

ARTICLE



The pupillary dynamics of patients with physiological anisocoria

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BACKGROUND: To evaluate static pupillometric measurements and making inter-ocular comparative analysis in healthy subjects for demonstrating the prevalence of physiological anisocoria in various lighting conditions and to compare the variations of the dynamic pupillometric measurements of the patients with physiological anisocoria.

METHODS: Automatic quantitative pupillometry system was used to measure pupillary diameters in low mesopic (0.1 cd/m²), high mesopic (1 cd/m²), low photopic (10 cd/m²) and high photopic (100 cd/m²) conditions. After inter-ocular comparison of these data, the prevalence of physiological anisocoria was detected in four different lighting conditions. The inter-ocular dynamic pupillometric parameters (amplitude, latency, duration and velocity of pupil contraction; latency, duration and velocity of pupil dilation) of these patients were further analysed.

RESULTS: After inter-ocular comparison of pupillary diameters of 195 participants [96 females (49.2%) and 99 males (50.8%)] with a mean age of 38.4 ± 18.9 years (range 7–78 years), six (3.1%) participants under high photopic; 11 (5.6%) participants under low photopic; 25 (12.8%) participants under high mesopic, and 34 (17.4%) participants under low mesopic illumination levels exhibited physiological anisocoria. The mean relative amplitude of anisocoric small pupils' contraction was lower than the mean relative amplitudes of pupil contraction of both isocoric and anisocoric large pupils ($p = 0.021$, $p = 0.035$, respectively). The mean velocity of anisocoric small pupils' contraction was lower than the mean velocity of anisocoric large pupils' contraction ($p = 0.013$).

CONCLUSIONS: The mean contraction amplitude and contraction velocity of smaller pupils was lower when compared to fellow larger pupils of anisocoric patients.

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INTRODUCTION

The pupil increases the depth-of-focus of the eye optically and improves the range of clear vision. It has a wide dynamic range and is controlled by the antagonistic interactions of the iris sphincter and dilator muscles, innervated by the parasympathetic and sympathetic pathways of the autonomic nervous system respectively [1, 2]. However, parasympathetic system activity plays a more dominant role than sympathetic system during the pupil constriction phase [3, 4].

Measurement of pupil diameter has gained importance in recent years in order to minimise the occurrence of scotopic phenomena such as halos, glare and monocular double vision after refractive surgeries [5, 6]. The average pupil diameter is affected by the factors including age, sex, iris colour, retinal and optic nerve health and optical media clarity; but, the most powerful determinant of pupil size is the luminous intensity of the incoming light [2, 7–11]. Clinicians measure the pupil size under room light and near total darkness. However, recent developments to automated infra-red pupillometry devices has allowed the control of stimulation parameters and the objective and quantitative measurement of pupil diameters and kinetic reflexes to light stimuli [12, 13]. Automated infra-red pupillometry systems which are installed with infra-red illumination and a high resolution camera technology allow to examine amplitude, latency and velocity of pupil contraction as an autonomic testing tool [14–16].

Anisocoria is a condition characterised by an unequal size of the pupils, usually defined as a 0.4 mm or more difference between the

diameters [17]. Anisocoria in the absence of any accompanying ocular or neurological pathology is known as 'physiological anisocoria' and is reported to be present in 8–43.1% of the population based on the different measurement methods [11, 14–19]. Differentiation of physiological anisocoria from an acquired cause is crucial in order to avoid unnecessary diagnostic work-up. The prevalence of physiological anisocoria is thought to decrease in bright light [11, 19]. Physiological anisocoria's mechanism is unknown; no pharmacological finding indicating the denervation of iris dilators and no damage to the peripheral nerves that innervate the sphincter and dilator muscles of the iris has been recorded. It is assumed that the supranuclear inhibition is not sufficiently balanced in parasympathetic nuclei in the midbrain [2, 4, 20].

