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Relationship Between Autonomic Nervous System Activity and Axial Length in Children

Authors' Contribution:
Study Design A
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Literature Search F
Funds Collection G

BCDEFG 1,2 **Mu Li***
BCDEF 1 **Qiongfang Xu***
BCD 1 **Xiaoqin Yan**
AEF 1 **Junming Wang**
ABCG 1 **Yan Xiang**

1 Department of Ophthalmology, Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, Hubei, PR China
2 Department of Ophthalmology, Wuhan Union Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, Hubei, PR China

* Mu Li and Qiongfang Xu contribute equal to this work

Corresponding Authors: Junming Wang, e-mail: eyedrwjm@163.com, Yan Xiang, e-mail: yanxiang@hust.edu.cn
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Background: The aim of this work was to compare autonomic nervous system activity between eyes with axial and non-axial myopia and to investigate the relationship between autonomic nervous system activity and axial length (AL) in children.

Material/Methods: Seventy-eight eyes of 78 children were included in this study. Static and dynamic pupillary responses, including pupil diameter, latency, and velocity of pupil contraction and dilation, were recorded using automatic pupillometry to evaluate autonomic nervous system activity. AL was measured using the IOL-Master device.

Results: In terms of static pupillary responses, the pupil diameter at mesopic condition (1 candelas/m^2) (PD1) (4.06±0.64 vs 3.80±0.87 mm, *P*=0.045) and pupil diameter at low photopic condition (10 candelas/m^2) (PD10) (3.40±0.49 vs 3.22±0.66 mm, *P*=0.046) were significantly larger in axial myopic eyes than in non-axial myopic eyes. In terms of dynamic pupillary responses, velocity of pupil contraction (Vel-C) (5.93±0.89 vs 6.75±1.60 mm/s, *P*=0.019) and velocity of pupil dilation (Vel-D) (2.28±0.38 vs 2.89±1.17 mm/s, *P*=0.002) were significantly slower in axial myopic eyes than in non-axial myopic eyes. Moreover, PD1 and PD10 were significantly and positively associated with AL, while Vel-C and Vel-D were significantly and negatively associated with AL (all *P*<0.05).

Conclusions: There was significant decrease in autonomic nervous system activity in axial myopia compared with non-axial myopia, and autonomic nervous system activity was significantly and negatively associated with AL in children. Decreases in autonomic nervous system activity in axial myopia may contribute to the excessive axial elongation in pediatric axial myopia.

Keywords: Autonomic Nervous System • Axial Length, Eye • Myopia • Reflex, Pupillary

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Background

Myopia is one of the leading ophthalmologic disorders worldwide [1]. The prevalence of myopia and high myopia are increasing globally at an alarming rate, particularly in East and Southeast Asia [2-6]. It is estimated that by 2050, myopia and high myopia will affect 5 billion and 1 billion people around the world, respectively [7]. Myopia typically develops from the age of 8 years old [8-10]. It is characterized by an excessive axial elongation, which mismatches the focal length of the eye (mainly determined by the refractive power of the cornea and lens), and is one of the leading causes of visual impairment and loss [1,7,11,12]. Therefore, myopia is a worldwide public health concern [1], and it is important to explore the pathogenesis and progression of myopia, and provide the basis and theory for the prevention and control of myopia.

The cause of myopia may be the mismatches between the optical axial length (AL) and the focal length of the eye (mainly determined by the refractive power of the cornea and lens); thus, the focus of light does not fall on the retina but in front of the retina [11,12]. In the first few years after birth, the refractive power of the cornea decreases. Later, during childhood, the refractive power of the lens also decreases [13,14]. Accompanying or shortly after changes in the refractive power of the lens during childhood, AL increases significantly and rapidly in childhood and/or teenage years. Myopia can be regarded as the result of an overshooting of the physiological process of emmetropization, and it occurs when the increase in AL exceeds the focal point of the eye [15,16]. The progression of myopia in children has been confirmed to be strongly associated with axial elongation [17,18]. The correlation between changes in AL and the progression of myopia is significant [18-22].

