.g. ability to learn,3 fatigue,4 anxiety,5), pupil size,6 media opacities,7 refractive error,8 and systemic treatments9-11 (nonrandom variability).

Several mathematical models have been proposed for measuring perimetry variability over repetitions, one of the simplest and most commonly used in clinical practice being test-retest variability (TRV). TRV has been defined as the mean value of the variances12 and standard deviations13 of threshold sensitivity at each location and is a measure of intratest variability (short-term fluctuations, SF) and long-term fluctuations (the variance in threshold sensitivities over that of SF).12

Studies of normal subjects, patients with suspected glaucoma, and patients with glaucoma have demonstrated that the amount of perimetric variability directly relates to the stage of the disease.11,13-15 There are currently no studies addressing the effect of intraocular pressure (IOP) reductions on visual field variability.

The purpose of this study was to investigate the changes in short- and long-term perimetric variability in patients with glaucoma undergoing surgically or medically induced IOP reduction and to compare these with a control group of eyes experiencing no change in IOP.

MATERIALS AND METHODS

This retrospective study involved three European sites: the Eye Clinic at San Paolo Hospital, Milan, Italy (site A); the Eye Clinic at Cheltenham General Hospital, Gloucestershire, UK (site B); and the Department of Ophthalmology, “Tor Vergata” University of Rome, Italy (site C). It was approved by the Ethics Committee of each site, and respected the tenets of the Declaration of Helsinki and national laws for the protection of personal data. Informed consent was obtained from all the participants.

The patients were selected to create three groups: a surgical group consisting of patients undergoing trabeculectomy, a medical group of patients in whom IOP was reduced by means of a change in medical treatment, and a control group.

The surgical group was created by inspecting the operation registers at the three sites for the period 2000 to 2005. The patients’ notes were retrieved and checked for eligibility. The patients who had undergone surgical techniques other than trabeculectomy (phacotrabeculectomy, deep sclerectomy, and viscocanalostomy) or experienced any complication with a possible impact on visual acuity or visual field were not considered for inclusion.

For the medical group, the notes of the patients attending each glaucoma service after 2000 were retrieved. The included patients had shown a reduction in IOP about midway through the follow-up due to a change in medical treatment (a switch from one treatment to another or the addition of another drug) and were matched to those in the surgical group in terms of age (differences of ±5 years were allowed).
best-corrected visual acuity (BCVA; limit of ±2 D), diagnosis, familiarity with visual field testing, mean defect (MD; limit of ±4 D), and postinterventional change in IOP (difference of less than ±10% compared with the surgical group).

The control group included the nontreated fellow eyes of the patients in the surgical group which, during the same duration of follow-up, did not have any changes in IOP or medical treatment.

The inclusion criteria for both glaucoma groups were (1) patients with primary open-angle glaucoma, pseudoexfoliative glaucoma, or pigmentary glaucoma; (2) no clinical evidence of progression detected by the patient’s usual physician during the pre- and postinterventional periods (for glaucomatous eyes, progression was allowed only during the peri-interventional period; definitions provided later in the article); (3) the presence of at least three reliable and stable visual fields during the pre- and postinterventional periods; and (4) white-on-white, full-threshold tests (Humphrey perimeter, 24-2 program; Carl Zeiss Meditec, Inc., Oberkochen, Germany).

The exclusion criteria were (1) secondary glaucomas; (2) the development of cataract or any disease affecting visual acuity and visual field at any time during the study period; (3) eye testing using different programs or perimeters than those stated herein.

We checked that the perimetric procedures were standardized between centers as carefully as possible by inspecting the patients’ notes: the patients were tested every 6 months in early-moderate cases and every 4 months in advanced cases. Visual field tests were always supervised by well-trainedstaff. They were performed at least 30 minutes after any other examination, and patients were allowed to adapt to ambient lighting for 30 minutes.

As perimetric stability is essential for calculating long-term variability, the visual fields of suitable patients were double-checked before enrollment to confirm the absence of progression during the pre- and postinterventional periods on the basis of the criteria given later in the Definitions section. In the surgical group, all the tests performed in the period between the first sign of progression and surgery were excluded from the analysis as a part of the peri-interventional period. Ophthalmic examination data, BCVA (measured using Snellen charts), refraction, and IOP were also recorded.

### Definitions

**Preinterventional period:** from the time of the first visual field examination included in the study to the time of the last visual field examination before progression was demonstrated.

**Peri-interventional period:** from the day after the last preinterventional visual field examination to the day before the first postinterventional examination.