In this study, we aimed to evaluate static pupillometric measurements for making inter-ocular comparative analysis in healthy subjects to detect the prevalence of physiological anisocoria in various lighting conditions and to compare the variations of the dynamic pupillometric measurements of the patients with physiological anisocoria.

PATIENTS AND METHODS

One hundred and ninety five subjects who were admitted for routine ophthalmological examination to the outpatient clinic of a single institution between January 2018 and July 2018 were enrolled for this prospective cross-sectional study. The written informed consent was obtained from each participant and all procedures were in compliance

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with the tenets of the Declaration of Helsinki. The study was approved by the Institutional Ethics Committee.

All participants underwent a detailed ophthalmological examination including best corrected visual acuity (BCVA) testing with Snellen chart, intraocular pressure (IOP) measurement with non-contact tonometry, anterior segment examination with slit-lamp biomicroscopy and fundus examination. The participants who had a BCVA of 20/20 or better for both eyes and exhibited spherical and cylindrical error ≤ 1 D were included; and the patients who have any history of ocular disorders (pseudoexfoliation syndrome, any type of glaucoma, strabismus, cataract, uveitis, keratitis, retinal diseases), surgery or trauma were excluded from the study. The patients who have any systemic disorders (such as diabetes, hypertension, neurological diseases, etc.), use any systemic medication (such as anti-prostate drugs, anticholinergics, etc.), and the ones who have a history of smoking or alcohol consumption were also excluded from the study.

Following detailed ophthalmological examination, the pupillometry was performed by the same examiner (MAS) using automatic quantitative pupillometry system (MonPack One, Vision Monitor System, Metrovision, Pérenchies, France) at 33 cm distance without mydriasis. All pupillary measurements were performed at the same time interval of the day (between 14:00 and 16:00) to reduce the effect of circadian variation on pupillary responses and in the same environmental conditions. The technical details of the device and the measurement protocol were published previously [21, 22].

The quantitative static and dynamic pupillometry measurements were taken from binocular pupils in a darkened room with precise control of stimulation parameters and near infra-red illumination (880 nm) and high resolution camera. The static pupillometry measurements were taken under four different illumination levels to measure pupillary diameters in low mesopic (0.1 cd/m²), high mesopic (1 cd/m²), low photopic (10 cd/m²) and high photopic (100 cd/m²) conditions with fifteen seconds adaptation time to each illumination level. The static pupillometry examinations repeated five times per illumination level and lasted ~2 min, depending on the subjects' compliance (e.g., blinking). After five minutes of darkness adaptation, dynamic pupillometry measurements were obtained for the duration of 90 s. Participants were analysed using full field white light flashes (stimulation ON time 200 ms, stimulation OFF time 3300 ms; total luminance 100 cd/m²; total corneal illuminance 20 lux). The images of both eyes were acquired and processed in real time (30 images/s). The automatic-release mode was used to decrease the examiner-induced errors and the average of three consecutive measurements were used for analysis. The data of the mean of the responses for both eyes of the patients were used for inter-ocular comparison of static and dynamic pupillometric parameters and for the comparison of dynamic pupillometric parameters between the subjects with anisocoria and those with no observable anisocoria.

The average response to successive visual stimuli (light flashes) was quantified using the parameters including baseline pupil diameter (mm); amplitude (mm), relative amplitude (%), latency (ms), duration (ms) and velocity (mm/s) of pupil contraction; latency (ms), duration (ms) and velocity (mm/s) of pupil dilation. Baseline pupil diameter for each eye was calculated as the average pupil diameter over a 5-second period prior to stimulus onset. Latency was defined as the elapsed time between light onset and the start of constriction. Pupil contraction amplitude (in mm) was the difference of pupil size at its peak contraction from baseline. To normalise pupillary responses, the absolute pupil contraction amplitude was converted to a relative pupil constriction amplitude in percent from baseline as described in the study of Kelbsch C et al. [13].

