***Chapter 5***
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# Recent Advances in Pupillometry

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## ABSTRACT

Importance of pupil analysis within the clinical setting has been extensively employed in patient management and was performed manually in the past. However, manual pupillary assessment can be associated with vital inaccuracies and inconsistencies and previous studies have shown significant inter-examiner disagreement within the manual analysis of pupillary reaction thus affecting the decision making in crucial clinical situations. Recently, automated pupillometry has been proposed as a device for objective, quantitative and repeatable measurements of pupillary reaction, size and symmetry to avoid the bias in manual assessment.Quantitative pupillometry can be used to create a normal database that can provide clinicians with the information needed to manage the patients as well as help determine the need for an immediate referral to an ophthalmologist. In addition to discussing the pupillary light reflex graph and its neural basis, this review article provides an overview of pupillometry. Also, a comprehensive list of the pupil parameters that various quantitative pupillometry devices can measure has been presented. The article concludes with an update on recent developments in pupillometry applications across a variety of fields.

*Keywords: Pupil; pupillary light reflex; static and dynamic pupillometry; quantitative pupillometry.*

## 1. INTRODUCTION

The pupil is the circular opening in the iris, the colored part of the eye. The iris is composed of contractile smooth muscles, sphincter pupillae and dilator pupillae which control the dynamics of pupil. Pupil diameter is influenced by the activity of complex neural pathways that respond to changes in ambient illumination and sympathetic and parasympathetic autonomic innervations. The intensity of light

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which is often measured in lux, lumen or candela, upon reaching the rods and cones significantly alters the pupillary measurements [1]. The increased sensitivity of rods and cones to blue and red light stimulus respectively helps in the accurate assessment of their function [2]. It is necessary to wait a while for the rods and cones to accomodate between stimuli. This time is necessary for the diameter of the pupil to return to its original state [3-5]. In normal individuals, the pupils appear black, perfectly round, and are of same size in both eyes. The size of the pupil varies from person to person, in bright light the diameter is about 2-4 mm, whereas in low light it is about 4-8 mm. In normal everyday situations, pupil size varies with ambient light. It contracts in response to bright environment and expands in response to dark environment, controlling the amount of light entering the eye. The sphincter pupillae, supplied by the oculomotor nerve, is the inner circular muscle that constricts the pupil upon parasympathetic stimulation. Innervated by sympathetic fibers from the cervical ganglion, the dilator pupillae muscle is the external radial muscle that causes dilation of the pupil [6]. Factors affecting mean pupil diameter include age, gender, iris color, retinal and optic nerve health, optical medium clarity, retinal illumination level, accommodation status, and various sensory and emotional states. However, the strongest factor affecting pupil size is ambient light [7].

## 2. PUPILLARY PATHWAYS

A normal pupillary reaction is a balance between the sympathetic and parasympathetic nervous systems.The parasympathetic nervous system consists of sphincter pupillae supplied by cholinergic nerves. The fibres start in the Edinger-Westphal nucleus near the oculomotor nerve, pass via midbrain, run in the main trunk of the oculomotor nerve and pass into the branch supplying the inferior oblique muscle, reaching the ciliary ganglion. From here, fibres pass via short ciliary nerves to sphincter pupillae of the iris causing constriction of the pupil. The sympathetic nervous system consists of dilator pupillae supplied by adrenergic fibres. It commences in the hypothalamus, pass downwards through medulla oblongata and run upto the neck of the superior cervical ganglion, from where they pass along the carotid plexus into the skull. They run over the anterior part of Gasserian ganglion and pass into the ophthalmic division of fifth nerve following the nasal branch, which finally leave to enter long ciliary nerves which enter the eye on each side of the optic nerve reaching the ciliary body and finally the dilator pupillae of iris causing dilatation of the pupil [8].

## 3. PUPILLARY LIGHT REFLEX (PLR)

It is initiated from rods and cones throughout the retina. If light enters the eye, the pupil of that eye contracts known as the direct response and the reaction shared equally by the pupil of the other eye is called the indirect/consensual response. The fibres pass through the optic nerve, partially decussate in the chiasma and enter the optic tract. The fibres then enter the pretectal region and relay in the pretectal nucleus. New fibres travel to the Edinger-Westphal nucleus on each side and via oculomotor nerve pass to the ciliary ganglion. Finally, they reach

sphincter pupillae of the iris via short ciliary nerves causing constriction of the pupil.

