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ORIGINAL ARTICLE

PUPIL CYCLE TIME AND PERIPAPILLARY PERFUSION IN ANGLE CLOSURE GLAUCOMA

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ABSTRACT

Introduction and Objective: *One of important roles in the pathogenesis of glaucoma is vascular condition. To enhance glaucoma management, the clinical assessment of ocular perfusion is required. The pupillary light reflex's afferent or efferent pathways may become impaired as a result of pupil cycle time (PCT) elongation. PCT is a simple objective method to measure the function of optic nerve, including glaucoma. The purpose of this study is to evaluate the connection between pupil PCT and peripapillary perfusion.*

Methods: *A cross-sectional study from Kariadi Hospital included 26 eyes with angle closure glaucoma and 26 eyes of healthy patients. Complete ophthalmologic examinations, PCT measurements, and OCT peripapillary angiography were performed on each patient. Patients with history of drugs use that can affect pupillary reflexes such as barbiturates, methyldopa, anaesthetics, and antidepressant, and patients with history of glaucoma attack are excluded. The comparisons between the two groups were examined, with a p<0.05 indicating statistical significance.*

Discussion: *The mean PCT of normal subjects was 943,4ms (882,4ms – 993,4ms) and angle closure glaucoma subject was 1789,5ms (1060ms – 4600ms). There were statistically significant difference of PCT value in angle closure glaucoma compared to normal subjects (P<0,05). Peripapillary flow index and peripapillary vessel density in closed angle glaucomatous eyes were lower than normal eyes (P<0.05). There is a significant relationship between PCT with peripapillary flow index and peripapillary vessel density. (P<0,05).*

Conclusion: *In angle closure glaucoma, prolonged PCT associated with decreased peripapillary perfusion as shown by decreases in peripapillary flow index and peripapillary vascular density.*

Keywords: *Pupil cycle time, Peripapillary flow index, Peripapillary vessel density, Glaucoma*

INTRODUCTION

Glaucoma is a syndrome of progressive optic neuropathies that cause structural and functional deficits due to apoptosis of retinal ganglion cells and progressive loss of retinal nerve fibers and optic nerve axons.[1] Vasculature plays important roles in glaucoma pathophysiology. To improve glaucoma management, a practical method for clinically evaluating ocular perfusion is required. According to some studies, glaucoma may be associated with vascular dysfunction, implying another imaging target for early diagnosis and monitoring of glaucoma.[2]

Pupil cycle time (PCT) has been used as an objective measure of optic nerve function in glaucoma and other ophthalmic diseases. The afferent or efferent pathways of the pupillary light reflex may be impaired if the PCT is prolonged. A small light beam or slit focused at the pupillary margin will cause regular persistent pupil oscillations. The pupil cycle time (PCT) is the average period of these cycles that can be easily measured and expressed in milliseconds (ms).[3]

The imaging modality that is frequently used to identify and characterize vascular pattern in various retinal layers is optical coherence tomography angiography (OCT-A). Due to its capacity to quantify the microcirculation in the optic nerve head and peripapillary region.[4]

The purpose of this study was to look at the relationship between PCT and peripapillary perfusion in angle-closure glaucoma patients. We also looked at how PCT measurements correlated with age, patient gender, glaucoma variation, best corrected visual acuity (BCVA), intraocular pressure (IOP), retinal nerve fiber layer (RNFL) thickness, and ganglion cell layer - internal plexiform layer thickness (GCL-IPL).[5]

METHODS

This cross sectional observational study was performed from January 2022 to March 2022, at Kariadi Tertiarry Hospital. The subjects were 26 eyes of patient that had primary angle closure glaucoma and 26 healthy patients. All of the patients had ophthalmologic examinations, such as best corrected visual acuity (BCVA), slit-lamp biomicroscopy, Goldmann applanation tonometry, gonioscopy, PCT measurement, OCT RNFL and OCT peripapillary angiography.