Anisocoria was defined as equal to or >0.4 mm difference of pupillary diameters between the right and left eyes [16]. In addition, an arbitrary criteria was proposed to find anisocoric pupil percentage rates in normal people under various lighting conditions. The pupils referred as anisocoric if the ratio of the difference between pupil diameters to smaller pupil diameter is equal to or above 6%.

Data were analysed using Statistical Package for the Social Sciences (SPSS Inc., Chicago, Illinois, USA) version 20.0. The distribution pattern of the variables was tested by visual (histogram and probability graphs) and analytical (Kolmogorov–Smirnov/Shapiro–Wilk test) tools. The independent *t* test was used for the normally distributed data; the Mann–Whitney *U* test used for nonnormally distributed data. The data from both eyes of all participants were used for statistical analysis. Gwet's AC1 statistic was used to test inter-ocular reliability. Differences in anisocoric and isocoric pupils were modelled with a generalised linear mixed model (GLMM, adjusted for age and gender). A two-tailed "*p*" value less than 0.05 was considered as statistically significant.

RESULTS

In total, 390 eyes of 195 participants [96 females (49.2%) and 99 males (50.8%)] with a mean age of 38.4 ± 18.9 years (range 7–78 years) met the inclusion criteria. The static and dynamic pupillometry parameters were not significantly different between males and females ($P > 0.05$ for all; 95% confidence interval). However, age was found to be statistically significantly and negatively correlated with pupillary diameters ($p < 0.001$ for all illumination levels). Among the dynamic pupillometry parameters, velocity of pupil contraction ($r = -0.439$, $p \leq 0.001$) and velocity of pupil dilation ($r = -0.233$, $p = 0.002$) were inversely and latency of pupil contraction ($r = 0.232$, $p = 0.001$) was positively correlated with age. Relative amplitude of pupil contraction, duration of pupil contraction, latency of pupil dilation and duration of pupil dilation were not statistically significantly correlated with age ($r = -0.002$, $p = 0.968$; $r = -0.057$, $p = 0.433$; $r = 0.024$, $p = 0.737$; $r = -0.080$, $p = 0.266$). There was no significant difference between the right and left eyes of the participants in terms of BCVA, spherical equivalent of refraction, IOP and static and dynamic pupillometry measurements ($P > 0.05$ for all; 95% confidence interval). The mean values of static and dynamic pupillometric parameters of both eyes of the study participants are shown in detail in Table 1 ($P > 0.05$ for all; 95% confidence interval).

Based on the anisocoria definition of equal to or more than 0.4 mm difference of pupillary diameters between the right and left eyes, 3.1% of the participants under high photopic, 5.6% under low photopic, 12.8% under high mesopic and 17.4% under low mesopic illumination levels exhibited anisocoria. According to the aforementioned arbitrary anisocoria definition, 16.4% of the participants under high photopic, 18.5% under low photopic, 19% under high mesopic and 20% under low mesopic illumination levels exhibited anisocoria. Prevalence of anisocoria based on different definitions (inter-ocular pupillary diameter differences more than 0.2, 0.4, 0.6 mm or 6%) under various lighting conditions are shown in detail in Table 2 and the prevalence of anisocoria (≥ 0.4 mm or 6%) based on different age groups are shown in Table 3.