However, the etiology of axial myopia remains elusive. Thus, no effective treatment has been established to control axial elongation or prevent the progression of myopia. Previous studies have reported that the autonomic nervous system innervates the iris, ciliary muscle, and choroid of the eye, and regulates accommodation, choroidal thickness (CT), choroidal rhythm, and pupillary responses, which are closely related to the development of myopia [23-26]. By regulating the choroid and sclera, the autonomic nervous system plays an important role in the development of myopia [27-30].

The sympathetic nerve originates from neurons in the superior cervical ganglion, and the parasympathetic nerve originates from neurons in the ciliary, trigeminal, and pterygopalatine ganglia [12,31]. The sympathetic nerve can release neurotransmitters like adrenaline and neuropeptide Y, and the parasympathetic nerve can release neurotransmitters like vasoactive intestinal peptide, acetylcholine, and neuronal nitric oxide synthase [12,32,33]. The pupil is controlled by 2 types of muscles with distinct nerve innervations: the pupillary dilator is innervated by the sympathetic nervous system, while the pupillary sphincter is innervated by the parasympathetic nervous system. Activation of the sympathetic nervous system can increase the pupil size, while activation of the parasympathetic nervous system can decrease the pupil size [34-36]. Thus, pupil size and its changes may be indicators of autonomic nervous system activity [37], and pupillary response recording could be an effective and useful method to evaluate autonomic nervous system activity [31,34-36,38].

However, to the best of our knowledge, no study has investigated the relationship between autonomic nervous system activity and optical AL. Moreover, considering that myopia begins during childhood [8-10], early observation during childhood might provide more information about the relationship between autonomic nervous system activity and AL than later during adulthood. Accordingly, this study compared the autonomic nervous system activity between axial and non-axial myopic eyes, and explored the relationship between autonomic nervous system activity and optical AL among children, hoping to provide novel information about the etiology of myopic axial elongation in children.

Material and Methods

Subjects

This study was conducted in accordance with the tenets of the Declaration of Helsinki, and was approved by the Ethics Committee of Tongji Hospital, Huazhong University of Science and Technology (TJ-IRB20210140). Written informed consent was obtained from all children and their guardians.

A total of 78 eyes of 78 children were included in this study. One eye from each participant was randomly selected. According to a previous study, we used AL instead of the dioptric value as the grouping criterion because the core of myopia is axial elongation, while dioptric values can be influenced by the refractive status of the cornea and lens [22,39]. The subjects were divided into 2 subgroups according to the individual AL: the axial myopia (AL ≥24.5 mm) and the non-axial myopia (AL <24.5 mm) groups. Among the recruited 78 eyes, 25 had axial myopia and 53 had non-axial myopia.

Subjects with best corrected visual acuity less than 20/20, a history of ocular disease other than refractive error, a history of ocular trauma, a history of ocular laser or surgery, a history of use of any other modalities other than single-vision spectacles for myopia control, including rigid contact lenses, multifocal soft contact lenses, orthokeratology lenses and atropine, or a history of systemic disease were excluded [40]. Furthermore,

