Original Article

How does high-refractive error affect quantitative pupillometry values?

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Purpose: To evaluate the static and dynamic pupil responses in differentiating eyes with high-refractive errors from emmetropic controls. **Methods:** The study was conducted using data obtained from 36 participants with high myopia, 26 participants with high hyperopia, and 38 age-gender-matched controls. The cycloplegic spherical equivalent refraction (SER), axial length (AL), and pupil responses were examined. In static pupillometry, pupil diameters were recorded at scotopic, mesopic, and photopic light intensities. The mean pupil dilation speed was calculated according to changes in pupil size over time, as dynamic pupillometry. **Results:** The mean scotopic and mesopic pupil diameters were smaller in high hyperopic eyes compared with high myopic and control eyes ($P < 0.05$). The photopic pupil diameter in the high hyperopic group was significantly lower than in the high myopic group ($P = 0.003$). There was no statistical difference between the high myopia and control groups regarding static pupillometry ($P > 0.05$). No significant difference was noted between the refractive groups regarding the speed of pupil dilation ($P = 0.241$). While SER and AL were correlated with scotopic and mesopic pupil diameters ($P < 0.05$), no correlation was observed with photopic pupil diameter or the speed of pupil dilation ($P > 0.05$). **Conclusions:** The difference in static pupil responses was prominent in high hyperopic eyes compared to high myopic and emmetropic eyes. Unlike static pupil responses, the speed of pupil dilation was not affected by high-refractive errors.

Key words: Dynamic pupillometry, high hyperopia, high myopia, pupil dilation speed, static pupillometry

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Pupil size is adjusted by contraction and dilation of the iris muscles in response to light to maintain visual acuity over a wide range of luminance and reduce the effect of bright light on photoreceptors. Although studies have suggested the light reflex as the most important determinant of pupil size, clinical investigations on other factors such as age, gender, refractive status, and iris color and their possible relationship with pupil size have also been postulated.[1-5]

It is well-established that pupil size decreases with increasing age and luminance.[1,3,4] Since there is a discordance between the axial length (AL) of the eye and its optical power, it is supposed that myopic eyes have larger pupil sizes than emmetropic and hyperopic eyes.[6-8] However, studies attempting to clarify the role of refractive status on pupil size have reported varied outcomes due to different methodologies.[3-5,9] Most previous studies compared the difference in mean pupil size while ignoring the relative influences of contributing factors.

Identifying the interactions between high-refractive errors and pupil responses is crucial to improving visual performance, especially in correcting high-refractive errors. Studies have thus been interested in the importance of pupil size in developing optical corrective approaches or refractive surgical procedures.[10-12] Precise determination of pupil diameter under all lighting conditions, imitating real life, is desirable. Recent advancements in pupillometry have enabled the analysis of static and dynamic pupil responses as part of the routine ophthalmological examination. In this regard, these automated systems provide objective and reproducible measurements of light responses under different ambient light conditions.[13]

Despite studies on factors affecting pupil physiology, the quantitative impact of high-refractive errors on pupillary responses has remained equivocal due to relatively limited studies in the literature.[9,14,15] Therefore, this study aimed to quantitatively evaluate the static and dynamic pupillary responses in patients with high-refractive errors and compare them with emmetropic participants to delineate their relationship.

Methods

This cross-sectional study was approved by the local ethical review committee (Registration number: 10354421-2023/13-06), and written informed consent was obtained from each participant. The study was performed in accordance with the Declaration of Helsinki.

Patients aged ≥18 years who were diagnosed with higher refractive error were enrolled in this study. Participants were divided into two groups based on the cycloplegic spherical equivalent refraction (SER). Myopia greater than −6.00 D was classified as the high myopia group, and hyperopia more than +4.00 D was classified as the high hyperopia group. The control group was composed of age and gender-matched

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healthy participants with SER of ± 1.50 D. Astigmatism higher than 1D was not included in all groups.

Participants with best corrected visual acuity (BCVA) ≥0.2 LogMAR, a history of previous ocular surgery or ocular disease (strabismus, amblyopia, nystagmus, uveitis), diseases affecting pupillary motility or the visual pathway, taking medications affecting pupillary reactions, and consuming alcohol, caffeine, or nicotine within the 24 hours before the examinations were excluded from the study. Participants with ocular media opacities and those who were uncooperative to undergo pupil measurement assessment were also excluded.