INCLUSION AND EXCLUSION CRITERIA

We included glaucoma patients who met the following requirements:

1. A rim defect of the optic disc (thinning or notching) or an NFL defect apparent on slitlamp biomicroscopy.
2. Gonioscopy with closed angles.
3. Best-corrected visual acuity above counting fingers.
4. Intraocular pressure of 21 mmHg or below.

Normal subject inclusion criteria:

1. Best-corrected visual acuity of 0.8 or better (on the Snellen visual acuity scale).
2. Intraocular pressure of 21 mmHg or less.
3. Typical appearance of the optic disc.

4. There is no fault in the visual field.

Exclusion criteria for glaucoma and normal patients were as follows:

1. Patients with suspected glaucoma, glaucoma attacks, and intraocular pressure greater than 21 mmHg.
2. Post ocular surgery, such as lens extraction and trabeculectomy.
3. Other illnesses such as corneal opacity or dystrophy, uveitis, rubeosis iridis, vitreous hemorrhage, retinal vascular diseases, previous ocular trauma or ocular surgery.
4. History of systemic disease that might affect autonomic function. Acute/subacute dysautonomias, chronic autonomic failure syndrome, hereditary autonomic diseases, metabolic diseases (chronic renal failure, chronic liver disease), inflammatory diseases (Guillain-Barré syndrome, transverse myelitis), infectious diseases, neoplasia (brain tumors, paraneoplastic, include adenocarcinomas of lung and pancreas), surgery (vagotomy and drainage procedures: "dumping syndrome") and trauma (cervical and high thoracic spinal cord transection).
5. History of neurologic or neuroophthalmologic disorders (multiple sclerosis, optic neuritis or neuropathies).
6. Using drugs that cause autonomic dysfunction (i.e., methyldopa, barbiturates, anaesthetics, antidepressant).
7. Diabetes mellitus were excluded due to the possible influence on pupillary reaction.
8. Patients not cooperative for PCT measurements, and all eyes with a refractive spherical equivalent (myopic or hyperopic) >5 D or with high astigmatism (>3 D).

MEASUREMENT OF PUPIL CYCLE TIME

Miller et al. described a method for measuring pupil cycle time.[5] The patient was requested to look into the distance from a slit lamp in a poorly lit room. A narrow, horizontally aligned, moderately intense laser beam 9 mm long and 0.5 mm wide was directed from below the lower inferior pupillary margin to initiate pupil cycle contraction and dilation. The time spent in seconds to complete 90 cycles (three runs of 30 cycles each) was multiplied by 1000/90 to obtain PCT in milliseconds/cycle.[3]

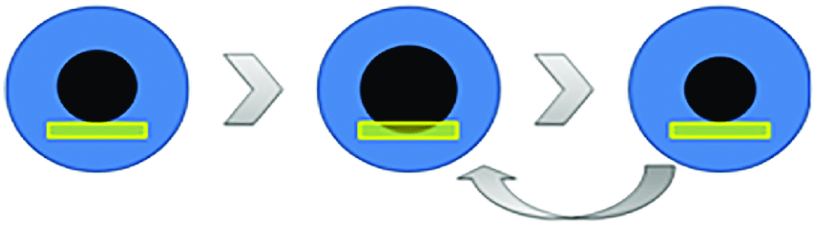

Figure 1. Pupil cycle time measurement.[5]

OPTICAL COHERENCE TOMOGRAPHY

Cirrus-HD OCT 5000 version 11.0 (Carl Zeiss Meditec Inc, Dublin, CA) was used for optical coherence tomography. The optic disc cube 200 x 200 technique, which photographs the optic disc in a 6 mm x 6 mm region, was used to measure peripapillary RNFL thickness. The average RNFL thickness was determined. The thickness of the macular GCL-IPL was measured using the macular cube 512 x 128 protocol, which photographs a 6 mm x 6mm area centered on the fovea. The machine software calculated the GCL-IPL thickness throughout an elliptical annulus (2 mm x 2.4 mm radius), excluding the center foveal region (0.5 mm x 0.6 mm radius).[3] Poor quality images with a signal strength index less than 6 were excluded from the analysis.