Pupil examination is an important part of ophthalmologic and neurologic evaluation. To assess the optic nerve dysfunction, the determination of pupillary size, reactivity, and consensual response is very crucial [9]. Various studies have laid significant emphasis on the importance of pupil analysis within the clinical setting which is employed extensively in patient management.Pupillometry is defined as the measurement of pupil size and reactivity. Pupillary response can be categorized into two types- the constriction of pupils in response to bright light known as Pupillary light response and Pupillary near response/accommodation- where the curvature of the lens changes, eyeballs converge and pupils constrict to control the amount of light entering the eye. All these physiological changes help in providing the best possible image to the brain and if the pupil fails to respond to light or darkness, it is considered to be an abnormal response. Conventionally, examination of pupillary reflex was done using a penlight or flashlight which was associated with significant variability between examiners in various studies [10-14].

Recently, various pupillometer devices have been introduced which are portable and lightweight. These devices use infrared light to assess the pupil's reflex to light, are easy to use as they require only minor cooperation from the participant and are able to provide objective measurements in a relatively contactless manner. Pupillometry can be broadly categorized as static or dynamic:

## 4. STATIC PUPILLOMETRY

Pupil size/Diameter (PD) is measured under different light conditions at a given time. This gives us information about the behavior of the pupil at different illumination levels. Following parameters are measured:

- Scotopic pupil diameter (PD)(0.1 cd/$m^2$ )
- Mesopic PD(1 cd/$m^2$ )
- Low photopic PD(10 cd/$m^2$ )
- High photopic PD(100 cd/$m^2$ )

## 5. DYNAMIC PUPILLOMETRY

Pupillometers generally consist of an infrared-sensitive image sensor coupled to a digital interface for automatic recording, processing, and transmission of pupillometer data. A pupillometer records the pupillary response in complete darkness, followed by a flash of white light. To achieve this, eyes are exposed to infrared light with wavelengths greater than 700 nm across the visual spectrum that do not induce pupillary reflex (PLR). Infrared illumination is therefore useful for capturing the dilation response of the pupil [6]. Various parameters of PLR can be used as indicators of modulation of sympathetic or parasympathetic

activity. Therefore, it provides an important index of autonomic nervous system function that is exploited for a wide range of clinical applications [7].

## 6. COMMERCIALLY AVAILABLE PUPILLOMETERS

They use infrared light for the measurement of dynamic pupillary parameters which increases their versatility in patients with varying iris colors and wide range of illumination conditions. They are portable, easy to use, rechargeable and offer easy data transferability to help in bedside diagnosis as well as in routine clinical settings. These devices have a set of clinically validated instructions to get accurate and reliable measurement of the pupillary parameters.They have a detachable smartguard which helps in proper positioning of the device to attain correct orientation for accurate readings. Their availability and relative high cost limits their use in resource limited settings. List of various commercially available pupillometers:

1) VIP-200 (NeurOptics Inc., Irvine, USA)
2) VIP-300 (NeurOptics Inc., Irvine, USA)
3) PLR-200 (NeurOptics Inc., Irvine, USA)
4) PLR-2000 (NeurOptics Inc., Irvine, USA)
5) PLR-3000 (NeurOptics Inc., Irvine, USA)
6) A-2000 small animal pupillometer (NeurOptics Inc., Irvine, USA)-binocular dual camera system, stimulates direct, consensual or both eyes simultaneously, multi-chromatic, designed for a variety of animal models, excel compatible
7) DP-2000 binocular infrared pupillometer (NeurOptics Inc., Irvine, USA)-binocular dual camera system, stimulates direct, consensual or both eyes simultaneously, multi-chromatic , automatic tracking and pupil detection, excel compatible
8) NPi-200 (NeurOptics Inc., Irvine, USA)
9) Neurolight Algiscan; IDMED, Marseille, France
10) MonPack One, Vision Monitor System, Metrovision, Pérenchies, France-multi-function stimulator combining all the tests needed for a complete thorough evaluation of visual functions- vision electrophysiology, psychophysical, oculomotor tests such as pupillometry, video-oculography and electronystagmography.
11) Pupil X (Albomed GmbH, Schwarzenbruck, Germany)-measures bilateral pupil sizes simultaneously under constant and adjustable illumination levels, facilitating measurements under scotopic, mesopic and photopic conditions, telecentric optical system with two focus free infrared cameras

