Illuminating Glaucoma: Linking Pupillary Light Responses to Functional and Structural Impairment in Ocular Hypertension and Primary Open-Angle Glaucoma

Iluminar o Glaucoma: Ligação entre as Respostas Pupilares e Alterações Funcionais e Estruturais na Hipertensão Ocular e no Glaucoma Primário de Ângulo Aberto

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ABSTRACT

INTRODUCTION: This study assessed the relationship between the pupillary light reflex and both functional and structural loss in patients with ocular hypertension (OHT) and primary open-angle glaucoma (POAG), using automated pupillometry, a precise method for measuring pupillary responses. By examining this relationship, the study seeks to provide insights into how changes in pupillary function correspond to glaucoma development, potentially improving diagnostic and monitoring methods.

METHODS: A cross-sectional study enrolling OHT and POAG patients across the whole spectrum of disease severity was conducted. Monocular dynamic pupillary responses were recorded using an automatic quantitative pupillometry system. The relative amplitude of pupil constriction was calculated as the percentage change in pupil diameter from onset to peak constriction. All patients underwent standard automated perimetry and optical coherence tomography within one year before pupillometry, and the relationship between pupillary responses and these parameters was analyzed.

RESULTS: The study included 136 eyes from 68 subjects (mean age 68.6 ± 10.2 years, 52.9% female). Significant correlations were found between all monocular pupillary light response parameters and structural and/or functional measurements, except for initial pupil diameter. When controlling for confounders (age and sex), the relative amplitude of pupil constriction remained significantly correlated with campimetric parameters - mean deviation (r=0.274, p=0.003), pattern standard deviation (r =-0.261, p=0.005), and visual field index (r=0.281, p=0.002). Retinal nerve fiber layer (r=0.271, p=0.003) and retinal ganglion cell complex (r=0.208, p=0.025) thickness were also significantly positively associated. Significant correlations were found between disease groups, particularly between the OHT group and early-stage POAG, for the relative amplitude (p= 0.011) and velocity (p= 0.003) of pupil constriction.

CONCLUSION: In glaucomatous eyes, reduced pupillary light responses were linked to more advanced visual field loss and structural retinal damage. These findings highlight automated pupillometry's potential as a precise, non-invasive tool for detecting functional and structural

impairments. Its ability to discern OHT from early-stage POAG further underscores its diagnostic value, allowing earlier intervention in at-risk patients. As the technology evolves, its increased accessibility could benefit both specialized clinics and community settings, enabling earlier diagnosis and better patient care.

KEYWORDS: Glaucoma, Open-Angle; Ocular Hypertension; Reflex, Pupillary; Retinal Ganglion Cells; Visual Field Tests.

RESUMO

INTRODUÇÃO: Este estudo avaliou a relação entre o reflexo pupilar à luz e a perda funcional e estrutural em doentes com hipertensão ocular (HO) e glaucoma primário de ângulo aberto (GPAA), utilizando pupilometria automatizada, um método preciso para medir respostas pupilares. Ao examinar essa relação, este estudo procura esclarecer como as alterações da função pupilar espelham o desenvolvimento do glaucoma, potencialmente melhorando os métodos de diagnóstico e seguimento.

MÉTODOS: Foi realizado um estudo transversal com doentes diagnosticados com HO e GPAA. As respostas pupilares dinâmicas monoculares foram gravadas através de um sistema de pupilometria quantitativa automática. A amplitude relativa da constrição pupilar foi calculada como a percentagem de alteração no diâmetro do início ao pico de constrição. Todos os doentes realizaram perimetria automatizada e tomografia de coerência previamente à pupilometria e a relação entre as respostas pupilares e estes parâmetros foi analisada.