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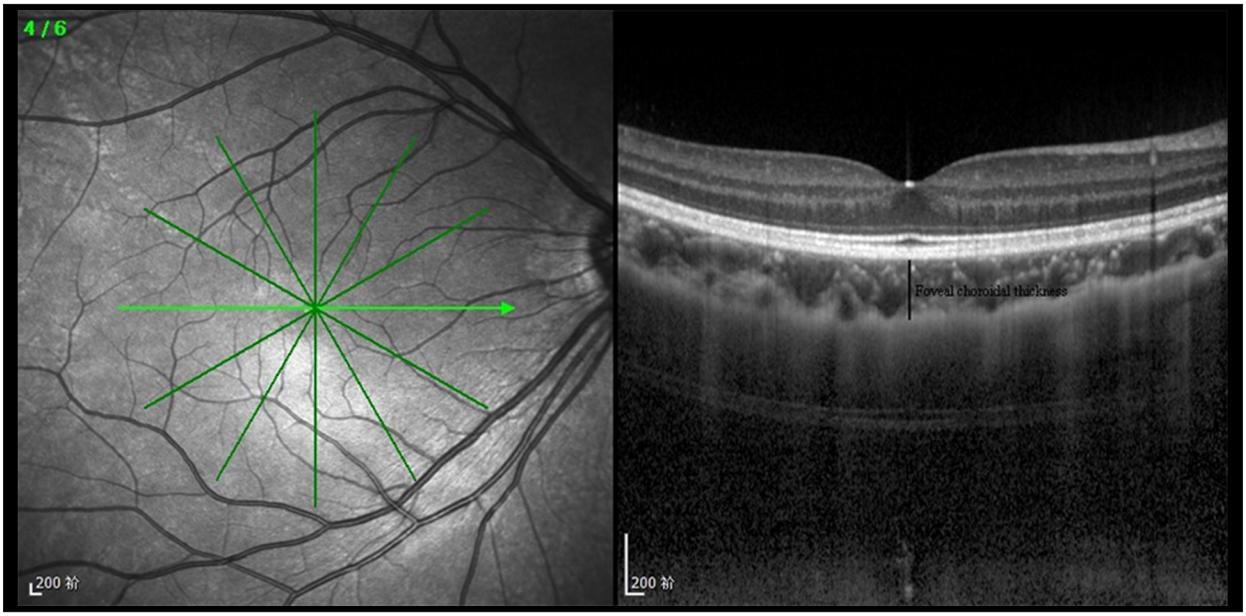

Figure 1. The measurement of foveal choroidal thickness (the black line).

subjects were instructed to take no medicines/food affecting the circulatory system 1 month before their participation, and to receive no caffeine for at least 24 hours before the study [41].

Optical Coherence Tomography (OCT) Image Acquisition and Measurement

OCT images of the choroid were obtained by the enhanced depth imaging (EDI) method of Spectralis® OCT device (Heidelberg Engineering, Heidelberg, Germany, software version 6.16.6.0). The EDI OCT images of the choroid were analyzed by a trained ophthalmologist (XC) in a masked manner. CT was defined as the distance from the outer portion of the hyperreflective line corresponding to the retinal pigment epithelium (RPE) – Bruch's membrane complex to the choroid–sclera interface [27] (**Figure 1**). To determine the intraobserver variability, the ophthalmologist (XC) re-measured CT at a separate session in a masked manner. The intraclass correlation coefficient value for CT measurements was 0.930.

Axial Length (AL) Measurement

AL measurements were performed using the IOL-Master device (IOL-Master 500; Carl Zeiss Meditec, Dublin, CA, USA, software version 5.5.0.0062) by a single trained ophthalmologist (YL) in a masked manner.

Measurements of Pupillary Response via Automatic Pupillometry

To evaluate autonomic nervous system activity, an automatic pupillometry system (MonCv3; Vision Monitor System, Metrovision, Pérenchies, France, software version Mon2018F) equipped with near-infrared illumination and a high-resolution camera (880 nm) was used for both static and dynamic measurements and for accurate determinations of the pupil diameter (PD) (accuracy, 0.1 mm). To minimize the influence of circadian and environmental variations on PD, automatic pupillometry measurements were performed by the same trained ophthalmologist (MZ) in a closed and darkened room with the illumination of <0.07 lux in the morning (9: 00 to 11: 00 AM) in a masked manner.

After 15 min of darkness adaptation, static pupillometry was conducted for static PD measurements under 4 standardized illumination conditions: scotopic (0 candelas (cd)/m^2; PD0), mesopic (1 cd/m^2; PD1), low photopic (10 cd/m^2; PD10), and high photopic (100 cd/m^2; PD100) conditions.

Dynamic pupillary responses were recorded when the pupil was exposed to automatic white light flashes (stimulation on-time 200 ms, stimulation off-time 3300 ms, total luminance 100 cd/m^2, and total intensity 20 lux) in the dark. Images were acquired and processed in real time (30 images/s), from which the pupillary contours were automatically outlined and recorded. The pupil dynamics were automatically quantified, including the latency of pupil contraction (Lat-C, ms), velocity of pupil contraction (Vel-C, mm/s), latency of pupil dilation (Lat-D, ms), and velocity of pupil dilation (Vel-D, mm/s).

