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Reversible structural and functional changes after intraocular pressure reduction in patients with glaucoma

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Abstract
Purpose The aim of this study was to evaluate structural and functional improvement following intraocular pressure (IOP) reduction in patients with glaucoma using Spectral Domain Optical Coherence Tomography (SD-OCT), Visual Field (VF) testing, and Visual Evoked Potentials (VEP).
Methods A total of 76 eyes from 61 patients underwent SD-OCT, VF and VEP testing. Sixty-two eyes were put in either an acutely high (group 1, IOP > 32 mmHg) or mildly high (group 2, IOP between 22 and 31 mmHg) IOP group and underwent a pressure-lowering intervention. Fourteen eyes with stable glaucoma were controls (group 3, IOP < 22 mmHg). SD-OCT, VF and VEP testing were subsequently performed on all patients at three follow-up visits. Results from these follow-up periods were analyzed for signs of functional and structural improvement.
Results Both group 1 and group 2 patients demonstrated significant decrease in the average cup to disc ratio ($p < 0.05$) following the intervention. Post-interventional reduction of cup volume was also significant for group 2 patients ($p < 0.05$). RNFL thickness changes were insignificant. Qualitative grading of VFs by two observers showed improvement in group 1 patients' VFs ($p = 0.021$). VEP measurements were mostly insignificant, with the exception of High Contrast Latency (LHC) deteriorating for group 2 patients in the first follow-up visit ($p = 0.025$).
Conclusions This study provides evidence for structural disc cupping reversal following IOP lowering interventions. These changes were not related to the amount of pressure lowering. While there was evidence of functional improvement as measured by VF testing, VEP was unable to detect any reversible changes.

Keywords Glaucoma reversibility · Optical coherence tomography · Visual fields · Visual evoked potentials

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Introduction

Glaucoma is a progressive optic neuropathy characterized by the degeneration of retinal ganglion cells (RGCs) and their axons. An increase in intraocular pressure (IOP) often leads to structural changes in the retinal nerve fiber layer (RNFL), optic nerve head, and results in subsequent visual field (VF) deficits. Although the exact mechanism for RGC loss in glaucoma is unknown, it has been suggested that RGCs may become reversibly dysfunctional before dying, challenging the convention that glaucomatous damage to visual function is irreversible [1–4].

Structural reversibility after glaucoma treatment is well documented. Reversible optic disc cupping following acute IOP lowering has been known to occur for decades. In 1982, Quigley et al. described an improvement in the appearance of the optic disc cup in 40 % of children with successful IOP lowering after trabeculotomy surgery [5–9]. More recently, others have identified subtle structural reversibility in the adult population—first by using stereoscopic disc imaging, and later by applying more sophisticated imaging modalities such as the Heidelberg Retina Tomograph (HRT) and Spectral-Domain Optical Coherence Tomography (SD-OCT) [6–11]. One of the suggested explanations for this phenomenon is the

anterior repositioning of a posteriorly displaced lamina cribrosa, resulting from changes in the translaminar pressure gradient [12, 13].

However, studies have reported conflicting findings regarding the concomitance of functional and structural reversal secondary to IOP lowering. Katz et al. previously showed VF improvement in nearly one-third of adult patients treated for glaucoma after 6 months [8]. Similarly, the Collaborative Initial Glaucoma Treatment Study (CIGTS) found lower IOP to be predictive of improvement in VF mean deviation (MD) [14]. Other functional parameters, such as contrast sensitivity and retinal function measured by multifocal electroretinography (ERG), have also been found to improve after IOP lowering surgical interventions in similar studies [4, 15, 16]. However, Tavares et al. did not find improvement in VF testing and Frequency Doubling Technology (FDT) perimetry 4.5 months after performing trabeculectomy [17]. Similarly, Sehi et al. did not find any improvement in RGC function measured using ERG following IOP pressure reversal using latanoprost 0.005 % [18]. This discrepancy could perhaps be due to the variability in the methods and techniques used to measure visual function. Nonetheless, such contradictory evidence calls for further investigation of functional reversibility in glaucoma patients in order to understand the true underlying phenomena.