Each participant underwent a complete ophthalmologic examination, including BCVA, intraocular pressure measurement using a Goldmann applanation tonometer, slit-lamp biomicroscopy, and a dilated posterior segment examination. One drop of cyclopentolate hydrochloride 1% was instilled three times at 10-minute intervals to obtain the cycloplegic SER. Autorefraction was performed using an automatic refractor keratometer NIDEK ARK-1 (NIDEK Co Ltd., Tokyo, Japan) 30 minutes after topical administration of the last drop, and an average of three measurements was taken. A noncontact Aladdin HW3.0 biometer (Topcon, Tokyo, Japan) was used to measure AL.

Pupil dilation and any contact examination procedures were avoided before the pupillometry assessment. Pupil responses were recorded using an automated pupillometry system integrated into the Sirius topography device (CSO, Firenze, Italy) by the same clinician (FY). This quantitative pupillometry system allows the evaluation of static and dynamic pupil diameters. After 5 min of dark adaptation, measurements were taken based on the methods of Prakash *et al*.[16] in the following order: scotopic (0.4 lux), mesopic (4 lux), and photopic (40 lux) luminance. Additionally, the light settings were verified by a photometer. Participants were asked to look at a target 3 m away and not to focus on the LED source to prevent the accommodative reflex.

Dynamic pupillometry (500 lux) was conducted at the end of the examination. Dynamic measurement captures pupil dilation and size from maximum illumination to a non-light condition. The mean pupillary dilation speed was calculated by dividing the changes in pupil size by the time interval, which was the difference between the 0^{th} and 15^{th} seconds (mm/s).

All measurements were taken at the same time of day (10:00 a.m to 12:00 p.m) to reduce the effect of circadian rhythm on pupillary function. Three consecutive recordings were captured under the same standardized scotopic room conditions to use pupillometry as the only light source, and the average of these recordings was considered for analysis. Only the right eye of each participant was chosen to obtain data in this cross-sectional study. All measurements were examined for differences in pupil sizes (scotopic, mesopic, and photopic) and mean pupil dilation speed data at 15 seconds.

Statistical analysis

Statistical data were analyzed using SPSS software version 23 (Statistical Package for the Social Sciences, Chicago, IL, USA). The normality of the variables was confirmed with the Kolmogorov-Smirnov test. Descriptive statistics are represented as mean ± standard deviation, numbers, and percentages. The Chi-square test was chosen to compare categorical variables. The comparisons of continuous variables between groups were carried out with Kruskal–Wallis H tests, followed by Dunn's post-hoc pairwise comparison. The one-way analysis of variance (ANOVA) test with post-hoc Bonferroni correction for pairwise comparison was used to compare statistically significant differences in pupillary responses between groups. Spearman correlation coefficient analysis was conducted to define the role of refractive error variables (SER and AL) on pupillometry responses. A *P* value below 0.05 was accepted as statistically significant.

Results

This study enrolled one hundred eyes of 100 patients (47 males and 53 females), comprising 36 from the high myopia group, 26 from the high hyperopia group, and 38 from the control group. Significant differences were observed between refractive groups in terms of BCVA, SER, and AL, but not for age and gender ($P = 0.003$, $P < 0.001$, $P < 0.001$, $P = 0.411$, and $P = 0.218$, respectively), as demonstrated in Table 1. The mean SER was −7.90 ± 1.81 D in the high myopia group, +5.02 ± 1.07 D in the high hyperopia group, and −0.30 ± 0.38 D in the control group. The mean AL was highest in the high myopia group and lowest in the high hyperopia group ($P < 0.001$).