Statistical Analysis

Data were analyzed using SPSS software (version 22.0; IBM Corp., Armonk, NY, USA) and EmpowerStats software (www.

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Table 1. Characteristics of the study subjects.

	Axial myopic group	Non-axial myopic group	*P*
Age (years)	11.28±1.84	10.68±1.86	0.176
Sex (male/female)	14/11	25/28	0.467
Axial length (mm)	25.11±0.54	23.47±0.88	<0.001*
Foveal choroidal thickness (μm)	212.0±38.1	262.7±71.9	<0.001*

* Significance of difference.

Table 2. Comparisons of static pupillary responses between axial and non-axial myopic groups.

	Axial myopic group	Non-axial myopic group	*P*
PD0 (mm)	5.67±0.71	5.61±1.40	0.752
PD1 (mm)	4.06±0.64	3.80±0.87	0.045*
PD10 (mm)	3.40±0.49	3.22±0.66	0.046*
PD100 (mm)	2.90±0.44	2.98±0.60	0.589
ΔPD1 (mm)	-1.61±0.69	-2.04±0.62	0.008*
ΔPD10 (mm)	-2.27±0.63	-2.62±0.55	0.016*
ΔPD100 (mm)	-2.76±0.62	-2.87±0.77	0.173

PD0 – pupil diameter at scotopic condition (0 candelas/m^2); PD1 – pupil diameter at mesopic condition (1 candelas/m^2); PD10 – pupil diameter at low photopic condition (10 candelas/m^2); PD100 – pupil diameter at high photopic condition (100 candelas/m^2); ΔPD1 – the differences between PD1 and PD0; ΔPD10 – the differences between PD10 and PD0; ΔPD100 – the differences between PD100 and PD0. * Significance of difference.

Table 3. Comparisons of dynamic pupillary responses between axial and non-axial myopic groups.

	Axial myopic group	Non-axial myopic group	*P*
Vel-C (mm/s)	5.93±0.89	6.75±1.60	0.019*
Vel-D (mm/s)	2.28±0.38	2.89±1.17	0.002*
Lat-C (ms)	193.40±76.67	219.92±64.02	0.254
Lat-D (ms)	826.64±69.68	841.34±89.94	0.437

Vel-C – velocity of pupil contraction; Vel-D – velocity of pupil dilation; Lat-C – latency of pupil contraction; Lat-D – latency of pupil dilation. * Significance of difference.

empowerstats.com, X&Y solutions, Inc. Boston, MA, USA). Data are presented as mean±standard deviation where applicable. The sample size evaluation was conducted with our pre-experimental results and the sample size calculation tool of EmpowerStats software (www.empowerstats.com, X&Y solutions, Inc. Boston, MA, USA). The normality of data was checked by Shapiro-Wilk test [27,43]. For data with normal distribution (foveal CT (FCT), PD0, the differences between PD1 and PD0 (ΔPD1), and the differences between PD10 and PD0 (ΔPD10)), the intergroup comparisons were performed by independent sample *t* test, while for data with non-normal distribution (age, AL, PD1, PD10, PD100, the differences between PD100 and PD0 (ΔPD100), Vel-C, Vel-D, Lat-C, and Lat-D), the intergroup comparisons were performed by Mann-Whitney *U* test. Associations between variables were calculated using Spearman's correlation analysis. Differences and associations were considered statistically significant if *P* values were lower than 0.05.

Results

As shown in **Table 1**, there were no significant differences in age and sex between the axial and non-axial myopic groups

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(both *P*>0.05). AL was significantly longer, and FCT was significantly thinner in the axial myopia group than in the non-axial myopia group (both *P*<0.001).

Comparisons of Static Pupillary Responses Between Axial and Non-Axial Myopic Groups

PD1 and PD10 were significantly larger in the axial myopic group than in the non-axial myopic group (*P*=0.045 and 0.046, respectively). In addition, ΔPD1 andΔPD10 were also significantly greater in the axial myopic group than in the non-axial myopic group (*P*=0.008 and 0.016, respectively) (**Table 2**).