## 7. SMARTPHONE PUPILLOMETER APPLICATIONS

They use built-in flash light of the smartphone to measure the relative change in pupil size and absolute pupil measurements in millimeters. It has the advantage of being cost-effective, more accessible and portable as compared to commercial and computer applications. An expert is needed for interpretation of the measured pupillary parameters. There is ambiguity regarding the proper positioning of the device as it lacks the surfaces and visual cues to attain correct

orientation for accurate readings as minute hand movements may induce significant errors in the measurement. Therefore, the reliability and accuracy of smartphone pupillometer varies from operator to operator. Variations in the iris color especially in individuals with darker shades of iris, makes it difficult for the visible light stimuli used in smartphones to measure pupillary parameters in comparison to infrared light used by most of the pupillometers. Use of visible light stimuli in different smartphones makes it difficult to measure pupillary parameters under various illumination levels due to variation in the iris colors especially in individuals with darker iris color as compared to infrared light used by most of pupillometers [15-17]. Various smartphone based pupillometers currently available are:

1) Reflex PLR analyzer by Brightlamp Inc., Indianapolis, IN, USA
2) Wadjet Pupil Gauge by Omar Solyman
3) Sensitometer$^{TM}$ (Kagen Air LLC, Appleton, WI)
4) Sober-EYE Inc., Menlo Park-CA, USA)
5) Pupil Screen

## 8. COMPUTER SOFTWARE PUPILLOMETER APPLICATIONS

They are based on algorithms that translate the camera feed into data points with the help of machine learning and advanced image processing. It has the ability to convert eye movements by use of sensor technology into a data stream that contains information about pupil position, gaze vector and point for each eye. Their use is limited as they require high resource settings (only available in hospital for use by trained examiners), expensive, disposable parts for each patient, not portable, require a power source, training is required, require additional software for analyzing the data. They do not take into account the cognitive and emotional state of an individual that may affect eye movements. They need to be complemented by biosensors to capture full picture of the human behavior in that very moment. Clinical grade pupillometers that work on wide variety of iris colors are currently very costly and found only in laboratory settings. These are available in different forms such as Screen-based (desktop), within VR headsets, Webcam-based and Glasses. Various computer softwares available are:

1) Measure X Windows
2) MEYE: Web app
3) Viewpoint Eye track system, Arrington Research, Scottsdale, AZ
4) Tobii eye trackers
5) Pupil EXT
6) Pupil Core by Pupil Labs
7) EyeLink 1000 Plus
8) Eye Tribe
9) Applied Science Laboratories (ASL), Bedford, Massachusetts eye trackers
10) Eye Rec Too
11) Dikablis eye trackers
12) Compact Integrated Pupillograph (CIP; AMTech, Dossenheim, Germany)
13) Iriscoder Dual C10641 (Hamamatsu Photonics, Hamamatsu, Japan)

14) ETL-100H Pupillometry Lab (ISCAN Inc., Woburn, MA, USA)
15) RK-7261 (ISCAN Inc., Woburn, MA, USA)

**Various parameters measured by the pupillometer devices are:**

- Maximum diameter-maximum pupil size before constriction
- Minimum diameter-pupil diameter at peak constriction
- % of change in pupil size
- Latency of constriction- time of onset of constriction following initiation of the light stimulus
- Constriction velocity-average of how fast the pupil diameter is constricting measured in millimeters per second
- Maximum Constriction velocity- maximum velocity of pupil constriction of the pupil diameter responding to the flash of light measured in millimeters per second
- Dilatation velocity-average pupillary velocity when, after having reached peak of constriction, pupil tends to recover and to dilate back to initial resting size, measured in millimeters per second

The latency period is followed by a period of rapid constriction of the pupil until it reaches the maximum constriction velocity (MCV), after which constriction of pupil gradually slows until the minimum diameter is reached. Once the peak constriction is reached, the pupil quickly dilates again or escapes to a partially constricted state during a prolonged light stimulus lasting from 1–2 up to 100 s, before slowly redilating again to the initial size [7] [Fig. 1].

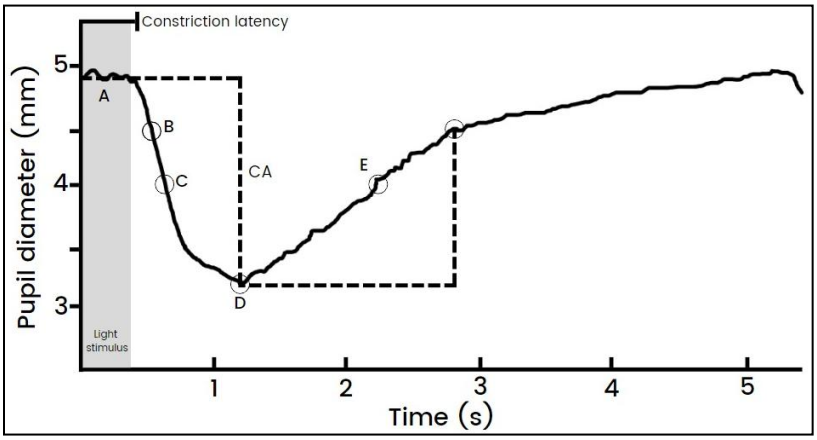


**Fig. 1. Pupillary light reflex (PLR) graph: A- Baseline pupil diameter, B-Maximum Constriction Velocity, C- Constriction Velocity, D- Minimum Pupil Diameter, E- Dilatation Velocity, CA- Constriction Amplitude**