All static and dynamic pupillometry parameters of the refractive groups are illustrated in Table 2. The mean scotopic and mesopic pupil diameters were smaller in high hyperopic

Table 1: Clinical and demographic characteristics of participants

	High myopia group (*n*=36)	High hyperopia group (*n*=26)	Control group (*n*=38)	*P*	*P*¹	*P*²	*P*³
Age (year)	26.03±5.80 (18 to 35)	29.54±8.30 (18 to 39)	26.18±5.45 (20 to 39)	0.411*	0.127	0.789	0.101
Male/Female	13/23	15/11	19/19	0.218¥	0.097	0.233	0.552
Visual acuity (LogMAR)	0.03±0.05 (0.00 to 0.15)	0.02±0.05 (0.00 to 0.15)	0.01±0.01 (0.00 to 0.05)	**0.003***	0.526	**0.002**	0.065
Spherical equivalent (D)	−7.90±1.81 (−6.00 to−12.50)	+5.02±1.07 (+4.00 to+7.75)	−0.30±0.38 (−1.25 to 0.25)	**<0.001***	**<0.001**	**<0.001**	**<0.001**
Axial length (mm)	25.88±0.60 (24.10 to 27.44)	21.73±0.60 (19.69 to 22.89)	22.82±0.46 (22.12 to 24.03)	**<0.001***	**<0.001**	**<0.001**	**<0.001**

*Kruskal–Wallis test; ¥Chi-square test; ¹Differences between high myopia and high hyperopia; ²Differences between high myopia and control; ³Differences between high hyperopia and control, Bold *P* values in P1, P2, and P3 columns show Dunn's test for post-hoc multiple comparisons eyes compared with high myopic and control eyes ($P < 0.001$ and $P < 0.001$, high myopia vs high hyperopia; $P < 0.001$ and $P = 0.024$, control vs high hyperopia, respectively). No significant difference was observed between high myopic and control eyes in regard to scotopic and mesopic pupil diameters ($P = 0.571$ and $P = 0.253$, respectively). The photopic pupil diameter in the high hyperopic group was significantly lower than in the high myopic group ($P = 0.003$). There was no difference in photopic pupil diameter when comparing the high-refractive error groups to the control group ($P > 0.05$). No significant difference in the speed of pupil dilation was noted between the refractive groups ($P = 0.241$).

The correlation coefficients of SER and AL with pupillometry parameters in high-refractive error groups are shown in Table 3. As depicted in Figs 1 and 2, scotopic and mesopic pupil diameters were positively correlated with AL but negatively correlated with SER ($P < 0.05$ for all). The interactions of photopic pupil diameter with these parameters did not reach a significance level ($P > 0.05$). No correlations were observed between SER and AL with the speed of pupil dilation ($P > 0.05$).

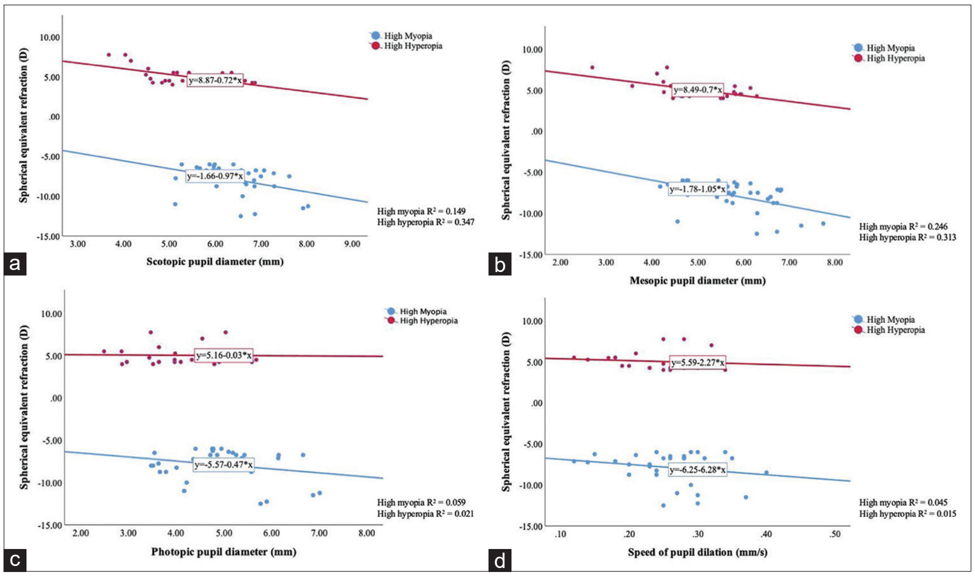

Figure 1: Scatter plot showing the relationship between SER and scotopic pupil diameter (a), mesopic pupil diameter (b), photopic pupil diameter (c), and pupil dilation speed (d) values