OPTICAL COHERENCE TOMOGRAPHY ANGIOGRAPHY

The ocular circulation is quantified by OCTA utilizing two parameters: flow index and vessel density. The average decorrelation values in the measured area are the flow index. Vessel density, the most commonly used OCTA characteristic, is defined as the percentage of the measured area occupied by vessels.[6]

In this study, we collected OCT angiography of the peripapillary retina on a spectral domain OCT system and measured peripapillary flow index and peripapillary vessel density. The peripapillary region was defined as a 700-µm-wide elliptical annulus extending from the optic disc boundary. The greatest flow (decorrelation value) projection from the inner limiting layer to retinal epithelial pigment produced an angiography of the retinal circulation.[2] The image quality of all OCT angiograms was evaluated. Poor quality images with a signal strength index less than 6 were removed from the study, as were registered image sets with residual motion artifacts (discontinuous vascular pattern or disc boundaries).

STATISTICAL ANALYSIS

Statistical software was used to conduct the analysis. The Saphiro Wilk Normality Test was used to determine the normality of the data. For non-categorical parameters, the

independent t-test or Mann-Whitney U test was used, while for categorical parameters, one-way anova was used. Spearman correlations were used to examine the relationships between PCT results and retinal nerve fiber layer thickness, ganglion cell layer thickness, peripapillary vascular density, and flow index. Logistic regression was used to examine the factors that influenced PCT. Statistical significance was defined as a P value less than 0.05.

RESULTS

In current study, we compared pupil cycle time and peripapillary perfusion in 26 angle-closure glaucoma patients to 26 normal people in this cross-sectional investigation. Table 1 summarizes the demographic and clinical characteristics for each group.

Table 1. Demographic Characteristics

Variable	Groups		p
	Angle-closure	Normal Subjects	
Age	61,5 (36 – 71)	58 (38 – 79)	0,304‡
Sex			
Male	13 (50)	20 (76,9)	0,084¥
Female	13 (50)	6 (23,1)	
Diagnose			
PAC	6 (23,1)	0 (0)	
PACG	14 (53,8)	0 (0)	
PACS	6 (23,1)	0 (0)	
Non Glaucoma	0 (0)	26 (100)	
Pupil diameter	3 (3 – 6)	3 (3 – 5)	0,404‡
CDR	0,8 (0,4 – 1)	0,4 (0,3 – 0,5)	<0,001§*
IOP	20,40 ± 2,55	14.94 ± 2,42	<0,001§*
RNFL	65,73 ± 10,87	100,46 ± 12,49	<0,001§*
GCL-IPL	62.15 ± 11,69	77,61 ± 15,40	<0,001§*

Notes : * Significant (p<0,05); ‡ Mann Whitney;
§ Independent t. PCT : Pupil Cycle Time, CDR : Cup Disc Ratio, IOP : Intra Ocular Pressure, RNFL : Retinal Nerve Fiber Layer, GCL-IPL : Ganglion Cell Layer-Inner Plexiform Layer.

Based on Table 1, there were clinically significant difference between CDR, IOP, RNFL, and GCL-IPL, in glaucoma patients and normal subjects. There was no correlation between age, sex and pupil diameter of the patients with glaucoma compared with normal subjects (P>0,05 ; p :0,304; p:0,084; p: 0,404 respectively). RNFL thickness and GCL-IPL thickness were significantly lower in the angle-closure glaucoma group compared with the healthy subjects (p<0.001) The results of the RNFL and GCL-IPL thickness analyses are presented in Table 1.