**Postinterventional period:** the time between the first and the last postinterventional visual field examinations.

**SF (intratest variability):** automatically calculated by the perimeter, in each test, as the mean of the standard deviations in the 10 locations included in the double threshold measurements. The differences between the two periods were calculated for each patient according to the following formula:

\[
\Delta SF = \frac{1}{m} \sum_{j=1}^{m} SF - \frac{1}{n} \sum_{i=1}^{n} SF,
\]

where \(n\) (ranging from 1 to \(m\)) indicates the number of postinterventional visual field examinations, and \(m\) (ranging from 1 to \(n\)) is the number of preinterventional visual field examinations.

**TRV:** defined in a series of visual field examinations as the mean of the square roots of the mean variances in each of the 54 locations tested by the 24-2 program. In the present study, the difference in TRV between the two periods was calculated for each patient according to the following formula:

\[
\Delta TRV = \frac{1}{54} \sum_{i=1}^{54} \sum_{j=1}^{m} (x_i - \bar{x})^2 - \frac{1}{54} \sum_{i=1}^{54} \sum_{j=1}^{n} (x_i - \bar{x})^2,
\]

where \(i\) (ranging from 1 to \(r\)) identifies the 54 locations, \(j_{\text{post}}\) (ranging from 1 to \(m\)) is the number of postinterventional visual field examinations, and \(j_{\text{pre}}\) (ranging from 1 to \(n\)) is the number of preinterventional visual field examinations.

**Stable visual field:** the absence of (1) the development of a new scotoma (defined as three or more contiguous points with \(P < 5\%\) or two or more contiguous points with \(P < 1\%\)); (2) the expansion of an existing scotoma into previously normal regions (defined as three or more contiguous points with \(P < 5\%\), or two or more contiguous points with \(P < 1\%\)); (3) the deepening of an existing scotoma (defined as a decrease in the probability or a reduction in sensitivity of at least 5 dB in three or more contiguous points or 10 dB or more in at least two contiguous points\(^{16}\)); and (4) a worsening probability for any perimetric index.

**Progression:** the presence of at least one of these changes.

**IOP assessment:** measured at each visit at 8 and 11 AM and at 2 and 5 PM (intervals of ±15 minutes were allowed), by glaucoma specialists using Goldmann applanation tonometry. Two measurements were taken (with a third in the case of a difference of ≥2 mm Hg between the first two), and the mean of two or median of three recordings was used for the analysis. During the pre- and postinterventional periods, fluctuations in IOP were calculated as the mean of the ranges (i.e., maximum IOP minus minimum IOP) recorded for each patient at each visit.

**Surgery**

Trabeculectomy was performed using a fornix-based conjunctival approach at 12 o’clock. After careful coagulation of the episcleral vessels, a rectangular flap of one-third scleral thickness was fashioned with a 45° microsurgical knife (site A) or a crescent knife (sites B, C), followed by sclerotomy using a 15° microsurgical knife (A) or Kelly’s punch (B, C), by paracentesis, and peripheral iridectomy. The scleral flap was sutured with two fixed (A, C) or releasable (B) 10-0 nylon sutures, and viscoelastic (A, C) or saline (B) solution was used to fill the anterior...
Avoid underpowering due to an incorrect estimate of surgery, a sample of at least 15 patients was needed for each group; to decide to consider 25 cases, which gives a statistical power of 90%.

All the field data of the study participants were stored and analyzed in spreadsheets (GB-STAT; Dynamic Microsystems Inc, Silver Spring, MD). The pre- and postinterventional data of each patient were compared by two-tailed $t$ test for paired data, and between-group differences were analyzed by means of a two-tailed $t$ test for independent data. Models of linear and second-degree regression were also used to inspect data associations.

### Results

Sixty-seven eyes of 50 patients fulfilling the inclusion and exclusion criteria, and with stable visual fields during the two study periods, were enrolled in the study: 25 in surgical group, 25 in the medical group, and 17 in the control group (surgical fellow eyes of the surgical group patients, excluding for four normal eyes, three eyes showing perimetric progression during the study period, and one blind eye).

The demographic data of the participants are shown in Table 1. The causes of progression leading to surgery or an increase in medical treatment are in Table 2, and the main results of the study in each group are in Tables 3, 4, and 5.

The surgical group was selected from 45 suitable patients identified from the surgery registers: 44% of the charts were excluded, mainly due to postoperative perimetric progression (26%) or cataract development (13%).