The inter-ocular comparison of dynamic pupillometry parameters in 34 participants who exhibited physiological anisocoria (≥ 0.4 mm) under low mesopic condition, and the comparison of these results with those of participants with no observable anisocoria were shown in detail in Table 4. There was a statistically significant difference between the mean absolute amplitudes of pupil contraction of the anisocoric small pupil, the fellow larger pupil and the isocoric pupil (GLMM, $p < 0.001$). The mean amplitude of anisocoric small pupils' contraction was lower than the mean amplitudes of pupil contraction of both isocoric and anisocoric large pupils ($p < 0.001$, $p < 0.001$, respectively, post-hoc test). There was also a statistically significant difference between the mean relative amplitudes of pupil contraction of the anisocoric small pupil, the fellow larger pupil and the isocoric pupil (GLMM, $p = 0.009$). The relative amplitude of anisocoric small pupils' contraction was lower than the relative amplitudes of pupil contraction of both isocoric and anisocoric large pupils ($p = 0.021$, $p = 0.035$, respectively, post-hoc test). There was a statistically significant difference between the mean velocities of pupil contraction of the anisocoric small pupil, the fellow larger pupil and the isocoric pupil (GLMM, $p = 0.043$). The mean velocity of anisocoric small pupils' contraction was lower than the mean velocity of anisocoric large pupils' contraction ($p = 0.013$, post-hoc test). Schematic graph of contraction amplitude in mm for small and large pupils of subjects with physiological anisocoria and pupils of subjects with no observable anisocoria were depicted in Fig. 1.

Bivariate correlation analysis showed that there was a negative correlation between baseline pupil diameter and relative amplitude of pupil contraction ($r = -0.221$, $p < 0.001$) of 161 healthy participants without physiological anisocoria, while no correlation

Table 1. Inter-ocular comparative analysis of baseline pupillometry characteristics of the study participants.

<i>n</i> = 195	Right mean + SD	Left Mean + SD	<i>p</i>
Photopic high PD (mm)	2.88 + 0.74 (2.1–4.1)	2.89 + 0.74 (2.1–4.1)	0.977
Photopic low PD (mm)	3.64 + 0.57 (2.3–5.3)	3.64 + 0.56 (2.4–5.3)	0.971
Mesopic high PD (mm)	4.85 + 0.95 (2.8–7.3)	4.86 + 0.96 (2.9–7.4)	0.961
Mesopic low PD (mm)	6.31 + 0.97 (3.5–8.7)	6.34 + 0.94 (3.3–8.8)	0.816
Baseline pupil diameter (mm)	5.67 + 0.91 (3.5–7.9)	5.69 + 0.88 (3.5–8.0)	0.783
Amplitude of pupil contraction (mm)	1.75 + 0.31 (0.9–2.5)	1.78 + 0.38 (0.7–4.3)	0.709
Amplitude of pupil contraction (%)	31.77 + 3.48 (18.00–41.67)	31.96 + 3.72 (20.00–53.03)	0.640
Latency of pupil contraction (ms)	253.1 + 61.0 (12–362)	257.8 + 61.7 (8–501)	0.756
Duration of pupil contraction (ms)	613.5 + 95.3 (424–1239)	615.4 + 96.2 (413–963)	0.961
Velocity of pupil contraction (ms/s)	5.64 + 0.92 (2.9–8.2)	5.68 + 1.08 (1.0–10.2)	0.986
Latency of pupil dilatation (ms)	866.6 + 79.5 (669–1267)	873.3 + 82.2 (700–1296)	0.561
Duration of pupil dilatation (ms)	1602.9 + 102.0 (1004–1831)	1581.1 + 120.5 (1104–1798)	0.148
Velocity of pupil dilatation (ms/s)	2.21 + 0.81 (1.3–7.8)	2.26 + 0.98 (0.4–8.6)	0.911

Mann–Whitney *U* test.

SD standard deviation.

Table 2. Prevalence of anisocoria based on various definitions of diameter difference under various light conditions (*n* = 195).

Luminous intensity	Cut-off	Anisocoria <i>n</i> (%)
Photopic high	≥0.2 mm	37 (19.0)
	≥0.4 mm	6 (3.1)
	≥0.6 mm	3 (1.5)
	≥6%	32 (16.4)
Photopic low PD	≥0.2 mm	64 (32.8)
	≥0.4 mm	11 (5.6)
	≥0.6 mm	5 (2.6)
	≥6%	36 (18.5)
Mesopic high PD	≥0.2 mm	83 (42.6)
	≥0.4 mm	25 (12.8)
	≥0.6 mm	8 (4.1)
	≥6%	37 (19)
Mesopic low PD	≥0.2 mm	103 (52.8)
	≥0.4 mm	34 (17.4)
	≥0.6 mm	23 (11.8)
	≥6%	39 (20)

PD pupillary diameter.

was observed between baseline pupil diameter and relative amplitude of pupil contraction ($r = 0.170$, $p = 0.154$) of the 34 participants who exhibited physiological anisocoria.