Table 2. Comparation PCT and OCT-A Parameter in Angle-Closure Glaucoma and Normal Patients

Variable	Groups		p
	Angle-closure	Normal Subjects	
PCT	1789,5 (1060 – 4600)	943,4 (882,4 – 993,4)	<0,001‡*
OCT A			
-Vessel density			
Inferior	39,83 ± 5,09	45,15 ± 2,53	<0,001§*
Superior	39,66 ± 3,66	43,47 ± 2,62	<0,001§*
Nasal	41,45 ± 2,77	45,54 ± 2,83	<0,001‡*
Temporal	42,08 ± 3,60	46,59 ± 2,82	<0,001§*
Average	40,72 ± 2,11	45,38 ± 1,85	<0,001‡*
-Flow index			
Inferior	0,38 ± 0,07	0,41 ± 0,04	0,031‡
Superior	0,32 ± 0,05	0,41 ± 0,04	<0,001‡*
Nasal	0,30 ± 0,06	0,42 ± 0,05	<0,001§*
Temporal	0,37 ± 0,08	0,43 ± 0,05	0,005§*
Average	0,34 ± 0,04	0,42 ± 0,05	<0,001§*

Notes : * Significant (p<0,05); ‡ Mann Whitney;
§ Independent t. PCT : pupil cycle time, OCT-A : Ocular Coherence Tomography Angiography.

In this study including patients with angle-closure glaucoma and age-matched normal subjects, the mean PCT and peripapillary vessel density was significantly reduced in the glaucoma group compared with the normal control group.

The mean PCT of glaucoma subjects was 1789,5 (1060-4600) ms and the mean PCT of normal subjects was 943,4 (882,4-993,4) ms. There were statistically significant difference PCT value on glaucoma compared to normal subjects (p<0,05).

The mean peripapillary vessel density glaucoma patients was 40,72 ± 2,11 and the mean peripapillary vessel density of normal subjects was 45,38 ± 1,85. Peripapillary vessel density in angle-closure glaucomatous eyes were lower than normal eyes (P<0.001). The mean peripapillary flow index glaucoma patients was 0,34 ± 0,04 and the mean peripapillary flow index of normal subjects was 0,42 ± 0,05. Peripapillary flow index in angle-closure glaucomatous eyes were lower than normal eyes (P<0.05).

Table 3. Average of PCT in various type of angle-closure glaucoma

Diagnose	PCT	p
PACS	1808,50 ± 60,00	0,011*
PAC	1679,60 ± 74,65	
PACG	2121,69 ± 948,58	

Note: Significant (P<0,05): ¶ One Way ANOVA

Table 3 showed the results of mean PCT in various type of primary angle-closure glaucoma. In this results showed there were a dominant lengthening of PCT 2121,69 ± 948,58

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ms in PACG. Prolonged PCT was also found in PACS and PAC.

Table 4. Correlation between PCT with CDR, Intraocular pressure (IOP), RNFL, GCL-IPL and OCT Angiography

Diagnose	PCT	
	p	r
CDR	<0,001	0,825
IOP	0,068	0,276
RNFL	<0,001	-0,634
GCL IPL	0,003	-0,426
OCT A		
Vessel density		
Inferior	<0,001*	-0,496
Superior	<0,001*	-0,512
Nasal	<0,001*	-0,561
Temporal	0,001*	-0,445
Average	<0,001*	-0,726
Flow index		
Inferior	0,037*	-0,291
Superior	<0,001*	-0,654
Nasal	<0,001*	-0,660
Temporal	0,012*	-0,347
Average	<0,001*	-0,596

Note : significant (P<0,05), spearman correlation, PCT : Pupil Cycle Time, CDR : Cup Disc Ratio, IOP : Intra Ocular Pressure, RNFL : Retinal Nerve Fiber Layer, GCL-IPL : Ganglion Cell Layer-Inner Plexiform Layer.