Visual evoked potentials (VEP) testing has been shown to detect visual dysfunction in glaucoma patients [19]. It provides a more objective means of testing glaucoma patients for visual functionality in comparison to the more subjective standard achromatic automated perimetry (SAP) method [19, 20]. Transient VEP was able to detect functional reversibility in glaucoma patients following medication with citicoline and nicergoline [21, 22]. The traditional VEP apparatuses are currently situated mostly in tertiary care centers since they lack portability and are expensive, making them suboptimal for clinical use in office setting. The Diopsys NOVA VEP-LX vision testing system (Diopsys, Inc., Pine Brook, NJ) is a novel transient VEP testing platform designed for use in the office [19]. The aim of this study was to investigate the presence of structural and corresponding functional reversibility in glaucoma patients following IOP reduction using transient VEP combined with SD-OCT and automated perimetry. To the best of our knowledge, this is the first study using the new Diopsys NOVA-LX VEP vision testing system to investigate reversible functional changes in patients with glaucoma.

Materials and methods

The study procedures were approved by the Institutional Review Board of Wills Eye Hospital and conducted according to the tenets of the Declaration of Helsinki and Health Insurance Portability and Accountability Act. Written informed consent was obtained from all patients.

Subjects

For this prospective cohort study, 61 patients were recruited from the Wills Eye Hospital Glaucoma Service. Patients with any form of glaucoma, including primary open-angle glaucoma (POAG), pesudoexfoliation glaucoma, low-tension glaucoma (LTG) and chronic angle-closure glaucoma, were eligible for inclusion. Glaucomatous eyes were defined to have glaucomatous optic nerve damage and repeatable VF abnormality based on glaucoma hemifield test results outside normal limits and pattern standard deviation and mean deviation outside 95 % normal limits.

Exclusion criteria included inability to obtain reliable VF or SD-OCT at baseline; VA less than 20/40; age < 18 or > 90 years; and any cause for VF loss other than glaucoma, including visually significant cataract, optic neuropathy, retinal disease, or spherical equivalent refractive error > +/− 5.00 D Sphere or > +/− 3.00 D cylinder.

The subjects were divided into three groups based on IOP. Group 1 consisted of patients with IOP > 32 mmHg, group 2 consisted of patients with IOP between 22 and 31 mmHg and group 3 (control group) consisted of patients who had IOP < 22 mmHg. Data collected included patient demographics, clinical findings, and diagnostic testing results.

Examinations

All three groups underwent baseline examinations (IOP, SD-OCT, VF, VEP). IOP was measured using Goldmann applanation tonometry. SD-OCT testing was performed on a Cirrus-HD OCT [Carl Zeiss Meditec, Dublin, CA, USA]. Furthermore, VFs were assessed using the Humphrey 24-2 Swedish Interactive Threshold Algorithm (SITA) Standard perimeter (Zeiss Meditec, Dublin, CA). VF examinations were repeated and the average of two visual field examinations was used as a baseline field.

For VEP examinations, we used the Diopsys NOVA-LX System to generate VEPs. We followed the VEP protocol previously reported by Prata et al., which differentiates P-cell and M-cell responses [19]. Three color-coded electrodes were used: the black electrode was placed on the patient's forehead near the hairline, the red electrode was placed on the inion and the green electrode was placed on the preaurical point after applying skin prep gel and conductive paste to each respective area. The display was viewed from a viewing distance of 1 m and the stimulus was presented on a 17-inch LCD monitor.

The display was viewed monocularly, using an eye patch through natural pupils with optimal refractive correction in place. Both eyes were tested both at low and high contrasts,

corresponding to a Michelson contrast of 15 and 85 % respectively. Each test displayed a 32 × 32 black/white checkerboard stimulus pattern with a check size of about 58.17 min of arc (equivalent to approximately 1°) and a red circular ring of diameter 1 cm in the middle, which served as the fixation target for patients. Both high and low contrast checkerboards were presented to patients for 20 s, during which measurements for high contrast amplitude (AHC), low contrast amplitude (ALC), high contrast latency (LHC) and low contrast latency were recorded (LLC). The collected data was then processed and displayed in a graphic plot (Fig. 1).

Intervention and follow-up

After performing baseline measurements, groups 1 and 2 received a pressure-lowering intervention: medication, laser, surgery, paracentesis, pulled Latina suture or a combination thereof. Patients in group 3 were used as a control, and did not receive any intervention.