The pupillary light reflex is driven predominantly by a unique subset of intrinsically-photosensitive retinal ganglion cells that contain melanopsin and project to the pretectum, specifically the olivarypretectal nucleus. These are strongly influenced by rod and cone inputs in addition to their slower, melanopsin-driven intrinsic responses [7].

Quantitative pupillometry can be used to create a normal database that can provide clinicians with the information needed to manage the patients as well as help determine the need for an immediate referral to an ophthalmologist.

## 9. CLINICAL APPLICATIONS

Pupillary dynamics such as amplitude, latency, velocity have been investigated in a variety of systemic and ocular diseases.

- Neurodegenerative disorders: Significant difference was observed in all the Pupillary light reflex (PLR) variables between patients with Alzheimer's disease (AD) and healthy participants except in the Minimum Pupil Diameter variable and Baseline Pupil Diameter after 2-min dark adaptation. Maximum Constriction Acceleration (ACmax) is the best predictor in classifying a subject as normal or with AD. Significantly lower values of ACmax and Maximum Constriction Velocity (VCmax) were observed in patients with Parkinson's Disease (PD) without coexisting cognitive impairment and with impairment as compared to normal individuals. VCmax and ACmax can be considered as the most sensitive indicators of cognitive and memory impairment, which reflects a cholinergic deficit [18].
- Isolated third nerve palsy: The maximum and minimum pupil sizes were smaller in the ischemic group as compared to the non-ischemic group and control group. Smaller maximum and minimum pupil sizes were observed in the diabetic patients of the ischemic group as compared to non-diabetic patients and controls. The other normal eye of the diabetic patients also showed a smaller pupil size as compared to non-diabetics and controls. Significant differences were also observed in other parameters like constriction ratio, average constriction velocity (ACV), maximum constriction velocity (MCV) and average dilation velocity (ADV) between the ischemic group and other groups. Digital pupillometry is a really useful tool in discriminating compressive lesions from microvascular ischemic third nerve palsy [19].
- Trauma: The location of the pupillomotor nuclei within the dorsal midbrain and efferent oculomotor nerve are important in the determining the compression of brainstem and the onset of transtentorial herniation [20]. Asymmetry of the pupil and their non-reactivity to light are important dilemmas in the triage of traumatic brain injury patients. Morris et al. [21] reported that loss of the PLR or development of anisocoria or pupil asymmetry >2 mm in patients who sustained traumatic brain injuries was correlated with increased morbidity and mortality rates. PLR could not be detected by manual examination when the reflex amplitude was less than

0.3 mm as studied by Larson et al. [22]. As part of a clinical evaluation, they found that NPi values provide a sensitive, noninvasive and quantitative means of monitoring acute and chronic pupillary function after traumatic brain injury [23].