Cup disc ratio (CDR) were found to be positively correlated with PCT measurements (r :0,825, p<0,001). Meanwhile, RNFL thickness, GCL-IPL Thickness and Average peripapillary vessel density and flow index were found to be negatively correlated with PCT measurements (r :-0,634, p<0,001 ; r :-0,426, p 0,003 ; r : -0,726, p<0,001 ; r : -0,596, p<0,001, respectively). The results of correlations analysis are summarized in Table 4.

DISCUSSION

Pupil cycle time (PCT) is the amount of time required for the pupil to constrict and redilate. Pupil cycle time has been used to test optic nerve function objectively.[3] Pupil cycle time is a quick, easy, and effective diagnostic test for optic nerve function.[7] It has the ability to be objective and quantitative for each eye. The mean PCT of glaucoma patients and normal persons in the current study were significantly different. The afferent pathway of the pupillary reflex arc is disrupted in glaucoma due to optic neuropathy. Glaucoma may develop if the PCT is prolonged.[4]

Clark et al. discovered a relationship between an apparent PCT prolongation in primary angle-closure glaucoma. The prolongation is caused by glaucomatous optic neuropathy, which

results in degeneration of the pupillary reflex arc's afferent pathways.[12]

Despite PCT assessment appears to be straightforward and reliable, these studies show a wide range of PCT values in glaucoma patients. This is a critical issue that calls into doubt the procedure's validity as a clinical diagnostic for optic nerve functions. In this investigation, there was no relation between pupil cycle time and age, gender, or pupil size in glaucoma. Milton and Longtin's investigations demonstrated the effect of pupil size on cycling time utilizing accommodative miosis and PCT at various levels of accommodation.[7]

We investigated the relationship between PCT results and OCT parameters including RNFL thickness, GCL-IPL thickness, and OCT angiography factors like peripapillary vascular density and flow index. Our findings clearly show that reducing RNFLT, GC-IPL thickness, average peripapillary vascular density, and flow index significantly lengthens PCT measures. In angle-closure glaucoma, there was a moderate to significant negative connection between PCT measures and RNFLT, GCL-IPL thickness, average peripapillary vascular density, and flow index.

Because of the increasing loss of retinal ganglion cells and their retinal nerve fiber layer, the pupil response in glaucoma eyes is likely to be reduced when compared to normal eyes. Glaucoma patients exhibit lower amplitude, slower velocity, and faster acceleration of pupil constriction than control participants, according to studies.[10] As a result of a decrease in the thickness of the retinal nerve fiber layer and ganglion cell layer, pupillary response is reduced, as demonstrated by the lengthening of PCT.

According to several research, glaucoma may be linked to vascular dysfunction.[2,11] According to the vascular theory, poor regulation of ocular blood flow causes periods of relative ischemia that damage neurons, resulting in thinning of the retinal nerve fiber layer and ganglion cell layer.[12] This study found that glaucoma patients had a longer PCT duration, which was associated with lessening of the peripapillary vascular density and flow index.

Our research has several limitations. We did not consider the medications the patient was taking, even glaucoma medications, systemic medications, or both of it. Antiglaucoma medicines may have an influence on the peripapillary arteries. The majority of glaucomatous eyes were receiving numerous antiglaucoma eyedrops.

CONCLUSION

We can conclude from this study that PCT was prolonged in patients with closed angle glaucoma. In glaucomatous eyes, OCT-A measures such as peripapillary vascular density and peripapillary flow index are significantly decreased. OCT-A values that represent microvasculars were likely reduced in angle-closure glaucoma eyes, indicating a dysregulation

of blood flow in these eyes. Prolonged PCT in glaucomatous eyes showed decreased peripapillary perfusion as seen by decrease peripapillary flow index andperipapillary vessel density. Pupil cycle time and quantitative OCT angiography may be relevant for future studies to identify their potential utility in glaucoma assessment. In future investigations, we can assess if OCT-A is capable of detecting a progressive decline in superficial vascular density in glaucomatous eyes when tracked over time in glaucoma patients.

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