All groups had three follow-up visits following their baseline examinations, during which IOP, VF, SD-OCT, and VEP measurements were repeated. Group 1 patients had their follow-up examinations 1 hour, 1 day and 3 months (±2 months window period) following the acute pressure lowering intervention. Group 2 patients had follow-up visits 2 months (±1 months window period), 6 months (±2 months window period), and 12 months (±4 months window period) after IOP reducing interventions. Group 3 controls had follow-up visits 2 months (±1 months window period), 6 months (±2 months window period) and 12 months (±4 months window period) after baseline measurements.

Statistical analysis

Continuous variables were summarized using medians and ranges, and categorical variables were summarized with counts and percentages. A student's *t*-test was used to evaluate the preoperative and postoperative VF MD and optic nerve head RNFL thickness. Changes in outcomes over time were analyzed using mixed effects linear regression with a fixed effect evaluation time. A first-order autoregressive covariance structure was assumed to account for correlation among repeated measurements from the same subject. A random intercept term was included to account for correlation among eyes from the same subject. Low IOP, High IOP, and stable subjects were analyzed separately. *p* values were not adjusted for multiple comparisons. Furthermore, two masked experienced observers reviewed VF and VEP printouts and determined whether patients' outcome deteriorated, improved or stayed the same between follow-ups. Qualitative measurements were analyzed by combining ratings from the two observers. If there were discrepancies between the ratings and one observer rated no change, the overall rating for that patient was based on rating from the other observer. If one observer noted improvement and the other reported deterioration, the field was assumed to have not changed. Odds ratio analysis was used to evaluate the predictions made by the observers. The time discrepancies amongst groups were adjusted for comparison using a logistic regression that accounted for timing of the visits. All analyses were performed using SAS version 9.3 (SAS Institute, Cary, NC).

Results

Sixty-one study subjects (38 males and 23 females) were enrolled in the study and divided into the three study groups, comprising a total of 76 eyes (Table 1). Both group 1 and group 2 patients experienced significant and sustained post-interventional IOP reduction, whereas group 3 patients had no significant deviation from initial IOP (Table 2). Group 1 patients experienced a mean IOP reduction from 44.9 to 21.3 mmHg ($p < 0.001$) between baseline and visit 1. During the same period, group 2 patients had their IOP lowered from 26.9 to 15.6 mmHg ($p < 0.001$), whereas group 3 control patients' mean IOP varied insignificantly from 14.2 to 13.8 mmHg ($p = 0.72$).

Significant post-interventional structural improvements were most apparent amongst group 2 patients, though some structural reversibility was also evident amongst group 1 patients (Table 3). For group 2 patients, the average cup-to-disc ratio decreased from 0.71 to 0.69 ($p = 0.0012$), 0.68 ($p = 0.0002$) and 0.68 ($p = 0.017$) during follow-up visits 1, 2, and 3, respectively. By contrast, for group 1 patients, the cup-to-disc ratio only decreased significantly at follow-up visit 2 from a baseline measurement of 0.76 to 0.72 ($p = 0.043$). No significant change was observed amongst group 3 controls. The cup volume for group 2 patients decreased significantly from a baseline measurement of 0.46 to 0.41 ($p = 0.001$) and 0.39 ($p = 0.006$) during follow-up visits 1 and 2, respectively. No significant change in cup volume was observed amongst group 3 control patients. Changes in average RNFL thickness were insignificant for all three groups for each follow-up period.

Unlike structural improvement, evidence for functional reversibility post-intervention was much more scarce (Table 4). There was no evidence of significant change in VF MD or PSD during the 3 periods in any of the three groups. Similarly, VEP measurements did not indicate functional improvements post-intervention. The only VEP parameter that changed significantly was the LHC for group 2, which deteriorated during follow-up visit 1 (from 117.0 ms at baseline to 125.7 ms, $p = 0.025$).