DISCUSSION

In this study, we performed an inter-ocular comparative analysis of static pupillometric measurements of healthy individuals in order to detect the subjects with physiological anisocoria in high photopic, low photopic, high mesopic and low mesopic lighting conditions; and investigated the autonomic functional differences between larger and fellow pupils of these subjects based on dynamic pupillometric parameters. The present study provides first evidence of the possible underlying mechanism in physiological anisocoria using dynamic pupillometry. Our results demonstrated a significant difference of the pupil contraction amplitude in the patients with physiologic anisocoria.

The pupillary diameters are well known to be affected with age [8, 22, 23]. Our study included patients with a wide range of ages and in consistency with previous studies, there was a negative correlation of pupil diameters with age in all four lighting conditions. Among the dynamic pupillometry parameters, velocity of pupil contraction, and velocity of pupil dilation values were inversely and latency of pupil contraction was positively correlated with age.

Few studies in the literature investigated the prevalence of physiological anisocoria and revealed 8–43.1% prevalence, depending on the definition of anisocoria, level of illumination and measurement method. Meyer tried to detect anisocoria by gross observation using a flashlight in 1947 [18]. Lam et al. used self-developing colour photographs of the pupils, taken by Loewenfeld-Roskoth pupil camera, in dim light in 1987, and used an infra-red video system under various lighting conditions to obtain the pupillary measurement in 1996 [17, 19]. In the recent studies, Steck et al. and Rickmann et al. demonstrated anisocoria in healthy subjects under constant and adjustable illumination levels with the monocular digital VIP-200 pupillometer (NeuroOptics, Irvine, CA, USA) and the binocular digital PupilX pupillometer (Albomed GmbH, Schwarzenbruck, Germany), respectively [15, 16]. Steck et al. reported that 23.8% of study participants exhibited physiological anisocoria in photopic condition, but in subgroup analysis, the percentage of physiological anisocoria increased under scotopic, low mesopic, and high mesopic light settings. Rickmann et al. found higher anisocoria under scotopic and mesopic illuminance condition compared to photopic illuminance condition. In the current study, anisocoria investigated by the automatic quantitative pupillometry system and the results (3.1% under high photopic; 5.6% under low photopic; 12.8% under high mesopic, and 17.4% under low mesopic illumination) were in agreement with the previously reported studies that the rates of physiological anisocoria found to be increased from photopic to low mesopic conditions when we defined anisocoria as equal to or more than 0.4 mm difference of pupillary diameters. However, this definition of anisocoria might potentially make our analysis biased. When analysis were made according to a ratio criterion of 6%, the percentage of anisocoric eyes became nearly even across different luminance conditions (16.4% under high photopic; 18.5% under low photopic; 19% under high mesopic, and 20% under low mesopic illumination).

Few studies investigated the relationship of anisocoria with age in the literature. The prevalence of anisocoria found to be

Table 3. Prevalence of anisocoria in different age groups for all illumination levels ($n = 195$).