Mean preinterventional IOP was 20.2 mm Hg (range, 13.0–30.0), which decreased to a mean of 14.5 mm Hg (range, 10.6–19.0) in the second period. Trabeculectomy therefore led to a mean pressure reduction of 5.7 ± 4.7 mm Hg ($P < 0.0001$; range 0–12.0), with a mean percentage decrease of 25% ± 17%, and a decrease in IOP fluctuations of 2.9 ± 4.4 mm Hg ($P = 0.003$). There was a substantial reduction in the number of eye drops used to control IOP after surgery (2.1 vs. 0.8; $P = 0.0001$).

In the postinterventional period, there was a myopic shift of approximately 0.5 diopters ($P = 0.032$), with no significant changes in astigmatism ($−0.03$ D vs. $−0.04$, $P = 0.83$) or BCVA (0.89 vs. 0.85, $P = 0.067$).

### Table 2. Causes of Progression Leading to Surgery or a Change in Medical Treatment

<table>
<thead>
<tr>
<th></th>
<th>Surgical Group</th>
<th>Medical Group</th>
</tr>
</thead>
<tbody>
<tr>
<td>Visual field (%)</td>
<td>7/25 (28)</td>
<td>3/25 (12)</td>
</tr>
<tr>
<td>IOP (%)</td>
<td>0/25 (24)</td>
<td>15/25 (60)</td>
</tr>
<tr>
<td>Optic nerve head (%)</td>
<td>0/25 (0)</td>
<td>0/25 (0)</td>
</tr>
<tr>
<td>Visual field + IOP (%)</td>
<td>12/25 (48)</td>
<td>7/25 (28)</td>
</tr>
</tbody>
</table>

### Table 3. Main Results in the Surgical Group

<table>
<thead>
<tr>
<th></th>
<th>Preinterventional Period</th>
<th>Postinterventional Period</th>
<th>Difference</th>
<th>$P$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Follow-up (months)</td>
<td>26.0 (16.7)</td>
<td>22.7 (13.1)</td>
<td>−3.3 (19.8)</td>
<td>0.41</td>
</tr>
<tr>
<td>Range</td>
<td>6; 64</td>
<td>6; 65</td>
<td></td>
<td></td>
</tr>
<tr>
<td>BCVA (Snellen)</td>
<td>20/22 (20/120)</td>
<td>20/24 (20/100)</td>
<td>−20/500 (20/250)</td>
<td>0.067</td>
</tr>
<tr>
<td>Range</td>
<td>20/40; 20/20</td>
<td>20/43; 20/20</td>
<td>−20/77; +20/400</td>
<td></td>
</tr>
<tr>
<td>Refraction (D)</td>
<td>−0.13 (1.87)</td>
<td>−0.61 (1.53)</td>
<td>−0.49 (0.88)</td>
<td>0.032</td>
</tr>
<tr>
<td>Range</td>
<td>−2.75; +2.75</td>
<td>−2.75; +0.75</td>
<td>−1.50</td>
<td></td>
</tr>
<tr>
<td>IOP (mm Hg)</td>
<td>20.2 (4.7)</td>
<td>14.5 (2.5)</td>
<td>−5.7 (4.7)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Range</td>
<td>13.0; 30.0</td>
<td>10.6; 19.0</td>
<td>0; −15.7</td>
<td></td>
</tr>
<tr>
<td>IOP fluctuations (mm Hg)</td>
<td>7.6 (4.5)</td>
<td>4.8 (3.3)</td>
<td>−2.9 (4.4)</td>
<td>0.003</td>
</tr>
<tr>
<td>Range</td>
<td>0; 18</td>
<td>0; 12</td>
<td>−13; +6</td>
<td></td>
</tr>
<tr>
<td>Number of eye drops*</td>
<td>2.1 (0.9)</td>
<td>0.8 (1.1)</td>
<td>−1.3 (1.4)</td>
<td>0.0001</td>
</tr>
<tr>
<td>Range</td>
<td>0; 3</td>
<td>0; 3</td>
<td>−1; −3</td>
<td></td>
</tr>
<tr>
<td>Number of visual field tests</td>
<td>4.2 (2.4)</td>
<td>3.6 (1.3)</td>
<td>−0.6 (2.8)</td>
<td>0.66</td>
</tr>
<tr>
<td>Range</td>
<td>3; 14</td>
<td>3; 7</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Mean defect (dB)</td>
<td>−12.2 (8.1)</td>
<td>−12.3 (8.9)</td>
<td>−0.1 (2.0)</td>
<td>0.76</td>
</tr>
<tr>
<td>Range</td>
<td>−1.15; −26.70</td>
<td>−1.11; −26.79</td>
<td>−1.67; +1.91</td>
<td></td>
</tr>
<tr>
<td>CPSD (dB)</td>
<td>7.0 (3.6)</td>
<td>7.1 (3.8)</td>
<td>+0.1 (1.8)</td>
<td>0.68</td>
</tr>
<tr>
<td>Range</td>
<td>0.86; 12.35</td>
<td>1.12; 12.48</td>
<td>−3.14; +4.39</td>
<td></td>
</tr>
<tr>
<td>Short-term fluctuation (dB)</td>
<td>3.0 (1.1)</td>
<td>2.7 (1.0)</td>
<td>−0.5 (1.4)</td>
<td>0.34</td>
</tr>
<tr>
<td>Range</td>
<td>1.62; 5.05</td>
<td>1.20; 4.04</td>
<td>−2.04; +2.94</td>
<td></td>
</tr>
<tr>
<td>Test-retest variability (dB)</td>
<td>2.90 (0.97)</td>
<td>2.53 (0.86)</td>
<td>−0.37 (0.46)</td>
<td>0.0006</td>
</tr>
<tr>
<td>Range</td>
<td>0.74; 4.71</td>
<td>0.63; 3.75</td>
<td>−1.21; +0.68</td>
<td></td>
</tr>
</tbody>
</table>