Qualitative analysis by the two masked observers mostly mirrored these observations as well. VEP readings did not demonstrate any significance for groups 1 or 2 (OR = 0.94,

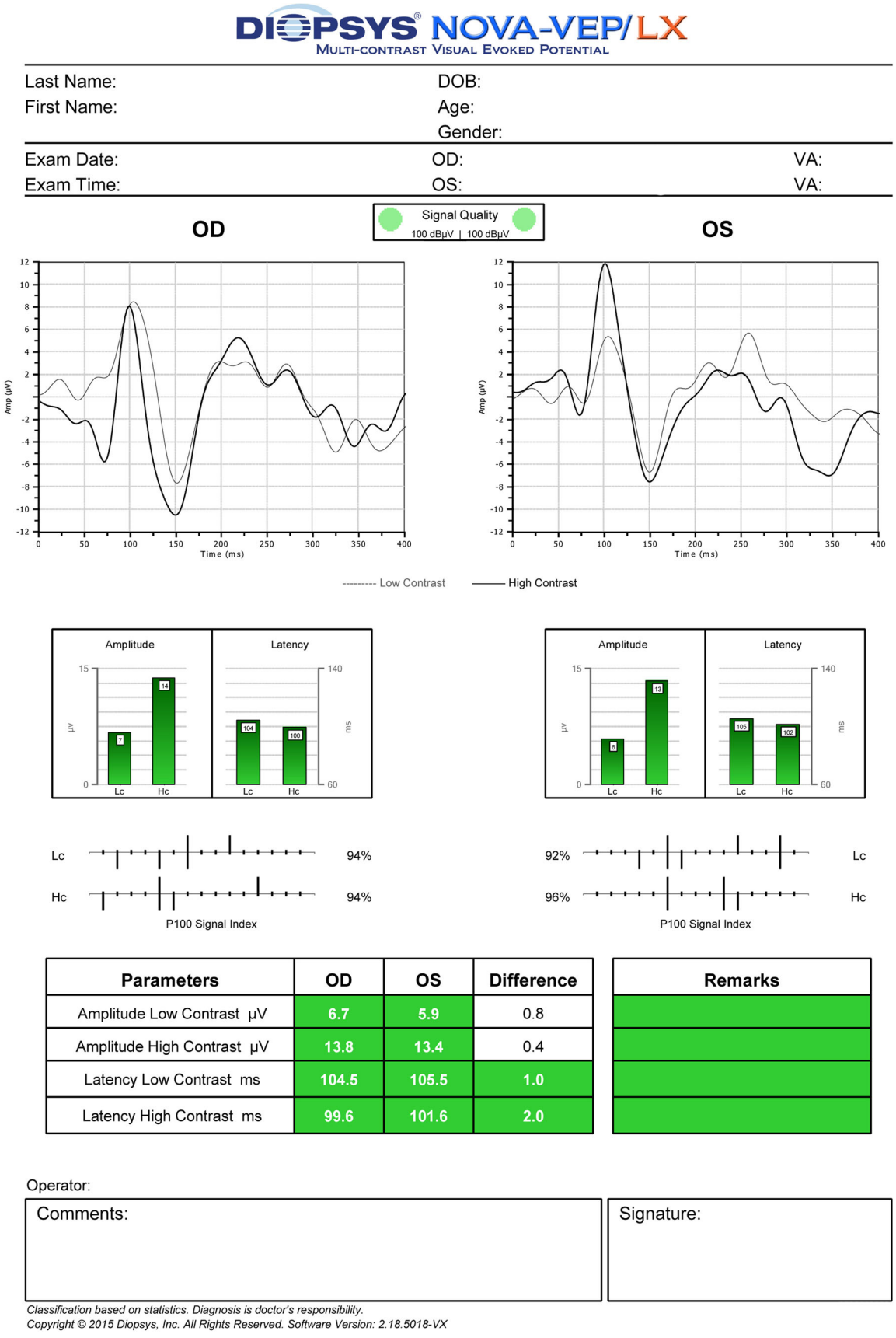

Fig. 1 Short-Duration transient Visual Evoked Potential printout, which shows the P100 response waveform in addition to quantitative test parameters