Cut-off	Illumination	0–10 years	11–20 years	21–30 years	31–40 years	41–50 years	51–60 years	>60 years
		($n = 16$)	($n = 30$)	($n = 29$)	($n = 24$)	($n = 31$)	($n = 44$)	($n = 21$)
≥0.4 mm	Photopic high	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	4 (9.1)	2 (9.5)
	Photopic low	2 (12.5)	2 (6.7)	0 (0)	1 (4.2)	0 (0)	2 (4.5)	4 (19)
	Mesopic high	2 (12.5)	3 (10)	2 (6.9)	5 (20.8)	0 (0)	7 (15.9)	6 (28.6)
	Mesopic low	4 (25)	3 (10)	5 (17.2)	3 (12.5)	4 (12.9)	5 (11.4)	10 (47.6)
≥6%	Photopic high	3 (18.8)	2 (6.7)	2 (6.9)	3 (12.5)	1 (3.2)	13 (29.5)	8 (38.1)
	Photopic low	2 (12.5)	4 (13.3)	0 (0)	4 (16.7)	3 (9.7)	11 (25)	12 (57.1)
	Mesopic high	2 (12.5)	4 (13.3)	2 (6.9)	8 (33.3)	3 (9.7)	9 (20.5)	9 (42.9)
	Mesopic low	4 (25)	3 (10)	5 (17.2)	4 (16.7)	4 (12.9)	7 (15.9)	12 (57.1)

Table 4. Comparison of dynamic pupillometry components according to physiologic anisocoria (≥0.4 mm).

	Isocoric	Anisocoric (small pupil)	Anisocoric (large pupil)	<i>p</i>
	Mean ± se	Mean ± se	Mean ± se	
Baseline pupil diameter (mm)	5.74 ± 0.05	5.27 ± 0.11	5.60 ± 0.11	<0.001**
Amplitude of pupil contraction (mm)	1.79 ± 0.02	1.58 ± 0.05	1.77 ± 0.05	<0.001**
Amplitude of pupil contraction (% of baseline)	32.28 ± 0.38	29.94 ± 0.91	32.36 ± 0.91	0.009*
Latency of pupil contraction (ms)	256.58 ± 4.3	244.97 ± 9.94	257.15 ± 9.94	0.381
Duration of pupil contraction (ms)	611.32 ± 6.28	634.81 ± 15.52	618.27 ± 15.52	0.368
Velocity of pupil contraction (mm/s)	5.66 ± 0.06	5.46 ± 0.15	5.81 ± 0.15	0.043*
Latency of pupil dilation (ms)	867.92 ± 5.34	879.78 ± 13.08	875.42 ± 13.08	0.697
Duration of pupil dilation (ms)	1593.3 ± 7.22	1569.26 ± 17.97	1606.28 ± 17.97	0.197
Velocity of pupil dilation (mm/s)	2.2 ± 0.06	2.4 ± 0.15	2.36 ± 0.15	0.435

Generalised Linear Mixed Models (GLMMs) were conducted, gender and age corrected estimates were reported as mean ± se.

* $p < 0.05$; ** $p < 0.01$.

increased with age, particularly over 60 years of age [16, 24]. Rickmann et al. defined any difference in diameters between right and left eyes as anisocoria in normal subjects and found that both the prevalence of anisocoria and the difference in pupil diameters increased in relation to age for all illumination levels by digital pupillometer [16]. Lam et al. found less anisocoria in the subjects with 25 years of age or less compared to the subjects with 50 years of age but this reduction was unable to reach statistical significance due to the small sample size of the study [17]. In our study, the distribution of anisocoria with age seems to increase above 60 years for all illumination levels.

Our study revealed significant difference between the smaller pupil and the fellow pupil in terms of amplitude of pupil contraction by using dynamic pupillometry in subjects with physiological anisocoria. Smaller pupils had significantly decreased pupil contraction amplitude and pupil contraction velocity with no difference in latency compared to fellow pupil. According to the assumption of parasympathetic innervation inequality in which smaller pupil may have increased baseline parasympathetic nervous system activity on the sphincter muscle, there might be a residual contraction without stimulus in the small pupils; therefore, the percentage of contraction response to the light stimuli might be lower in the small pupils than large pupils in subjects with physiological anisocoria. In addition, consideration has been given in our study as to how this reduced dynamic range of the small pupils' movement might be affected by the baseline pupil diameter of the subjects. We hypothesise that the relatively miotic pupil may reduce the effect of stimulus depending on the pupil size and cause reduced contraction amplitude. However, a negative correlation was observed between the baseline pupil diameter and the relative contraction amplitude across a wide range of pupil size in the healthy subjects. Furthermore, the