Table 2: Comparisons of pupillometry characteristics of the refractive groups

	High myopia group (*n*=36)	High hyperopia group (*n*=26)	Control group (*n*=38)	*P*	*P*¹	*P*²	*P*³
Scotopic pupil diameter (mm)	6.41±0.72 (5.13 to 8.03)	5.36±0.89 (3.68 to 6.87)	6.32±0.58 (4.99 to 7.35)	**<0.001**	**<0.001**	0.571	**<0.001**
Mesopic pupil diameter (mm)	5.83±0.85 (4.18 to 7.74)	4.96±0.87 (2.70 to 6.29)	5.51±0.66 (4.21 to 6.78)	**<0.001**	**<0.001**	0.253	**0.024**
Photopic pupil diameter (mm)	4.96±0.93 (3.48 to 7.01)	4.22±0.91 (2.49 to 5.68)	4.51±0.63 (3.08 to 5.69)	**0.002**	**0.003**	0.062	0.517
Speed of pupil dilation (mm/s)	0.26±0.06 (0.12 to 0.40)	0.24±0.05 (0.12 to 0.34)	0.27±0.07 (0.15 to 0.41)	0.241	0.884	0.499	0.278

*ANOVA test. ¹Differences between high myopia and high hyperopia; ²Differences between high myopia and control; ³Differences between high hyperopia and control, Bold *P* values in all columns indicate the results of post-hoc Bonferroni pairwise comparisons

Table 3: Correlation coefficients of SER and AL with pupillometry parameters in high-refractive errors

	High myopia				High hyperopia			
	SER		AL		SER		AL	
	r	*p*	*r*	*p*	*r*	*p*	*r*	*p*
Scotopic pupil diameter (mm)	−0.421	**0.011**	0.332	**0.048**	−0.452	**0.021**	0.463	**0.017**
Mesopic pupil diameter (mm)	−0.502	**0.002**	0.408	**0.013**	−0.413	**0.036**	0.565	**0.003**
Photopic pupil diameter (mm)	−0.072	0.678	0.152	0.376	−0.014	0.946	0.290	0.151
Speed of pupil dilation (mm/s)	−0.105	0.542	0.342	0.061	−0.261	0.197	0.157	0.444

*Spearman's correlation coefficient, bold *P* values indicate the results of Spearman's correlation, and *r* values indicate Spearman's correlation coefficients

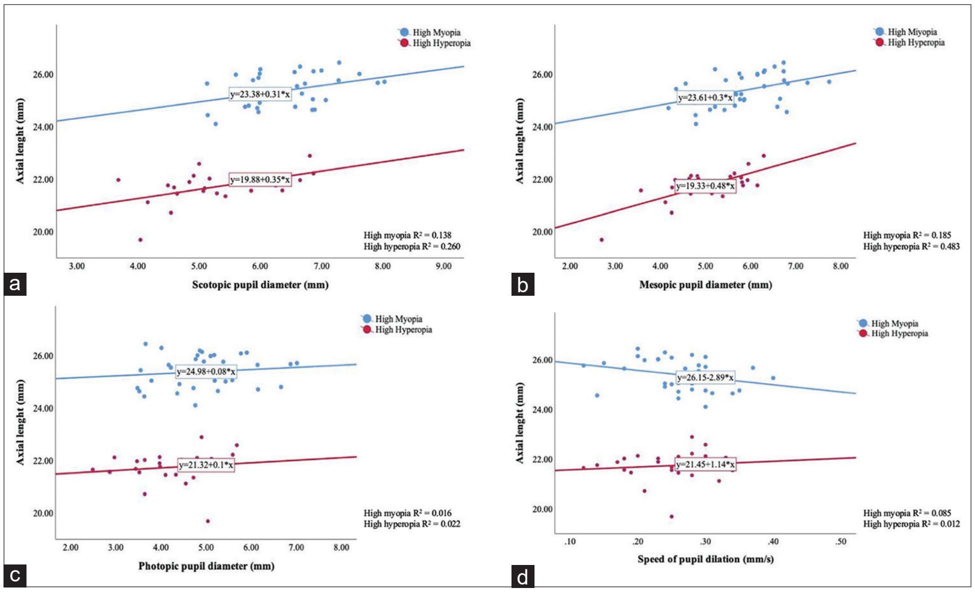

Figure 2: Scatter plot showing the relationship between AL and scotopic pupil diameter (a), mesopic pupil diameter (b), photopic pupil diameter (c), and pupil dilation speed (d) values