Table 1 Demographic characteristics of patients enrolled in the study

		Group 1 (IOP > 32 mmHg)	Group 2 (IOP 22–32 mmHg)	Group 3 (IOP < 22 mmHg)
Number of Subjects (Eyes)		*n* = 6 (8 eyes)	*n* = 44 (54 eyes)	*n* = 11 (14 eyes)
Median Age [years; (Range)]		65.5 (55–75)	65.5 (27–84)	60 (45–79)
Sex	Male	5 (83 %)	25 (57 %)	8 (73 %)
	Female	1 (17 %)	19 (43 %)	3 (27 %)
Race	Caucasian	3 (50 %)	23 (52 %)	8 (73 %)
	African American	3 (50 %)	16 (36 %)	2 (18 %)
	Hispanic	0 (0 %)	3 (7 %)	1 (9 %)
	Asian	0 (0 %)	2 (5 %)	0 (0 %)

IOP Intraocular Pressure, *mmHg* millimeters of mercury

95%CI 0.25–3.55; $p = 0.93$). However, by combining all three visits and using a repeated measures ordinal logistic regression to model the data, and time adjusting the odds ratios to account for timing differences amongst the groups, group 1 patients had a significant odds ratio of 4.39 (95 % CI 1.25, 15.40; $p = 0.021$) of having an improved VF versus group 3 controls, whereas group 2 patients had a similar odds ratio approaching significance at 2.79 (95 % CI 0.83, 9.32; $p = 0.096$). The two observers had a 31.2 % which corresponded to a kappa of 0.52 with 95 % CI = 0.39, 0.64.

Discussion

While there is a consensus that reversal of disc cupping occurs following glaucoma surgery, it is still unclear if functional improvements occur at the same time. In this study, we evaluated the relationship between structural and functional reversibility following IOP-lowering interventions using SD-OCT, perimetry and VEP, and found little evidence of functional reversibility following structural changes amongst patients with moderate to late stage glaucoma. Despite segmenting our study population into a major and mild IOP group, and using two independent visual function outcomes, significant improvement was evident only in qualitative analyses of VF charts by two independent observers.

We observed significant and sustained reduction of IOP amongst both treated patient groups following the intervention. Accompanying the IOP reduction, we observed several markers of significant structural changes. For example, the cup-to-disc ratio and cup volumes for patients in both group 1 (with baseline IOP >32 mmHg) and 2 (with baseline IOP 22–32 mmHg) showed significant structural improvement following intervention. This is similar to the structural reversal following IOP reduction reported by Parrish and Mochizuki, who have observed improvements in optic nerve cupping following IOP-lowering interventions [10, 11]. We further found that structural improvements were not related to the amount of pressure lowering: both low and high pressure groups demonstrated significant structural changes post-intervention. Although structural changes were statistically significant before and after IOP-lowering intervention, the mean differences

Table 2 Average intraocular pressures of each patient group at baseline prior to the pressure lowering intervention and in the three subsequent follow-up periods

Visit	Group 1[a] (IOP > 32 mmHg)	Group 2[b] (IOP 22–32 mmHg)	Group 3[c] (IOP < 22 mmHg)
Baseline – Mean IOP, mmHg (95 % CI)	44.9 (39.3, 50.6)	26.9 (25.8, 27.9)	14.2 (9.6, 18.8)
Visit 1 – Mean IOP, mmHg (95 % CI) [*p* value][d]	21.3 (15.5, 27.2) [< 0.001]	15.6 (14.4, 16.8) [< 0.001]	13.8 (9.2, 18.5) [0.72]
Visit 2 – Mean IOP, mmHg (95 % CI) [*p* value][d]	19.7 (14.0, 25.4) [< 0.001]	15.6 (14.3, 17.0) [< 0.001]	13.4 (8.8, 18.1) [0.46]
Visit 3 – Mean IOP, mmHg (95 % CI) [*p* value][d]	19.2 (12.2, 26.3) [< 0.001]	16.9 (15.2, 18.6) [< 0.001]	14.9 (10.3, 19.6) [0.48]

IOP Intraocular Pressure, *CI* Confidence Interval, *mmHg* millimeters of mercury

[a] Visit numbers correspond to: 1 hour, 1 day and 3 months (±2 months window period) post intervention

[b] Visit numbers correspond to: 2 months (±1 months window period), 6 months (±2 months window period), and 12 months (±4 months window period) post intervention

[c] Visit numbers correspond to: 2 months (±1 month window period), 6 months (±2 months window period) and 12 months (±4 months window period) after baseline visit