Comparisons of Dynamic Pupillary Responses Between Axial and Non-Axial Myopic Groups

Vel-C and Vel-D were significantly slower in the axial myopic group than in the non-axial myopic group (*p*=0.019 and 0.002, respectively), while Lat-C and Lat-D showed no significant differences between axial and non-axial myopic groups (*p*=0.254 and 0.437, respectively) (**Table 3**).

Relationship Between Pupillary Responses, Foveal Choroidal Thickness, and Axial Length

In terms of the parameters of static pupillary response, PD1 and PD10 were significantly and positively associated with AL (both *P*=0.003). In addition, ΔPD1 and ΔPD10 were also significantly and positively associated with AL (*P*=0.013 and 0.040, respectively). In terms of the parameters of dynamic pupillary response, both Vel-C and Vel-D were significantly and negatively associated with AL (*P*=0.004 and 0.005, respectively), and FCT was also significantly and negatively associated with AL (*P*<0.001) (**Figure 2**).

Discussion

The progression of emmetropization can be considered as the adaptation of the length of the optical axis in relationship to the refractive power of the lens and cornea. When the AL exactly matches the refractive powers of the lens and cornea, emmetropia occurs. When the AL of the eye exceeds the focal length formed by the optical components, it results in axial myopia [11,12]. The etiology of the pathologic increase of AL in myopia remains unknown. In this study, we found significant differences in pupillary responses between eyes with axial vs non-axial myopia. Moreover, pupillary response was significantly associated with AL. These results indicate that there were significant differences in autonomic nervous system activity between eyes with axial and non-axial myopia, and that ocular axial elongation is associated with changes in autonomic nervous system activity in children.

Pupillometry has been proven to be a useful and low-cost tool for evaluating autonomic nervous system activity and can reveal subclinical defects of autonomic function in various diseases [38,44]. The high speed of pupillary response can reflect autonomic nervous system activity. Among them, the diastolic velocity of the pupil usually indicates a higher efficiency of sympathetic nervous activity, whereas the systolic velocity of the pupil usually indicates more efficient parasympathetic nervous activity [31,36,44]. Therefore, pupillary responses, especially Vel-C and Vel-D, were used to evaluate autonomic nervous system activity in this study.

Previous studies have indicated the close relationship between the pupil and autonomic nervous system activity [34-36,38,44]. In terms of the static comparison of pupil size, a previous study revealed that the size of the myopic pupil was larger than that of the emmetropic and hyperopic pupils [45,46]. In addition, a subgroup analysis of myopic eyes reported that the pupil size of super-high myopia was larger than that of high myopia [47]. These results are highly consistent with our findings, which showed that PD1 and PD10 were significantly larger in axial myopia than in non-axial myopia, indicating the relative hyperactivation of sympathetic nervous system (compared with parasympathetic nervous system) in axial myopia. In terms of dynamic pupillary responses, both Vel-C and Vel-D were significantly slower in the axial myopic group than in the non-axial myopic group, indicating that the autonomic (both sympathetic and parasympathetic) nervous system activity decreased in axial myopia. Given the results of static and dynamic pupillary responses together, we speculated that axial myopia might have decreased autonomic (both sympathetic and parasympathetic) nervous system activity, and the decrease in parasympathetic nervous system activity might be greater than the decrease in sympathetic nervous system activity, leading to the relative hyperactivation of sympathetic nervous system (compared with parasympathetic nervous system) in axial myopia.