Data are the mean (±SD). D, diopter (spherical equivalent). Bold items, $P < 0.05$.

* Fixed combinations counted as 2 eye drops.
### Table 4. Main Results in the Medical Group

<table>
<thead>
<tr>
<th></th>
<th>Preinterventional Period</th>
<th>Postinterventional Period</th>
<th>Difference</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Follow-up (months)</td>
<td>13.7 (8.4)</td>
<td>14.8 (6.1)</td>
<td>1.1 (10.6)</td>
<td>0.65</td>
</tr>
<tr>
<td>Range</td>
<td>6.47</td>
<td>6.26</td>
<td></td>
<td></td>
</tr>
<tr>
<td>BCVA (Snellen)</td>
<td>20/22 (20/150)</td>
<td>20/22 (20/150)</td>
<td>0 (0)</td>
<td>0.50</td>
</tr>
<tr>
<td>Range</td>
<td>20/40; 20/20</td>
<td>20/40; 20/20</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Refraction (D)</td>
<td>+0.50 (2.12)</td>
<td>+0.45 (2.22)</td>
<td>-0.05 (1.67)</td>
<td>0.43</td>
</tr>
<tr>
<td>Range</td>
<td>-4.50; +2.75</td>
<td>-5.00; +2.75</td>
<td>-0.5; +0.75</td>
<td></td>
</tr>
<tr>
<td>IOP (mm Hg)</td>
<td>19.0 (2.7)</td>
<td>15.0 (2.6)</td>
<td>-4.0 (2.0)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Range</td>
<td>13.1; 22.8</td>
<td>10.4; 18.7</td>
<td>-2.7; -4.1</td>
<td></td>
</tr>
<tr>
<td>IOP fluctuations (mm Hg)</td>
<td>8.2 (4.7)</td>
<td>4.5 (2.2)</td>
<td>-3.7 (4.1)</td>
<td></td>
</tr>
<tr>
<td>Range</td>
<td>2.24</td>
<td>2.8</td>
<td>-17; +1</td>
<td></td>
</tr>
<tr>
<td>Number of eye drops*</td>
<td>2.0 (0.9)</td>
<td>3.0 (0.8)</td>
<td>+1.0 (0.6)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Range</td>
<td>1; 4</td>
<td>2; 4</td>
<td>+1; +2</td>
<td></td>
</tr>
<tr>
<td>Number of visual field tests</td>
<td>3.2 (0.4)</td>
<td>3.3 (0.6)</td>
<td>+0.1 (0.4)</td>
<td>0.58</td>
</tr>
<tr>
<td>Range</td>
<td>3; 4</td>
<td>3; 5</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean defect (dB)</td>
<td>-9.3 (6.7)</td>
<td>-10.0 (6.7)</td>
<td>-0.7 (1.2)</td>
<td>0.020</td>
</tr>
<tr>
<td>Range</td>
<td>-1.97; -24.38</td>
<td>-2.20; -26.57</td>
<td>-2.19; +2.10</td>
<td></td>
</tr>
<tr>
<td>CPSD (dB)</td>
<td>8.5 (3.5)</td>
<td>8.6 (3.0)</td>
<td>+0.1 (1.4)</td>
<td>0.75</td>
</tr>
<tr>
<td>Range</td>
<td>2.75; 14.20</td>
<td>3.36; 13.83</td>
<td>-2.47; +2.34</td>
<td></td>
</tr>
<tr>
<td>Short-term fluctuation (dB)</td>
<td>2.3 (0.8)</td>
<td>2.3 (1.1)</td>
<td>0.0 (1.3)</td>
<td>0.89</td>
</tr>
<tr>
<td>Range</td>
<td>0.95; 4.13</td>
<td>0.32; 5.61</td>
<td>-3.81; +2.28</td>
<td></td>
</tr>
<tr>
<td>Test-retest variability (dB)</td>
<td>2.58 (0.53)</td>
<td>2.72 (0.67)</td>
<td>+0.14 (0.69)</td>
<td>0.37</td>
</tr>
<tr>
<td>Range</td>
<td>1.34; 3.40</td>
<td>1.14; 4.20</td>
<td>-2; +1.24</td>
<td></td>
</tr>
</tbody>
</table>