[d] *p* value when compared to pre-intervention visit

Table 3 Mean Spectral-Domain Optical Coherence Tomography measurements of structural parameters at baseline and after pressure lowering interventions

Measurement	Visit*	Group 1 (IOP > 32 mmHg)[a]	Group 2 (IOP 22–32 mmHg)[b]	Group 3 (IOP < 22 mmHg)[c]
Disc Area (mm^2), Mean, (95 % CI)[*p* value][d]	Baseline	1.63 (1.42, 1.84)	1.93 (1.78, 2.07)	1.79 (0.68, 2.90)
	1	1.64 (1.43, 1.85) [0.78]	1.90 (1.76, 2.04) [0.18]	1.78 (0.67, 2.89) [0.95]
	2	1.67 (1.46, 1.88) [0.11]	1.88 (1.73, 2.02) [0.034]	1.76 (0.71, 2.81) [0.77]
	3	1.63 (1.42, 1.84) [0.98]	1.85 (1.71, 2.00) [0.014]	1.76 (0.71, 2.82) [0.79]
Average Cup-to-Disc Ratio, Mean, (95 % CI) [*p* value][d]	Baseline	0.76 (0.64, 0.88)	0.71 (0.66, 0.76)	0.76 (0.65, 0.88)
	1	0.74 (0.62, 0.85) [0.14]	0.69 (0.64, 0.74) [0.001]	0.77 (0.66, 0.89) [0.74]
	2	0.72 (0.61, 0.84) [0.043]	0.68 (0.62, 0.73) [<0.001]	0.75 (0.62, 0.88) [0.75]
	3	0.72 (0.60, 0.84) [0.11]	0.68 (0.63, 0.74) [0.017]	0.77 (0.64, 0.89) [0.93]
Cup Volume (mm^3), Mean, (95 % CI)[*p* value][d]	Baseline	0.46 (0.28, 0.65)	0.46 (0.35, 0.56)	0.36 (0.01, 0.70)
	1	0.44 (0.25, 0.62) [0.37]	0.41 (0.31, 0.51) [0.010]	0.37 (0.02, 0.71) [0.49]
	2	0.43 (0.25, 0.62) [0.14]	0.39 (0.28, 0.49) [0.006]	0.34 (−0.01, 0.69) [0.42]
	3	0.41 (0.23, 0.60) [0.065]	0.39 (0.28, 0.51) [0.053]	0.36 (0.02, 0.71) [0.90]
Average RNFL Thickness (μm), Mean, (95 % CI) [*p* value][d]	Baseline	74.3 (67.4, 81.2)	75.5 (70.0, 81.1)	70.4 (55.9, 84.9)
	1	76.0 (68.9, 83) [0.26]	74.9 (69.3, 80.5) [0.57]	69.4 (54.9, 83.9) [0.18]
	2	75.2 (68.3, 82.2) [0.57]	73.8 (68.0, 79.6) [0.27]	68.9 (54.5, 83.3) [0.20]
	3	74.1 (67.0, 81.2) [0.94]	74.7 (68.4, 80.9) [0.68]	67.4 (53.0, 81.8) [0.073]

RNFL Retinal Nerve Fiber Layer, *IOP* Intraocular Pressure, *CI* Confidence Interval, *mmHg* millimeters of mercury

[a] Visit numbers correspond to: 1 hour, 1 day and 3 months [±2 months window period) post intervention

[b] Visit numbers correspond to: 2 months (±1 months window period), 6 months (±2 months window period), and 12 months (±4 months window period) post intervention

[c] Visit numbers correspond to: 2 months (±1 month window period), 6 months (±2 months window period) and 12 months (±4 months window period) after baseline visit

[d] *p* value when compared to baseline visit

were relatively small, and therefore may not be detected by clinical examination of the optic nerve head.

These observations are also similar to what was observed by Tavares et al., who observed no relationship between glaucoma filtration surgery and visual outcome tests [17]. Though Tavares et al. used SAP and frequency doubling technology perimetry, there was no improvement in any functional parameters following pressure reduction surgery. Though the patients in the Tavares study had a much lower baseline IOP of 20.7 mmHg, we found similar observations among patients with higher baseline IOP. In addition to not seeing a change in VEP parameters, there was no significant improvement in VF MD and PSD parameters. This contrasts what was found by Wright et al. and Katz et al., who observed a significant improvement in VFs following IOP reduction [8, 23]. However, though the MD and PSD parameters failed to show significant improvement in our study, grading the VFs qualitatively using a method similar to that used by Katz et al. did reveal significant and a trend toward significant functional improvement amongst group 1 and group 2 patients, respectively. This suggests that functional reversibility amongst our patients did occur, though improvement is subtle and difficult to detect using quantitative parameters individually. An overall assessment using multiple parameters together may be necessary to detect changes.