Myopia might be related to certain changes in autonomic nervous system activity, and this change could be related to the degree of myopia [28]. Myopic subjects are reported to have more accommodation lag and accommodation sensitivity than emmetropic subjects, and one of the underlying reasons may be related to the impaired function of the sympathetic and parasympathetic nervous systems in myopia [28,48]. In addition, Schmid et al reported that sympathectomy had an effect on ocular dimensions, and parasympathectomy could significantly influence AL, CT, and choroidal day-night fluctuation rhythm [49]. After parasympathectomy, AL and the fluctuation of CT increase, indicating that the parasympathetic nervous system influences CT and participates in the neural control mechanism of axial elongation [25,49]. Previous studies also indicate that the autonomic nervous system may play an

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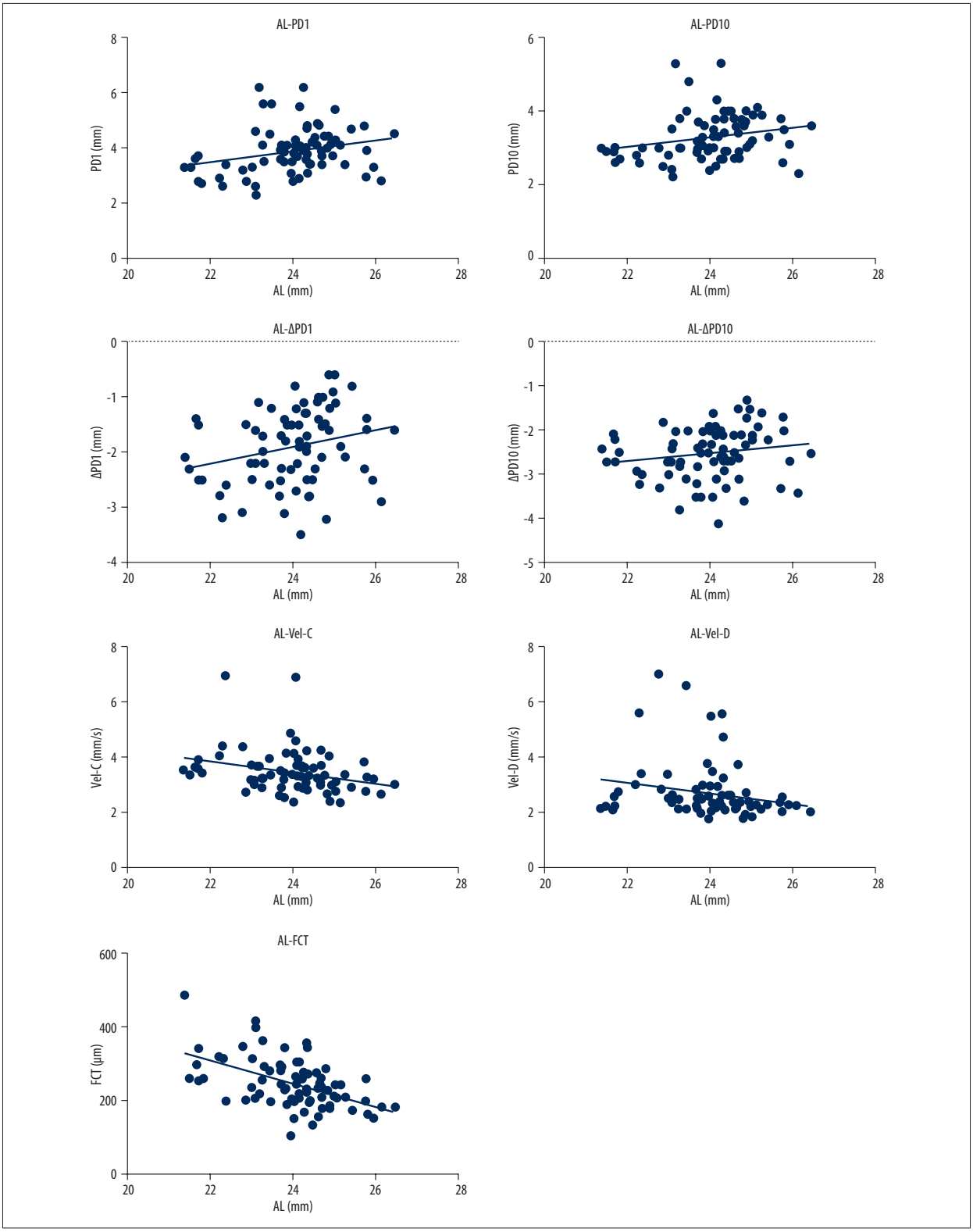