RESULTADOS: O estudo incluiu 136 olhos de 68 doentes (idade média de 68,6 ± 10,2 anos, 52,9% do sexo feminino). Encontraram-se correlações significativas entre todos os parâmetros de resposta pupilar monocular, excetuando o diâmetro inicial, e as medidas estruturais e/ou funcionais. Ao controlar para idade e sexo, a amplitude relativa da constrição pupilar manteve correlação significativa com os parâmetros campimétricos: *mean deviation* (r=0,274, *p*=0,003), *pattern standard deviation* (r =-0,261, *p*=0,005), and *visual field index* (r=0,281, *p*=0,002). A espessura da camada de fibras nervosas da retina (r=0,271, *p*=0,003) e do complexo de células ganglionares (r=0,208, *p*=0,025) também demonstraram associações positivas significativas. Foram encontradas correlações significativas entre os grupos, particularmente entre o HO e GPAA inicial, para a amplitude relativa (*p*=0,011) e velocidade (*p*=0,003) da constrição pupilar.

CONCLUSÃO: Em olhos glaucomatosos, respostas pupilares reduzidas foram associadas a perdas campimétricas mais avançadas e danos estruturais da retina, destacando o potencial da pupilometria como ferramenta precisa e não invasiva para detetar comprometimento funcional e estrutural. A capacidade de discernir HO de GPAA inicial reforça o seu valor diagnóstico, permitindo intervenções precoces em doentes de risco. Com a evolução tecnológica, uma maior acessibilidade pode permitir uma melhor gestão de recursos no diagnóstico de glaucoma, possibilitando melhores cuidados.

PALAVRAS-CHAVE: Células Ganglionares da Retina; Glaucoma de Ângulo Aberto; Hipertensão Ocular; Reflexo Pupilar; Testes de Campo Visual.

INTRODUCTION

Primary open angle glaucoma (POAG) is the most common form of glaucoma,[1] and a leading and increasing cause of irreversible visual impairment and blindness worldwide.[2,3] It is characterized by a chronic progressive optic neuropathy that results in the degeneration of retinal ganglion cells and its associated visual field loss.[4,5] Traditional diagnostic strategies, focusing on optic coherence tomography (OCT) assessment of the retinal nerve fiber layer (RNFL) and ganglion cell complex (GCC) and visual field defects using standard automated perimetry (SAP),[4] have an elevated cost-efficiency burden, making a population screening of the disease currently unsustainable,[6] and a tight follow-up financially straining, which can limit accessibility and frequent monitoring.[7]

However, the early detection of POAG remains crucial, as this disease is frequently underdiagnosed[8] and timely intervention can prevent irreversible damage,[9] therefore, there is a pressing need for diagnostic tools that can accu-

rately identify the disease at its initial stages, particularly to differentiate ocular hypertension (OHT) from early-stage POAG, crucial to adequate the eagerness of treatment.

Historically, the swinging flashlight test has been a common tool for detecting relative afferent pupillary defects, often signaling asymmetric glaucomatous damage. While useful, it is limited by subjectivity and moderate sensitivity, especially in early glaucoma detection.[10,11] Pupillometry offers a significant advancement, and has emerged as a potential non-invasive tool for assessing autonomic dysfunction by providing an objective, quantitative assessment of the pupillary light reflex (PLR).[12-15]

Thus, pupillometry appears as an ideal candidate for early detection of subtle impairments, potentially aiding in clinical decision-making, in both diagnosis and follow-up of glaucoma patients, and offering deeper insights into the pathomechanism of glaucoma.[16]

Previous studies have demonstrated a correlation between pupillometry and standard automated perimetry (SAP) or visual field (VF) testing, suggesting that pupillometry can serve as an effective tool in assessing functional impairment in glaucoma.[17,18] Pupillometry has also shown significant potential in correlating pupillary responses with structural damage markers in glaucoma, particularly RNFL thickness[17,19] and retinal ganglion cell loss,[20,21] making it a promising non-invasive tool for early detection and monitoring of structural and functional changes in glaucoma.

Additionally, prior investigations have demonstrated that pupillometric evaluations can effectively distinguish between the eyes of glaucoma patients and those of healthy controls.[15,22,23] With the advancement of technology, pupillometry also offers significant potential as a portable and accessible diagnostic tool, particularly in community care and telemedicine.[24,25]

Despite the promising potential of automated pupillometry as a non-invasive, cost-effective tool for detecting and monitoring glaucoma, it is still unclear the extent to which the PLR correlates with glaucoma severity, and whether pupillometry can accurately distinguish between patients with OHT and early-stage POAG. This study seeks to address this gap in the literature by evaluating the relationship between the PLR and both functional and structural damage, with hopes of contributing with valuable insights that could enhance glaucoma screening, improve diagnostic accuracy, and ultimately refine patient management strategies in clinical and community settings.