Our study has several limitations. Firstly, the relatively small sample size of group 1 and group 3 patients made it difficult to establish significance in our statistical tests. Moreover, we grouped our patients by their baseline IOP rather than the type of IOP-lowering intervention they received (e.g., surgery, medications, lasers), and therefore it is difficult to compare our results to other studies that investigate each type of intervention separately. Secondly, the clinical heterogeneity in the study population—specifically the multiple types of glaucoma patients—makes it tough to generalize results to a specific type of glaucoma, especially due to small sample sizes. Thirdly, the short follow-up time of 3 months for group 1 patients precluded the possibility of assessing longer term VF improvement in patients with acute IOP lowering interventions. Moreover, the follow-up times amongst the three groups were different, which made group-to-group comparisons difficult. Fourthly, our study included a subset of patients who mostly had moderate to advanced glaucoma. Therefore, it does not preclude the possibility of reversible VEP changes in earlier stages of the disease, as observed by Ventura et al.

Table 4 Mean functional parameters measured by visual fields and visual evoked potentials at baseline and in each of the follow-up periods

Measurement	Visit	Group 1 (IOP > 32 mmHg)[a]	Group 2 (IOP 22–32 mmHg)[b]	Group 3 (IOP < 22 mmHg)[c]
Visual Field Mean Deviation (dB) Mean, (95 % CI)[*p* value][d]	Baseline	−13.3 (−20.6, −6.0)	−8.7 (−11.1, −6.4)	−13.2 (−21.1, −5.2)
	1	−14.1 (−21.3, −6.8) [0.091]	−8.3 (−10.7, −6.0) [0.13]	−8.6 (−17.0, −0.1) [0.15]
	2	−13.8 (−21.1, −6.6) [0.37]	−8.5 (−10.9, −6.1) [0.61]	−9.4 (−18.3, −0.5) [0.35]
	3	−14.8 (−22.1, −7.5) [0.066]	−9.4 (−11.8, −6.9) [0.21]	−10.4 (−19.6, −1.1) [0.54]
Visual Field Pattern Standard Deviation (dB) Mean, (95 % CI)[*p* value][d]	Baseline	6.3 (3.9, 8.8)	4.9 (3.9, 5.9)	6.8 (2.0, 11.5)
	1	4.0 (1.4, 6.7) [0.17]	5.1 (4.0, 6.1) [0.42]	5.8 (1.0, 10.5) [0.48]
	2	5.0 (2.6, 7.4) [0.43]	5.1 (4.0, 6.2) [0.41]	6.7 (2.0, 11.5) [0.97]
	3	4.1 (0.8, 7.4) [0.28]	5.0 (3.8, 6.2) [0.76]	6.4 (1.6, 11.1) [0.78]
VEP ALC (μV) Mean, (95 % CI)[*p* value][d]	Baseline	7.9 (5.1, 10.6)	9.3 (7.6, 11.0)	11.2 (2.5, 19.9)
	1	8.2 (4.8, 11.5) [0.85]	7.5 (5.5, 9.4) [0.071]	3.8 (−4.5, 12.2) [0.097]
	2	7.8 (5.0, 10.6) [0.93]	9.4 (7.1, 11.7) [0.92]	N/A[e]
	3	7.7 (4.6, 10.8) [0.90]	8.5 (3.4, 13.7) [0.77]	N/A[e]
VEP AHC (μV) Mean, (95 % CI)[*p* value][d]	Baseline	10.7 (7.0, 14.5)	12.7 (8.0, 17.4)	12.1 (3.5, 20.6)
	1	9.5 (4.8, 14.1) [0.59]	12.1 (7.3, 16.9) [0.64]	12.5 (−4.0, 29.0) [0.96]
	2	9.2 (5.4, 12.9) [0.28]	12.4 (7.4, 17.5) [0.86]	N/A[e]
	3	12.1 (7.8, 16.4) [0.47]	11.9 (4.0, 19.7) [0.81]	N/A[e]
VEP LLC (ms) Mean, (95 % CI)[*p* value][d]	Baseline	130.3 (117.7, 142.9)	120.8 (112.5, 129.0)	122.7 (108.1, 137.4)
	1	120.9 (104.4, 137.5) [0.27]	127.5 (117.6, 137.3) [0.30]	136.9 (115.9, 158.0) [0.29]
	2	132.9 (120.2, 145.5) [0.70]	122.8 (111.5, 134.0) [0.72]	N/A[e]
	3	121.6 (106.1, 137.1) [0.29]	119.5 (92.5, 146.5) [0.93]	N/A[e]
VEP LHC (ms) Mean, (95 % CI)[*p* value][d]	Baseline	126.1 (115.8, 136.3)	117.0 (111.5, 122.5)	114.1 (91.7, 136.5)
	1	110.1 (95.7, 124.5) [0.06]	125.7 (119.3, 132.2) [0.025]	139.8 (117.3, 162.2) [0.061]
	2	123.1 (112.9, 133.4) [0.66]	124.2 (116.1, 132.2) [0.11]	N/A[e]
	3	118.8 (105.3, 132.2) [0.38]	127.5 (108.6, 146.5) [0.29]	N/A[e]