Data are the mean (±SD). D, diopter (spherical equivalent). Bold items, P < 0.05.

* Fixed combinations counted as 2 eye drops.

A median of four visual fields was obtained in both the pre- and postinterventional periods, each of which lasted about 2 years (the peri-interventional period lasted 12.5 ± 0.9 months).

Although three quarters of the patients underwent surgery due to visual field deterioration (in isolation or associated with an increased IOP; Table 2), only negligible changes in MD and corrected pattern standard deviation (CPSD) occurred throughout the study (0.1 dB). The mean change of 0.3 dB in SF (from 3.0 to 2.7 dB) was also not statistically significant.

However, there was a reduction in test-retest variability in 76% of the eyes: the preoperative values of 2.90 ± 0.97 dB declined to 2.53 ± 0.86 dB after surgery, with a difference of 0.37 dB (P = 0.0006). Similar results were obtained when only the first three tests for each period were considered (2.68 ± 1.09 dB vs. 2.33 ± 0.95 dB, P = 0.0025) and when hypervariable locations were excluded from the analyses of both periods (2.69 ± 1.10 dB vs. 2.52 ± 0.98 dB, P = 0.0022). A hypervariable location was arbitrarily defined as having a difference in mean sensitivity between the pre- and postinterventional periods exceeding the 95th upper or lower percentiles, that corresponded to more than ±7 dB.

The medical group also showed a significant decrease in IOP, which changed from 19.0 ± 2.7 mm Hg at the beginning of the study to 15.0 ± 2.6 mm Hg in the second period (P < 0.0001). A similar decrease was also observed in MD (P = 0.0007) and CPSD (P = 0.0001). The percentage of eyes with worsening in MD and CPSD was 10% in the preoperative period and 4% in the postoperative period (P = 0.0001).