Discussion

The present study revealed that the difference in static pupil responses was prominent in high hyperopic eyes compared to high myopic and emmetropic eyes. As a dynamic response, the pupil dilation speed was similar between the groups, pointing to an independent value in pupillometry analysis. Furthermore, the interactions of SER and AL with pupil responses may support our hypothesis.

Conflicting studies have been published in the literature about the effect of refractive status on pupil size. A study by Winn *et al*.[3] in their study of healthy individuals aged 17–83 years reported that pupil size reduced with increasing age for each luminance, and refractive errors did not exert a significant effect on pupil width. Another study by Orr *et al*.[9] confirmed no influence of refractive error when the confounding factor of age was removed in young participants wearing refractive correction. Despite these opposing views, recent studies have addressed the magnitude of preoperative refractive errors as a determinative factor on mesopic pupil size in refractive surgery candidates.[5,17]

Studies have proven that pupil size was larger in myopes and emmetropes than in hyperopes when measured under varying lighting conditions.[1,5,17,18] In a cohort of 219 participants aged 20 to 69 years, similar results have been reported under scotopic and mesopic lighting conditions by Lee *et al*.[18] In a study reviewing medical records of 412 refractive surgery candidates, Çakmak *et al*.[5] mentioned a larger mesopic pupil size in myopia than in hypermetropia. It is noteworthy that there is a non-homogeneous distribution of participants across age and refractive error groups. In a large-scale retrospective study on 13.959 refractive surgery candidates, the differences in mesopic pupil size between all the refractive groups (myopic astigmatism, hyperopic astigmatism, and high astigmatism) have also been reported.[17] In this regard, the astigmatism values of all participants limited any effect of astigmatism on pupil diameter in our cohort.

Guillon *et al*.[1] emphasized that the refractive error was a differentiating factor, but only in the youngest population (≤21 years) at low luminance and in the early presbyopic population (43-52 years) at medium and high luminance. According to pupil photographs using an infrared video camera system, the higher myopes (>–3.63 D) had larger pupil diameters than the low myopes, emmetropes, and hyperopes in the youngest population.[1] In a later study, Lee *et al*.[18] mentioned that the most influential factor affecting pupil size was age, and the second factor was the refractive state, followed by the illuminance below 50 years of age. Given the wide range of refractive errors between the groups in the aforementioned studies, it is not possible to draw any conclusions about pupil size in those with high-refractive errors. This present study extends previous works by revealing the effect of high-refractive errors in different illumination conditions in the prepresbyopic population.

In their study of patients aged 6–40 years with hyperopic anisometropic amblyopia, Yetkin *et al*.[14] demonstrated lower scotopic pupil diameter in high hyperopic eyes (ranging from +2.25 D to +7.75 D) than in healthy eyes. It was stated that these findings were associated with the possibility of anisocoria and abnormalities in the development of the visual system in amblyopia.[14] In the current study, similar relevance was also found in mesopic luminance but did not reach a significance level in photopic luminance. Kızıltoprak *et al*.[15] reported no difference in scotopic and mesopic pupil diameters in high myopic amblyopic eyes (ranging from −3.50 D to −13.00 D) compared to control eyes, similar to our findings. On the other hand, patients with myopic amblyopia had larger pupil diameters at low photopic and high photopic compared to healthy controls.[15] In agreement with these studies, our study suggests that high-refractive errors may also produce variability in static pupil responses under different light intensities, even without amblyopia.

Similarly, these studies on anisometropic amblyopia have reported no differences in the dilation component of dynamic pupil responses between the study and healthy eyes.[14,15] As reported by Yetkin *et al*.,[14] only the amplitude of pupil contraction was noted to be decreased in high hyperopic eyes compared to control eyes in dynamic pupillometry. It is known that distinguishing normal from pathological variation could be difficult for Relative afferent pupillary defect (RAPD) smaller than 0.3 log units.[19] Meanwhile, the magnitude of SER and AL did not correlate with the pupil dilation speed in our study, even in the presence of interactions with pupil diameter. Thus, the speed of dilation seems to be independent of these parameters.