decrease in the amplitude and velocity of pupil contraction in the small pupils of the anisocoric healthy subjects could be attributed to unequal retinal receptor excitation to the same stimulus caused by a possible interocular difference in photoreceptor distribution of the anisocoric pupils. Conversely, the difference in the amplitude of pupil contraction could be attributed to clinically undetectable mechanical properties of the iris which affect the amplitude measurements more than latency and are known to constrain the movement of the pupil that occurs after the onset of contraction [25]. Pupil latency reveals visual processing delays in parallel with the amount of afferent damage, and in this context, is similar to the visual evoked potential [26]. In our study, the difference in the latency of pupil contraction between the anisocoric pupils was found to be statistically insignificant in healthy participants.

To the best of our knowledge, this study is the first to investigate dynamic pupillometry differences in subjects with physiological anisocoria by using automatic quantitative pupillometry system. In addition to the many strengths of this study, there are some limitations, such as the small sample size and cross-sectional nature. Moreover, there is no consensus on whether instantaneously detected anisocoria in healthy subjects should be defined as physiological anisocoria or random pupillary changes. Therefore, these results are needed to be confirmed by additional longitudinal studies investigating whether pupillary changes remain stable over time.

In conclusion, the amplitude and velocity of pupil contraction of smaller pupils were lower when compared to fellow larger pupils in the patients with physiological anisocoria.

Summary

What was known before

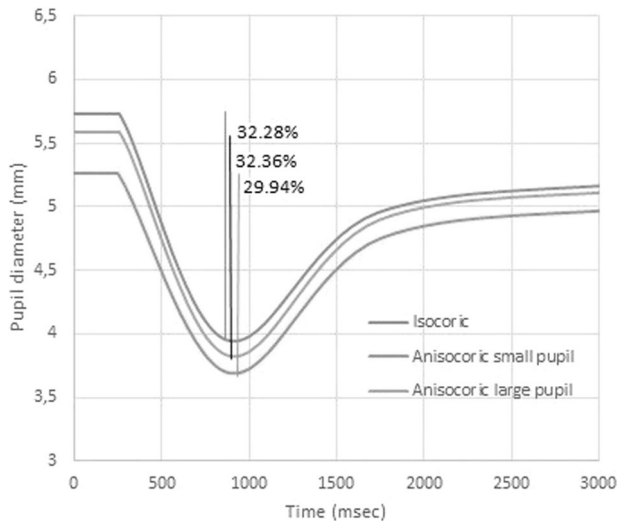


Fig. 1 Schematic graph of contraction amplitude in mm for small and large pupils of subjects with physiological anisocoria and pupils of subjects with no observable anisocoria. % refers to relative contraction amplitude corrected for baseline pupil diameters.

- The prevalence of physiological anisocoria is between 8% and 43.1%, depending on the definition of anisocoria, level of illumination and measurement method.
- The rates of physiological anisocoria increases from photopic to scotopic conditions.

What this study adds

- This study demonstrated that the amplitude and velocity of pupil contraction of smaller pupils were lower when compared to fellow larger pupils in the patients with physiological anisocoria.
- These findings may have value for interpreting the significance of the previous study results and planning the design of future studies using dynamic pupillometry.

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AUTHOR CONTRIBUTIONS

Study conception and design: HKH, MAŞ, SD, PY. Acquisition of data: HKH, NY. Analysis and interpretation of data: HKH, MAŞ, NY, SD, PY. Drafting of paper: HKH, MAŞ, NY, SD, PY. Critical revision: HKH, MAŞ, PY.

COMPETING INTERESTS

The authors declare no competing interests.

ADDITIONAL INFORMATION

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