### Table 5. Main Results in the Control Group

<table>
<thead>
<tr>
<th></th>
<th>Preinterventional Period</th>
<th>Postinterventional Period</th>
<th>Difference</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Follow-up (months)</td>
<td>24.0 (15.3)</td>
<td>22.9 (14.5)</td>
<td>-1.1 (14.8)</td>
<td>0.33</td>
</tr>
<tr>
<td>Range</td>
<td>6; 42</td>
<td>6; 42</td>
<td></td>
<td></td>
</tr>
<tr>
<td>BCVA (Snellen)</td>
<td>20/22 (20/130)</td>
<td>20/23 (20/87)</td>
<td>-20/1000 (20/150)</td>
<td>0.43</td>
</tr>
<tr>
<td>Range</td>
<td>20/28; 20/20</td>
<td>20/30; 20/20</td>
<td>-20/500; 0</td>
<td></td>
</tr>
<tr>
<td>Refraction (D)</td>
<td>-0.23 (2.05)</td>
<td>-0.41 (1.92)</td>
<td>-0.18 (1.22)</td>
<td>0.26</td>
</tr>
<tr>
<td>Range</td>
<td>-3.75; +3.25</td>
<td>-3.75; +2.75</td>
<td>-0.75; +0.50</td>
<td></td>
</tr>
<tr>
<td>IOP (mm Hg)</td>
<td>17.2 (3.5)</td>
<td>18.3 (4.0)</td>
<td>+1.1 (1.7)</td>
<td>0.44</td>
</tr>
<tr>
<td>Range</td>
<td>10.6; 23.0</td>
<td>12.8; 24.5</td>
<td>-1.8; +2.6</td>
<td></td>
</tr>
<tr>
<td>IOP fluctuations (mm Hg)</td>
<td>5.5 (3.1)</td>
<td>6.4 (4.7)</td>
<td>+0.9 (4.0)</td>
<td>0.40</td>
</tr>
<tr>
<td>Range</td>
<td>0; 10</td>
<td>0; 13</td>
<td>-5; +11</td>
<td></td>
</tr>
<tr>
<td>Number of eye drops*</td>
<td>1.6 (1.1)</td>
<td>2.0 (1.2)</td>
<td>+0.4 (0.8)</td>
<td>0.14</td>
</tr>
<tr>
<td>Range</td>
<td>0.3</td>
<td>0.4</td>
<td>-1; +2</td>
<td></td>
</tr>
<tr>
<td>Number of visual field tests</td>
<td>4.0 (2.4)</td>
<td>3.7 (1.6)</td>
<td>-0.3 (2.2)</td>
<td>0.44</td>
</tr>
<tr>
<td>Range</td>
<td>3; 12</td>
<td>3; 7</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean defect (dB)</td>
<td>-7.3 (9.5)</td>
<td>-6.5 (9.6)</td>
<td>+0.8 (1.1)</td>
<td>0.03</td>
</tr>
<tr>
<td>Range</td>
<td>+1.84; -28.97</td>
<td>+1.79; -28.55</td>
<td>-1.67; +1.91</td>
<td></td>
</tr>
<tr>
<td>CPSD (dB)</td>
<td>4.1 (3.8)</td>
<td>3.8 (3.5)</td>
<td>-0.3 (1.1)</td>
<td>0.60</td>
</tr>
<tr>
<td>Range</td>
<td>0.75; 12.44</td>
<td>1.02; 11.71</td>
<td>-2.43; +1.60</td>
<td></td>
</tr>
<tr>
<td>Short-term fluctuation (dB)</td>
<td>1.9 (1.11)</td>
<td>2.4 (1.7)</td>
<td>+0.5 (1.3)</td>
<td>0.19</td>
</tr>
<tr>
<td>Range</td>
<td>0.87; 4.50</td>
<td>0.92; 6.39</td>
<td>-2.09; +2.70</td>
<td></td>
</tr>
<tr>
<td>Test-retest variability (dB)</td>
<td>2.04 (0.76)</td>
<td>2.06 (0.85)</td>
<td>+0.02 (0.54)</td>
<td>0.91</td>
</tr>
<tr>
<td>Range</td>
<td>0.35; 3.14</td>
<td>0.65; 4.25</td>
<td>-1.10; +1.11</td>
<td></td>
</tr>
</tbody>
</table>

Data are the mean (±SD). D, diopter (spherical equivalent). Bold items, P < 0.05.

* Fixed combinations counted as 2 eye drops.
The change was comparable to that observed in the surgical group ($P = 0.11$), with the mean decrease of $21\%\pm 10\%$ being achieved by increasing the number of eye drops from $2.0 \pm 0.8$ to $3.0 \pm 0.9$ ($P < 0.0001$).

There were no changes in refraction or BCVA in this group. The follow-up was shorter than in the surgical group (nearly 1 year for both periods), and a median of three visual fields were obtained in both the pre- and postinterventional periods.

The main cause for seeking to reduce IOP was the increase in IOP observed during follow-up visits (88% of cases). Visual field deterioration was the second cause (40%), with MD deteriorating by $0.7 \pm 1.2$ ($P = 0.02$) at follow-up.

The variability indices did not significantly change during the study: SF was stable over time ($2.3 \pm 0.8$ vs. $2.3 \pm 1.1$; $P = 0.89$) and, although TRV slightly increased ($2.58 \pm 0.53$ vs. $2.72 \pm 0.67$), the difference was not statistically significant ($P = 0.37$). Forty percent of the patients showed improvements in both parameters.

The control group did not show any statistically significant changes during the study except for a reduction in MD ($-7.5 \pm 9.5$ mm Hg vs. $-6.5 \pm 9.6$ mm Hg; $P = 0.03$). IOP was $17.2 \pm 3.5$ mm Hg in the first part of the study and $18.3 \pm 4.0$ mm Hg in the second ($P = 0.44$). The variability indices remained stable, with improvements in both SF and TRV in 41% of the patients: SF was $1.9 \pm 1.1$ dB before surgery and $2.4 \pm 1.7$ dB afterward ($P = 0.19$); the corresponding figures for TRV were $2.04 \pm 0.76$ and $2.06 \pm 0.83$ dB, respectively ($P = 0.65$).