MATERIAL AND METHODS

This cross-sectional study was conducted between July 2020 and July 2024 at the Ophthalmology Department, Unidade Local de Saúde Vila Nova de Gaia/Espinho, Vila Nova de Gaia, Portugal. The study was conducted in accordance with the tenets of the Declaration of Helsinki. Patients with OHT and POAG across the entire spectrum of disease severity, following the definitions set by the European Glaucoma Society Guidelines, were included. Glaucoma severity staging was also classified according to the European Glaucoma Society's revised staging (simplified Hodapp's classification). Participants were required to be 18 years of age or older at the time of enrollment. All subjects were clinically evaluated and treated by the same multidisciplinary team.

Exclusion criteria included refractive error exceeding ± 5 diopters of sphere or ± 3 diopters of cylinder, ocular trauma, inflammation, or eye surgery within the previous six months, and any prior glaucoma laser treatment or surgery. Additional exclusion factors included any physical abnormalities of the pupil observed on slit-lamp examination, retinal or neurological diseases, diabetes mellitus, media opacities affecting the quality of OCT imaging, and unreliable results from the SAP visual field examination.

Pupillary light reflex was assessed using an automatic quantitative pupillometry system (MonPack One, Vision Monitor System, Metrovision, Pérenchies, France). Monocular and binocular dynamic pupillary responses to monochromatic white light stimuli were recorded from both eyes and analyzed (Fig. 1). Pupillometry measurements were performed under controlled scotopic lighting conditions, after 5 minutes of dark adaptation, to ensure consistency. The relative amplitude of pupil constriction (%) was quantified as the percentage change in pupil diameter from the onset of constriction to its peak.

$$\text{Relative Amplitude of Pupil Constriction}(\%) = \left(\frac{D_{\text{onset}} - D_{\text{peak}}}{D_{\text{onset}}}\right) \times 100$$

Where:
· D_{onset} is the pupil diameter at the onset of constriction.
· D_{peak} is the pupil diameter at the peak of constriction.

Twelve consecutive measures per eye were averaged and values were collected for data analysis, including: initial pupil diameter (mm), amplitude (mm), latency (ms), velocity (mm/s), and duration of pupillary constriction (ms), as well as latency (ms), duration (ms) and velocity (mm/s) of pupillary dilation.

All participants underwent a comprehensive ocular examination, SAP and OCT within one year before pupillometry. The examination included medical history, best-corrected visual acuity (BCVA) measurement, slit-lamp biomicroscopy, intraocular pressure (IOP) measurement

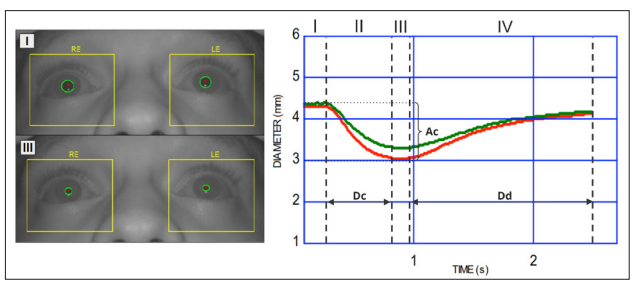

Figure 1. A. Example of the pupillary light reflex waveform illustrating the parameters measured in this study. B. Automatic definition of pupillary contour by the pupillometry device with peak dilation (I) and constriction (III). I - latency of constriction; II - constriction phase; III - latency of dilation; IV - dilation phase; Ac - amplitude of constriction; Dc - duration of constriction; Dd - duration of dilation.

using iCare® or Goldmann applanation tonometry and dilated fundus examination; SAP (Humphrey Field Analyzer 3, Carl Zeiss Meditec, Dublin, CA, USA) was utilized to assess VF loss, yielding key parameters such as mean deviation (MD), pattern standard deviation (PSD), and visual field index (VFI). The Heidelberg OCT SPECTRALIS® (Glaucoma module premium edition, Heidelberg Engineering Inc., Franklin, MA, USA) was used to measure RNFL and GCC thickness.