Previous studies have indicated that 20% to 70% of expected pupil diameter could be predicted by age, spherical and astigmatic refractive error, and luminance.[1,5] Mesopic pupil size was inversely proportional to the magnitude of spherical equivalent, as postulated by Çakmak *et al*.[8] This inverse relationship was also detected in our population with high-refractive errors at scotopic and mesopic luminance levels. Likewise, a positive correlation between AL and pupil size has been established.[20] The correlations of pupil responses with SER and AL can be presumed to strengthen our hypothesis.

Smaller pupil sizes in hyperopes than in myopes and emmetropes may have been the result of the relationship between pupil magnification and the chief ray angle.[8,18,21] The chief ray angle produces the appearance of the pupil larger than the iris. The entrance of the pupil is formed by the cornea and is placed approximately 0.5 mm in front of the real pupil. This virtual image of the pupil has also been in approximately 14% magnified form.[8,21] It should be kept in mind that higher corneal power and steeper cornea result in a larger pupil entrance than the iris. Despite conflicting evidence, the ocular biometric parameters, such as AL, white-to-white, anterior chamber depth, and vitreous depth, are also known to be larger in myopia.[1-3,22]

Guillon *et al*.[1] mentioned that the magnitude of changes in pupil diameters reduced as luminance was enhanced, and the most prominent difference in pupil diameters among refractive status was achieved at low luminance. It is well known that the optimal assessment of pupillary reactivity is achieved under low-light conditions.[23] Therefore, the lack of interactions at photopic luminance could be explained by a lesser degree of differentiation in pupil responses at high luminance in our study. Considering relatively small effects, multifactorial confounding factors, such as the state of adaptation, the level of alertness, intelligence, and cognitive processes, have also been postulated in the complexity of pupil responses.[24,25] The discrepancies in our results could have been attributed to causative and developmental factors as confounders of our study.

This study had some limitations. The small sample size of our population may have limited the generalizability and validity of the results. Also, it could not provide any information about predicting pupil responses, as reported in previous studies.[1,5] Second, the fixation target of the pupillometry system used in the current study may have led to biased pupil diameters toward the smaller side at each luminance. In myopia, the pupil size is expected to be larger at a near distance because less accommodation is required than in hyperopia and emmetropia. Thus, the possible influences of accommodation must be taken into consideration, especially in the prepresbyopic cohort. Finally, the Sirius device is not able to comprehensively monitor the dynamic component of pupil response, including the speed of pupil contraction and the amount of miosis over time. Nonetheless, the shortcomings of measurement algorithms and technical differences of the devices used in previous studies limit their usability in pupil analysis rather than in automated pupillometry systems.

Conclusion

High-refractive errors have a noticeable impact on pupil diameters but not on pupil dilation speed compared to age and gender-matched healthy emmetropes. Smaller pupils for high hyperopes than high myopes and emmetropes were pronounced under low and mesopic luminance levels. Assessment of pupil responses in patients with high-refractive errors should be kept in mind as a routine component of a thorough refractive workup. Future studies are warranted to better delineate the clinical implications of altered static and dynamic pupil responses in high-refractive errors.

Author contribution

All authors attest that they meet the current ICMJE requirements to qualify as authors.

Contributions of authors: Design of the study (DOK); conduct of the study (DOK, FY);

Collection and management of data (FY); analysis and interpretation of data (DOK, FY);

Preparation of manuscript (DOK, FY); review or approval of manuscript (DOK, FY).

Ethical approval

Ethical approval was obtained from the Ethics Committee of Alanya Alaaddin Keykubat University, Approval Date: 27.09.2023, Approval number: 10354421-2023/13-06, and the study was designed to adhere to the Declaration of Helsinki. Informed consent was obtained from each parent or legal guardian before the examination.

Data availability statement

The datasets generated and/or analyzed in the current study are available from the corresponding author upon reasonable request. Data are not publicly available, and further enquiries can be directed to the corresponding author.

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Conflicts of interest: There are no conflicts of interest.

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