Individual preinterventional SF was higher in the surgical group than in the medical patients ($P = 0.04$) and control subjects ($P = 0.01$). Postinterventional SF and differences in SF were similar in all groups.

### Table 6. Parameters Significantly Correlating with TRV and Its Changes after Surgery

<table>
<thead>
<tr>
<th>Predictor</th>
<th>$P$</th>
<th>$R^2$</th>
<th>Regression Formula</th>
</tr>
</thead>
<tbody>
<tr>
<td>Predictors for Preinterventional TRV</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>0.05</td>
<td>0.16</td>
<td>$y = 0.0341x + 0.6095$</td>
</tr>
<tr>
<td>Preoperative MD</td>
<td>N.A.</td>
<td>0.69</td>
<td>$y = -0.0145x^2 + 0.3794x + 1.3483$</td>
</tr>
<tr>
<td>Preoperative CPSD</td>
<td>0.02</td>
<td>0.20</td>
<td>$y = 0.1206x + 2.0603$</td>
</tr>
<tr>
<td>Preoperative SF</td>
<td>0.05</td>
<td>0.22</td>
<td>$y = 0.4459x + 1.7632$</td>
</tr>
<tr>
<td>Predictors for Changes in TRV</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Preoperative TRV</td>
<td>0.02</td>
<td>0.21</td>
<td>$y = 0.2202x - 0.2719$</td>
</tr>
<tr>
<td>Preoperative SF</td>
<td>0.02</td>
<td>0.27</td>
<td>$y = 0.246x - 0.3807$</td>
</tr>
<tr>
<td>Change in IOP (MD worse than $-15$ dB)</td>
<td>0.05</td>
<td>0.36</td>
<td>$y = 0.0799x + 0.3137$</td>
</tr>
</tbody>
</table>

FIGURE 1. Frequency distribution of TRV in the three study groups. (■) Surgical group, (□) control group, and (△) medical group.

FIGURE 2. Regression analysis comparing preinterventional mean defect and variability. (●) TRV ($R^2 = 0.5522$; $y = -0.0103x^2 + 0.2702x + 1.5788$); (△) SF ($P < 0.0001$; $R^2 = 0.4109$; $y = -0.0808x + 1.6173$).

Individual preinterventional TRV was similar for surgical and medical patients ($P = 0.16$), whereas it was significantly lower in control eyes ($P < 0.01$). The distribution of the individual changes in TRV in the three groups is shown in Figure 1. The individual improvements in TRV were higher in the surgical group than in the medical ($P = 0.004$) or control ($P = 0.015$) groups, with no difference between the medical and control ($P = 0.55$) groups.

The preinterventional variability indices were very heterogeneous in all three groups but, as shown in Figure 2, they correlated well with preinterventional MD. A second-degree model of regression demonstrated a good correlation ($R^2 = 0.55$) between TRV and preinterventional MD, with TRV progressively increasing for MD between 0 and $-13$ dB and decreasing for MD worse than $-13$ dB (in the surgical group, a plateau was reached at $-15$ dB). MD was also a positive predictor of SF ($P < 0.0001$; $R^2 = 0.41$).

To explain the reduction in TRV in the surgical group, we inspected all the possible combinations between the variability indices and the demographic, perimetric, and clinical variables by means of regression analysis. The significant results are shown in Table 6. Age and preoperative MD, CPSD, and SF were positive predictors of preoperative TRV. The change in TRV was predicted by preoperative TRV and SF. The change in IOP was a positive predictor only in the case of the subgroup of patients with an MD worse than $-15$ dB. None of the other parameters correlated with TRV or its changes. In particular, we evaluated the possible role of topical β-blockers and α-agonists as a source of the increase in perimetric variability because of the well-known possibility that they may induce sys-
ter.10 –15
did not evaluate the effects of IOP reduction on this parame-
which were not significantly different in both interventional
surgery, TRV was similar in the patients using and not using
adrenergic agents (\( P = 0.15 \)). Similarly, the number of eye
drops used after trabeculectomy did not affect the amount of
the change in TRV (\( P = 0.33 \)).