The relationship between pupillary light response and SAP/OCT parameters was analyzed, adjusting for the potential confounding factors age and sex. The association between pupillary response amplitude and glaucoma severity was further examined using correlation coefficients to identify any significant links with functional and structural outcomes. Pupillometric parameters were analyzed and compared between OHT and POAG severity groups.

Statistical analysis was conducted using SPSS (v25.0, IBM Corp.). Spearman's correlation coefficient was calculated between PLR measurements and visual field (MD, PSD) and OCT (RNFL, GCC) parameters. A partial correlation was used to control for confounding variables. The one-way ANOVA test was employed to assess for differences in PLR between the disease groups, and a Games-Howell post hoc test was performed. Statistical significance was set at $p < 0.05$.

RESULTS

A total of 136 eyes from 68 subjects, with a mean age of 68.6 ± 10.2 years (IQR 63.5-76.0), and 52.9% female, were included in the study. The participants consisted of 22.1% with OHT and 77.9% with POAG, subdivided into 45.6% early-stage, 19.9% moderate-stage, and 12.5% advanced-stage. The median BCVA was 0.1 ± 0.126 logMAR (IQR 0.1-0.2) and the median IOP was 16 ± 3.86 mmHg (IQR 14-18.75). A detailed description of the clinical features of the sample is presented in Table 1.

We found moderate and weak statistically significant correlations between all unilateral stimulated pupillary light PLR parameters - relative pupil constriction, amplitude of constriction, latency of constriction, and velocity of constriction - and both structural and functional measurements, except initial pupil diameter, which did not show a significant association (Table 2A). For the bilateral light stimulus, moderate and weak statistically significant correlations were also found between all PLR parameters—relative pupil constriction, amplitude of constriction, latency of constriction, and velocity of constriction—and functional and/or structural parameters, except initial pupil diameter (Table 2A).

When controlling for the potential confounders age and sex, the relative amplitude of pupil constriction in response to unilateral stimulus was significantly correlated with visual field parameters (Fig. 2A, B), including MD (r=0.274, p=0.003), PSD (r=-0.261, p=0.005), and VFI (r=0.281, p=0.002). Additionally, RNFL (r=0.271, p=0.003) and GCC thickness (r=0.208, p=0.025) were also significantly associated with relative pupil constriction amplitude (Fig. 2C, D). Similarly, absolute pupil constriction amplitude maintained significant correlations with all functional and structural parameters (Table 2B).

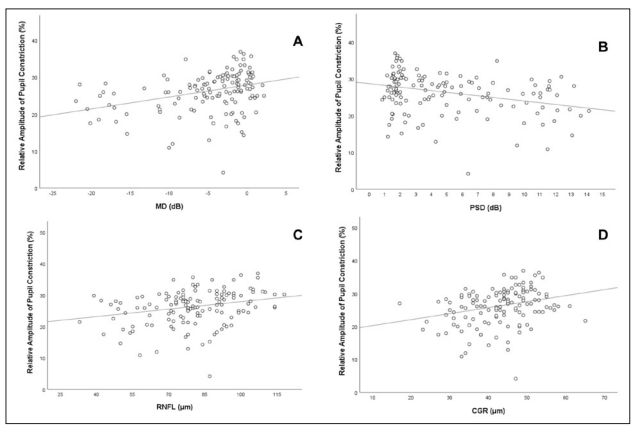

Figure 2. Relationship between relative amplitude of pupil constriction and functional and structural features in eyes with OHT and POAG. A. Correlation with visual field mean deviation. B. Correlation with visual field pattern standard deviation. C. Correlation with OCT retinal nerve fiber layer thickness. D. Correlation with OCT retinal ganglion cell complex thickness.

Significant correlations were also kept between velocity of pupillary constriction and MD (r=0.228, p=0.014), PSD (r=-0.281, p=0.002), VFI (r=0.240, p=0.005), and RNFL thickness (r=0.220, p=0.017), independent of age and sex, though no significant correlation was found with GCC thickness (p=0.126).