VEP Short Duration Transient Visual Evoked Potential, *ALC* Amplitude at Low Contrast, *AHC* Amplitude at High Contrast, *LLC* Latency at Low Contrast, *LHC* Latency at High Contrast, *IOP* Intraocular Pressure, *CI* Confidence Interval, *mmHg* millimeters of mercury

[a] Visit numbers correspond to: 1 hour, 1 day and 3 months [±2 months window period) post intervention

[b] Visit numbers correspond to: 2 months (±1 months window period), 6 months (±2 months window period), and 12 months (±4 months window period) post intervention

[c] Visit numbers correspond to: 2 months (±1 month window period), 6 months (±2 months window period) and 12 months (±4 months window period) after baseline visit

[d] *p* value when compared against baseline visit

[e] VEP values were not calculated for visits 2 and 3 of group 3 due to missing data

[1, 4]. Fifthly, IOP was not measured at the same time of the day for all patients, thereby allowing for diurnal changes in IOP to act as a confounding factor in measurement. Sixthly, not all tests were applied in the same manner: although VF testing was repeated twice at baseline, only one VEP test was done at that visit. Repeating VEP testing twice could have improved its sensitivity. Furthermore, it is possible that patients in group 1 may have had corneal edema secondary to markedly elevated IOP, which may have cleared following the IOP-lowering intervention, and this could have acted as a confounding factor in improving visual fields. Lastly, a possible underlying trend could have been obscured since the VF we were using to measure functional reversibility is subject to significant test re-test fluctuations.

In conclusion, we demonstrated evidence of structural reversal amongst patients with moderate to late stage glaucoma following both mild and acute IOP lowering interventions using SD-OCT. However, we observed very little evidence of VF or VEP improvement following these interventions. Though looking at VF charts suggested subtle VF improvement following IOP reduction, VEP testing did not demonstrate any such improvement. Further longitudinal studies, particularly using electrophysiological studies and a larger sample size, are needed to explore the relationship between functional and structural reversibility.

Compliance with ethical standards

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Conflict of interest Dr. L. Jay Katz is a consultant for Diopsys Inc. Drs. LJ Katz and Michael Waisbourd receive research support from Diopsys Inc. Dr. Alberto Gonzalez is an employee of Diopsys, Inc. Dr. George L. Spaeth, Mr. Osama Ahmed and Mrs. Jeanne Molineaux certify that they have no affiliations with or involvement in any organization or entity with any financial interest (such as honoraria; educational grants; participation in speakers' bureaus; membership, employment, consultancies, stock ownership, or other equity interest; and expert testimony or patent-licensing arrangements), or non-financial interest (such as personal or professional relationships, affiliations, knowledge or beliefs) in the subject matter or materials discussed in this manuscript.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent Informed consent was obtained from all individual participants included in the study.

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