**DISCUSSION**

In this study, we compared the changes in short- and long-term
perimetric variability occurring in patients with glaucoma after
both medical and surgical IOP reduction. The two groups were
highly comparable thanks to the close matching of subjects,
and only slight differences in perimetric variability were found
over the observation period, apart from a decrease in TRV
occurring after surgery. This reduction, though statistically
significant, was relatively small (0.37 dB), but it was a common
finding (76% of patients), and it represented a mean decrease
of 13% with respect to preoperative TRV.

Our results are difficult to compare to those in other studies
as, to our knowledge, only partially pertinent data are available.
In the CIGTS, TRV was expressed as the pooled SD estimates of
individual MD. At baseline, a global value of 1.4 was found, but
data comparing surgical and medical patients were not report-
ed.17 Other studies calculating TRV in patients with glaucoma
did not evaluate the effects of IOP reduction on this paramet-
ter.10 –15

In our dataset, a direct relationship between the improve-
ment in TRV and the amount of the decrease in IOP after
trabeculectomy was observed only in cases with an MD worse
than 15 dB (\( n = 12/25 \)).

Apart from the decrease in IOP, other factors may explain
the behavior of TRV in the surgical group. The smaller fluctu-
ations in IOP that seem to occur after trabeculectomy18 may
have favorably affected TRV, thus justifying the differences
among the surgical, medical, and control groups. Unlike Kon-
stas et al.,18 our retrospective data did not include 24-hour IOP
fluctuations, as only periodical diurnal curves were drawn,
which were not significantly different in both interventional
groups. It is worth noting that 24-hour fluctuations in IOP,
which influence the perimetric progression of POAG,19,20
could also induce changes in a perimetric parameter such as
TRV, although this hypothesis is up to now only speculative.

Another factor explaining the reduced TRV in the surgical
group may be the decrease in medical treatment after trabec-
ulectomy. As a consequence, surgical group patients were likely
to experience not only fewer systemic and local side effects,
but also smaller IOP fluctuations due to the peak-trough effects
of medications and better compliance with a simpler therapeu-
tic regimen; however, TRV did not significantly change in the
subgroup of approximately 45% of patients who discontinued
\( \beta \)-blockers and \( \alpha \)-agonists after surgery. In contrast, local con-
ditions after trabeculectomy (discomfort, conjunctival bleb)
may interfere with the patients’ perimetry performance.

A decrease in TRV due to familiarity with the test may be an
important confounding factor, but this was not the case in the
control group of non-surgically treated fellow eyes, in which
TRV remained stable throughout the study period.

Worsening MD during the peri-interventional period may
reduce TRV, as patients in the perimetric end stage of the
disease encounter a “floor effect” accompanied by a reduction
in TRV, a fact that has been reported17 and that is confirmed by
our data (Fig. 2). However, only small differences in MD be-
tween the pre- and postoperative periods were observed in the
surgical group (a mean of −0.1 dB, ranging from −1.67 to
+1.91 dB).

TRV may also be influenced by a difference in the number of
locations with above-normal variances or the different num-
ber of tests in the pre- and postinterventional periods. How-
ever, the results did not change when hypervarying locations
in the pre- and postinterventional periods were excluded from
the analysis or when only the first three examinations in each
period were analyzed.

The conclusions of this study may be limited in some way
by the heterogeneity of the cases in terms of the duration of the
study periods, disease severity, treatment efficacy, and variabil-
ity indices. As in all retrospective studies, a selection bias could
occur and weaken the comparisons between the surgical and
medical treatment groups: despite the close matching between
interventional groups, patients undergoing trabeculectomy had a
higher rate of perimetric progression (76% vs. 40%; Table
2), a fact that could give more opportunity for improvement
than in other groups and a regression to the mean. However,
the rigorous confirmation of perimetric stability in both peri-
ods (progressive fields were not included in the analyses as a
part of the peri-interventional period, see the Definition sec-
tion) and the similar preinterventional TRV in both interven-
tional groups should, at least potentially, have limited the regres-
sion to the mean.

The positive effects of trabeculectomy have been shown in
terms of optic nerve head damage,21 stability of spatial contrast
sensitivity,22 and reduced progression at standard automated
perimetry testing.23,24 but this is the first study to suggest that
it could also reduce visual field variability over time in com-
parison with a group of patients in whom a similar IOP reduc-
tion was obtained by means of medical treatment. Further
studies are needed to determine whether this decrease in TRV
after glaucoma surgery may enable earlier detection of subtle
perimetric changes in this group of patients.

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