No significant correlations were observed under bilateral light stimulus, except for negative correlations between pupillary constriction latency and both RNFL thickness (r=-0.203, p=0.029) and VFI (r=-0.200, p=0.031), when controlling for confounders. Although MD, PSD, and GCR approached significance, they did not reach it (p=0.062; 0.063; 0.069).

No statistically significant correlations were found between initial pupil diameter, duration of constriction, or dilation-related metrics (latency, duration, velocity) with any of the functional or structural parameters after controlling for confounders.

These correlations are illustrated in detail in Table 2B.

Table 1. Clinical, functional and structural features of the OHT and POAG eyes enrolled in the study.

Sample size (number of eyes)	136
BCVA (logmar, median [IQR])	0.1 (0.1 - 0.2)
IOP (mmHg, median [IQR])	16.0 (14.0 – 18.5)
Diagnosis	
OHT	30/136 (22.1%)
Early POAG	62/136 (45.6%)
Moderate POAG	27/136 (19.9%)
Severe POAG	17/136 (12.5%)
Visual field parameters (dB, median [IQR])	
MD	-2.84 (-6.73 – -0.86)
PSD	3.50 (1.79 – 7.59)
OCT parameters (µm, median [IQR])	
RNFL thickness	80.00 (71.00 – 92.75)
GCC thickness	44.00 (37.00 – 49.00)

Table 2.
A - Spearman's correlation coefficients (rho) for the relation between pupil light responses and functional and structural parameters.

N = 136		Monocular light stimulus					Bilateral Light Stimulus				
		Relative Pupil Constriction	Initial Pupil Diameter	Amplitude of Constriction	Latency of Constriction	Velocity of Constriction	Relative Pupil Constriction	Initial Pupil Diameter	Amplitude of Constriction	Latency of Constriction	Velocity of Constriction
MD (dB)	rho	.337	-.050	.226	-.188	.252	.249	-.134	.096	-.258	.138
	P Value	.000	.561	.008	.029	.003	.003	.120	.268	.002	.108
PSD (dB)	rho	-.266	.047	-.176	.166	-.225	-.199	.128	-.070	.223	-.143
	P Value	.002	.586	.040	.053	.009	.020	.139	.419	.009	.096
VFI (%)	rho	.331	.011	.267	-.160	.286	.286	-.087	.164	-.219	.208
	P Value	.000	.905	.003	.081	.002	.002	.344	.073	.016	.023
RNFL (µm)	rho	.296	.030	.256	-.334	.215	.228	-.005	.175	-.391	.164
	P Value	.000	.729	.003	.000	.012	.008	.957	.042	.000	.056
GCC (µm)	rho	.315	.086	.312	-.343	.272	.317	.032	.254	-.447	.232
	P Value	.000	.329	.000	.000	.002	.000	.720	.003	.000	.007

B - Partial correlation coefficients (r) for the relation between pupil light responses and functional and structural parameters - controlled for age and sex.

N = 136		Monocular light stimulus					Bilateral Light Stimulus				
		Relative Pupil Constriction	Initial Pupil Diameter	Amplitude of Constriction	Latency of Constriction	Velocity of Constriction	Relative Pupil Constriction	Initial Pupil Diameter	Amplitude of Constriction	Latency of Constriction	Velocity of Constriction
MD (dB)	r	.274	-.051	.214	-.072	.228	.167	-.133	.063	-.174	.092
	P Value	.003	.587	.021	.441	.014	.073	.155	.499	.062	.328
PSD (dB)	r	-.261	.021	-.212	-.007	-.281	-.135	.122	-.029	.174	-.122
	P Value	.005	.820	.023	.940	.002	.150	.192	.758	.062	.192
VFI (%)	r	.281	-.069	.207	-.097	.234	.163	-.143	.057	-.200	.089
	P Value	.002	.460	.025	.301	.012	.081	.126	.546	.031	.340
RNFL (µm)	r	.271	.007	.229	-.182	.220	.144	-.025	.099	-.203	.113
	P Value	.003	.938	.014	.051	.017	.123	.791	.291	.029	.226
GCC (µm)	r	.208	.011	.191	-.154	.143	.168	-.018	.136	-.170	.090
	P Value	.025	.905	.040	.099	.126	.071	.848	.147	.069	.334

MD, mean deviation; PSD, pattern standard deviation; VFI, Visual Field Index; RNFL, retinal nerve fiber layer; GCC, ganglion cell complex.