- Autism: Children and adults with autism spectrum disorder (ASD) reported an atypical PLR [24-27]. Longer latency, reduced constriction amplitude [26,28] and reduced constriction velocity [28] were reported as compared to children without ASD.
- Alcohol:Both baseline pupillary diameter and peak constriction amplitude following a 600 nm wavelength light stimulus at exhaled breath alcohol concentrations of ≥0.25 mg/L demonstrated a significant increase in chromatic pupillometry studies [29]. Significant decreases in pupil diameter, constriction amplitude and velocity were observed following a high dose of alcohol (1 g/kg body weight) as compared to the control group, suggesting inhibition of parasympathetic nerve activity [30,31]. Prolonged latency and decreased constriction velocity were observed in participants undergoing alcohol withdrawal.
- Recreational drugs: Significant increase in latency and decrease in constriction amplitude and velocity due to an indirect central parasympathetic inhibition, is a characteristic pupillary response to 3,4 methylene dioxy methamphetamine and tetra hydro cannabinol [32-34]. In addition, mydriasis and a reduction in the PLR recovery time was reported following MDMA intoxication to increased noradrenaline and serotonin signaling caused by increased sympathomimetic activity [34].
- Exposure to toxins and toxic chemicals: Organophosphates, a family of chemicals that include nerve agents and insecticides, inhibit cholinesterase activity and increase levels of Acetylcholine (Ach) at neuronal synapses. A local increase in ACh causes contraction of the pupillary sphincter muscle, resulting in dose-dependent miosis [35-38]. PLR is also decreased after organophosphate exposure as a result of the development of tolerance to cholinergic agonists and desensitization of muscarinic ACh receptors in retinal tissue after long-term exposure [37,39,40]. Organophosphates inactivate cholinesterase at both muscarinic and nicotinic receptor sites, and their dominant nicotinic action on preganglionic fibers of the sympathetic nervous system leads to paradoxical dilation or mydriasis in certain situations leading to increased innervation of dilator muscles [41,42]. All other parameters, including maximum and minimum pupil sizes, constriction and dilatation velocity, and percentage change in pupil size, were lower in clinically intoxicated patients than in controls, with the exception of latency of constriction [43].
- Response to infections: Signals from vagal afferent fibers ultimately project to the locus coeruleus region of the brain. The locus coeruleus has a dual effect on PLR, ultimately leading to mydriasis [44,45]. First, it contributes to the outflow of the sympathetic nerve innervating the dilator pupillae muscle. Second, it suppresses parasympathetic outflow by inhibiting the EW nucleus. Alterations in cholinergic signaling can affect PLR directly through ACh receptors located in the iris sphincter and indirectly through alterations in parasympathetic nervous system function.

Therefore, measuring PLR using dynamic pupillometry may detect systemic changes in parasympathetic and sympathetic nervous system function in response to infection and inflammation [7].

- Horner syndrome: PLR measured with digital pupillometry revealed distinct inter-eye difference in Horner syndrome both at baseline and after apraclonidine 0.5% test. Baseline inter-eye difference in maximal pupil sizes and dilation lag measured by T75 was equally effective in the diagnosis of Horner syndrome compared to the reversal of anisocoria after apraclonidine instillation [46].
- Retinal disorders: Using pupillometry, Jain et al. [47] observed altered pupillary dynamics in the early stages of diabetic retinopathy and further observed that the dynamics deteriorated with the increasing severity of retinopathy.Evidence of parasympathetic dysfunction in diabetic patients is measurable in the absence of clinically observable signs of diabetic retinopathy, whereas evidence of sympathetic dysfunction becomes apparent only in moderate to severe cases of (nonproliferative) diabetic retinopathy [48]. Dynamic pupillometry may be an inexpensive and clinically relevant test, but its sensitivity and specificity need to be determined before it can be used as a screening tool for diabetic retinopathy [48].
- Sleep- McLaren et al. [49] examined forty-nine patients by pupillometry and their sleepiness was assessed by using the multiple sleep latency test (MSLT). The patients were classified as having ‘mild’,‘moderate’, or ‘severe’ sleepiness, based on this.The median values of most pupillometric variables in the sleepiest patients (mean sleep latency less than 5 min) were significantly greater than those of well-rested, normal volunteers. Variables based on the low-frequency spectra of pupillary fatigue waves were significantly different between the groups of mildly and severely sleepy patients. Massar et al. [50] evaluated sustained performance on a vigilance task, combining this with an effort-based decision-making task and pupillometry. Pupillometry revealed that arousal was modulated during sleep deprivation in a value-based manner, and moment-to-moment fluctuations in pupil diameter were directly predictive of performance.

## 10. CONCLUSION

Qualitative pupil measurements obtained with handheld light sources makes it difficult to compare multiple measurements over time. Therefore, due to its portability and high accuracy, quantitative automated pupillometry may fill an unmet need if further research supports its value as an early diagnostic tool for ocular and extra-ocular disorders. Additionally, they might improve data standardization and lower the variance amongst medical teams. For the examination of pupillary response, different static and dynamic pupil parameters are helpful in clinical departments like ophthalmology, neuropsychology, and psychiatry. There is currently no established measurement methodology or gold standard pupillometer for measuring pupil parameters. The method of illumination, the protocol, and the pupillometry technology (equipment and

software) used for the measurements all vary. The diagnostic potential and accuracy of pupil measurements in patients must be standardized. The range of normal values in the general population, different age groups, iris colors, as well as in various ocular and extra-ocular disorders that manifest changes in pupil size, will need to be determined in future research. If this technique is utilized to monitor subjects in subsequent studies, we are certain that many additional applications will be discovered.

## COMPETING INTERESTS

Authors have declared that no competing interests exist.

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**Special Award:**

**He has received the following awards:**

1. Winner of ASCRS Foundation's 2007 Annual Research Grant
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3. Winner of Archives of Ophthalmology September 2010 monthly quiz
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