A statistically significant correlation was observed between disease groups concerning the relative amplitude of pupil constriction (Table 3). Significant differences were found between the OHT group (30.36 ± 3.66%) and all other groups: early POAG (26.39 ± 8.37%, p=0.011), moderate POAG (24.35 ± 5.23%, p<0.000), and advanced POAG (22.33 ± 3.95%, p<0.000). Additionally, a significant difference was also observed between the early and advanced POAG groups (p<0.000), though no significant differences were found between the moderate POAG group and either the early POAG (p=0.507) or advanced POAG groups (p=0.406). Significant intergroup differences were also observed regarding the velocity of pupillary constriction between the OHT group (4.93 ± 0.87 mm/s) and all other groups (Table 3): early POAG (4.18 ± 1.03 mm/s, p=0.003), moderate POAG (3.87 ± 0.82 mm/s,

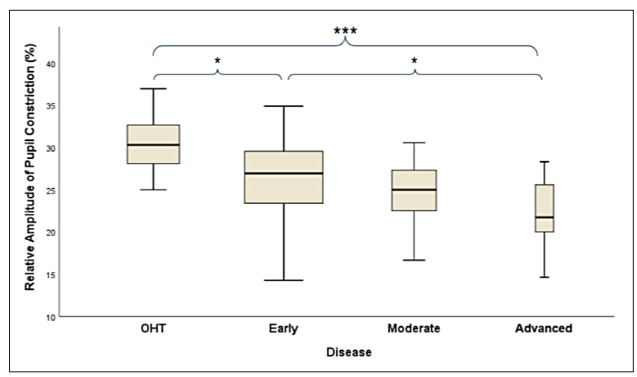

Figure 3. Relative amplitude of pupil constriction and pupillary constriction for each disease group: ocular hypertension, early, moderate and advanced primary open angle glaucoma. *p<0.05, ***p< 0.001.

Table 3. Post-hoc Games-Howell Test Results for Relative Amplitude and Velocity of Pupil Constriction Between Disease Groups.

N = 136			Mean Difference	Std. Error	*p*-value	95% Confidence Interval	
						Lower Bound	Upper Bound
Relative Amplitude of Pupil Constriction	Early	OHT	-3.975	1.256	.011	-7.263	-.686
		Moderate	2.040	1.463	.507	-1.804	5.884
		Severe	4.055	1.431	.031	.267	7.843
	Severe	OHT	-8.030	1.169	.000	-11.200	-4.859
		Early	-4.055	1.431	.031	-7.843	-.267
		Moderate	-2.014	1.389	.476	-5.737	1.707
Velocity of Pupil Constriction Constriction	Early	OHT	-.750	.206	.003	-1.292	-.207
		Moderate	.309	.204	.435	-.229	.848
		Severe	.535	.241	.140	-.119	1.190
	Severe	OHT	-1.285	.258	.000	-1.981	-.589
		Early	-.535	.241	.140	-1.190	.119
		Moderate	-.226	.256	.814	-.919	.467

$p<0.000$), and advanced POAG (3.64 ± 0.84 mm/s, $p<0.000$). However, no other statistically significant differences were identified between other groups. Fig. 3 presents the relative amplitude of pupil constriction for each disease group.

DISCUSSION

Automated pupillography is a quick and objective method for detecting damage to the anterior visual pathway. Previous studies have explored its diagnostic ability in glaucoma, with many demonstrating moderate to good correlations between pupillography measurements and visual field or OCT parameters.[17,18,20,21]

The majority of these studies have focused on calculating a RAPD score and evaluating its relationship with inter-eye asymmetry in glaucomatous damage.[21,26-30] However, fewer studies have specifically examined the correlation between monocular PLR measurements and the magnitude of functional and structural loss in glaucoma.[17,18]

In our study, the relative amplitude of constriction and constriction velocity emerged as the most reliable indicators of glaucomatous damage. Monocular PLR showed a moderate association with VF defects - a reduced pupil constriction and slower velocity correlating with decreased MD and VFI, and increased PSD. Additionally, the percentage of constriction was negatively correlated with RNFL and GCC thickness, and velocity with RNFL. These parameters were the strongest predictors of both functional and structural loss, making them potential quantifiable markers for assessing disease status.

These findings suggest that pupillary responses effectively reflect both visual field loss and ganglion cell function. Eyes with greater campimetry defects exhibited a smaller and slower pupillary constriction, indicating that pupillary responses accurately translate visual field loss, consistent with previous studies.[17,18,28] Similarly, eyes with thinner RNFL and GCC also showed smaller and slower pupillary constriction, suggesting that these responses may be indicative of ganglion cell function. This observation aligns with earlier research as well.[17,19-21]

Interestingly, while both monocular and binocular light stimulation showed moderate to weak statistically significant correlations between PLR parameters and functional and/or structural measurements, further analysis adjusting for confounders revealed a notable difference. After adjustment, the correlations for bilateral stimulation diminished, indicating that monocular stimulation may provide a more reliable assessment of pupillary responses in real-world clinical settings. This is a notable advantage over the swinging flashlight test, which requires binocular stimulation and may struggle to detect asymmetry in early glaucoma.[10,11]

Several factors likely contribute to the increased sensitivity of monocular stimulation. In early glaucoma, one eye is often more affected than the other, and by isolating the response of the targeted eye, sensitivity is enhanced, allowing for early detection of damage that may be missed with bilateral testing, where the less affected eye's response can mask abnormalities. Monocular testing also minimizes the influence of inter-eye variability from non-glaucomatous factors, making observed differences more directly attributable to glaucomatous damage. These advantages suggest that monocular PLR offers a more accurate and reliable method for detecting early or asymmetric/unilateral disease.

Additionally, integrating machine learning and AI into pupillometry could enhance sensitivity by detecting subtle patterns and automating analysis, particularly through multiview learning, by synthesizing pupillometry data with other clinical information, imaging, laboratory results, and medical histories, to provide more comprehensive diagnostics.[31]

Our study reinforces the findings of Bayraktar *et al*,[22] showing that dynamic pupillary parameters, such as relative

amplitude and constriction velocity, are superior to static measures like pupil diameter in reflecting glaucoma staging. Dynamic metrics offer greater diagnostic reliability by providing a more specific reflection of autonomic dysfunction, as they are less influenced by external factors, making them more robust indicators of glaucomatous changes.

Martucci *et al*[12] and Chang *et al*[15] had previously demonstrated a significant relationship between pupil constriction percentage, constriction velocity, and glaucoma stage. Our study supports these findings, as statistically significant differences in the relative amplitude of pupil constriction were observed across different disease stages. Additionally, a clear trend of reduced constriction amplitude with increasing disease severity was noted, as shown in Fig. 2.

Our findings further enhance previous descriptions of the diagnostic usefulness of pupillometry, not only in distinguishing between healthy and patients with glaucoma as previously described in the literature,[15,22,23] but by discerning between OHT and early POAG. In our study, we observed statistically significant differences in PLR parameters, particularly the relative amplitude of pupil constriction and constriction velocity, between the OHT and early POAG groups. This supports the hypothesis that pupillometry can detect subtle autonomic dysfunction in the visual pathway, suggesting it could serve as a complementary diagnostic tool, alongside OCT and VF testing in the comprehensive assessment of glaucoma.

The lack of statistical significance in PLR between moderate and other POAG groups may be due to several factors. First, the smaller sample size of patients with moderate and advanced POAG likely reduced statistical power, affecting the robustness of the findings. Second, the arbitrary cut-off of the severity classification may not fully capture the continuous nature of glaucoma progression, making it harder to detect subtle correlations. Our continuous severity data suggested a clear relationship between worsening structural and functional parameters and changes in PLR, but this categorization may obscure these subtle changes. Third, pupillometry may be better suited for detecting early disease changes, with its sensitivity decreasing in advanced stages due to the narrowing dynamic range of pupillary responses. Future research is needed to clarify and further investigate these findings.

This discriminatory capacity between OHT and early POAG is critical because OHT patients are at risk of developing glaucoma, but not all will progress. Early detection of autonomic dysfunction through PLR may suggest that these individuals are transitioning from a high-risk state (OHT) to the early stages of glaucoma. By identifying these early functional changes, clinicians may opt for a more proactive approach, potentially initiating or intensifying treatment earlier than they would based on traditional measures alone, such as IOP or VF assessments, preventing the onset of more severe glaucomatous damage, preserving vision and improving long-term outcomes.

This early detection holds potential for screening programs. As a non-invasive, quick, and cost-effective method, pupillometry is ideal for large-scale screening, allowing for the identification of patients who should be further investigated. It enables clinicians to prioritize resources for those needing immediate intervention while monitoring lower-risk OHT patients. This targeted approach could enhance the efficiency and cost-effectiveness of glaucoma management globally, particularly in resource-limited settings with restricted access to advanced tools like OCT and VF testing.

Another major advantage of pupillometry-based methods is its ease of use, with minimal training needed for operators. Previous literature demonstrated that pupillometry can be adapted in the form of portable devices, incorporated into specialized goggles, or even into smartphone applications.[22,25,32-35] If evidence continues to support the reliability of pupillometry systems using short, cost-effective, patient-friendly testing protocols,[36] alongside the development of a comprehensive normative population database,[37] it could become an ideal screening tool.

Our study has several limitations that may affect result interpretation. First, it was conducted at a single institution, with all patients managed by the same multidisciplinary team, ensuring consistency but limiting generalizability. Although we applied strict inclusion and exclusion criteria, undiagnosed factors, such as non-glaucomatous conditions, may influence the PLR and impact outcomes. Additionally, our focus on eyes with OHT and POAG restricts the applicability of these findings to other types of glaucoma. Finally, since patients without ocular comorbidities were selected, the findings may not reflect typical clinical settings where multiple ocular pathologies are frequently the norm, not the exception.

CONCLUSION

Our study highlights the potential of automated pupillometry as a valuable tool for detecting both functional and structural impairments in glaucomatous eyes. Reduced pupillary light responses were significantly correlated with greater visual field loss as well as RNFL and GCC thinning. The relative pupil constriction and the velocity of constriction, dynamic parameters, emerged as the most reliable indicators, showing consistent and significant correlations with both functional and structural damage, indicating their superiority as diagnostic markers over static measurements.

Monocular stimulation proved to be more sensitive in detecting early functional and structural changes, as it allows for the isolated assessment of each eye, preventing the healthier eye from masking the damage in the affected one. This highlights the potential of monocular pupillometry as a more precise and reliable approach for early detection and monitoring of glaucoma.

Our findings demonstrate, for the first time, that pupillometry has the potential to effectively distinguish between OHT and early-stage POAG using dynamic pupillary responses - something that current screening methods may not easily capture. This early differentiation is crucial, as it enables clinicians to intervene proactively, preventing disease progression in patients with early-stage POAG while avoiding unnecessary treatment in those with OHT.

Additionally, this capability may be particularly valuable in screening programs or resource-limited settings, where early identification of high-risk individuals can greatly improve disease management and access to timely treatment. Its simplicity allows for easy deployment in community-based applications, offering a feasible alternative to more expensive, technically complex diagnostic machines.

Despite its potential, further large-scale studies are needed to validate the clinical efficacy of pupillometry in both early detection and ongoing management of glaucoma. With additional research, this non-invasive and objective tool could significantly enhance glaucoma screening as well as the efficiency and cost-effectiveness of glaucoma management globally, especially in underserved populations.

CONTRIBUTORSHIP STATEMENT / DECLARAÇÃO DE CONTRIBUIÇÃO

DFC: Data collection and analysis and writing the first draft.
CCF: Data analysis and review.
JSF and JS: Review.
ACR: Data collection.
JC and DM: Review and editing.
ES: Editing.
All authors approved the final version to be published.

DFC: Recolha e análise de dados e redação do primeiro rascunho.
CCF: Análise e revisão dos dados.
JSF e JS: Revisão.
ACR: Recolha de dados.
JC e DM: Revisão e edição.
ES: Edição.
Todos os autores aprovaram a versão final a ser publicada.

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