Figure 2. Relationship between pupillary responses, foveal choroidal thickness and AL. AL – axial length; PD1 – pupil diameter at mesopic condition (1 candelas/m^2); PD10 – pupil diameter at low photopic condition (10 candelas/m^2); ΔPD1 – the differences between PD1 and PD0; ΔPD10 – the differences between PD10 and PD0; Vel-C – velocity of pupil contraction; Vel-D – velocity of pupil dilation; FCT – foveal choroidal thickness.

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important role in the development of myopia [27-29]. Thus, we speculated that the changes in autonomic nervous system activity observed in this study might contribute to axial elongation in myopia. Children with lower autonomic nervous system activity may be more susceptible to axial elongation and the development of myopia.

It has been proposed that the choroid and sclera are primarily involved in the progression of axial elongation [27,30,50-53], and AL could have a significant influence on CT [54,55]. In this study, we observed a significant decrease in FCT in myopic eyes, and FCT was significantly and negatively associated with AL. Previous studies have indicated that compared with emmetropic and hyperopic eyes, myopic eyes have a thinner choroid [56,57], and this decrease in CT was associated with the degree of myopia [58]. Moreover, other studies have indicated that, in children, myopic eyes showed a trend of choroidal thinning, while non-myopic eyes showed a trend of choroidal thickening [59,60]. The myopic changes in CT and choroidal circulation might further result in scleral ischemia and hypoxia, leading to the impairment and remodeling of the sclera. The sclera, undergoing remodeling and thinning, would be unable to resist the force of axial elongation, causing further AL increase and progression of myopia [27,58,61]. Moreover, scleral ischemia and hypoxia can activate certain down-stream signaling pathways and accelerate the progression of myopia [62]. In addition to choroidal blood flow, CT can also contribute to emmetropization by adjusting the retina to the focal plane of the eye (choroidal accommodation) [11]. Choroidal blood flow and CT are regulated by the autonomic nervous system (sympathetic nervous stimulation causes a substantial reduction in choroidal blood flow and CT [31,63-66], and the parasympathetic input to the choroid has a vasodilation effect and serves to increase choroidal blood flow and CT [31,32,67,68]). The intrinsic rhythm of the choroid is also influenced by the autonomic nervous system (the choroid possesses a network of intrinsic choroidal neurons that lie in the choroidal stroma [12,32,69], and these intrinsic choroidal neurons appear to receive both sympathetic and parasympathetic input, suggesting they are controlled by the autonomic nervous system [70,71]). In addition, the choroid can release certain autonomic neurotransmitters (eg, vasoactive intestinal peptide, nitric oxide) [12,24,31,71] and change the permeability of the choroid, making the growth factor released by the choroid more easily arrive at the sclera, and further remodel the scleral extracellular matrix [11,61,72,73]. Thus, changes in autonomic nervous system activity in myopia may accelerate the progression of axial elongation and myopia by regulating the choroid and sclera.

The present study has certain limitations. First, it is a cross-sectional but not longitudinal study. Thus, the causality between the changes in autonomic nervous system activity and the axial elongation could not be fully determined. Second, the sample size was relatively small. Third, studies with animal models are needed to reveal the specific mechanism of autonomic nervous system activity on axial elongation in myopia, and the respective role of sympathetic and parasympathetic nervous systems in axial elongation in myopia. Forth, previous research has indicated that the reliability of AL measurements in myopic eyes may be limited, with traditional AL being longer for long eyes [74].

Conclusions

Our study showed that axial myopia can have decreased autonomic (both sympathetic and parasympathetic) nervous system activity, and the decrease in parasympathetic nervous system activity may be greater than the decrease in sympathetic nervous system activity, leading to the relative hyperactivation of sympathetic nervous system (compared with parasympathetic nervous system) in axial myopia. Decreases in autonomic nervous system activity in axial myopia may contribute to the excessive axial elongation in pediatric axial myopia.

Declaration of Figures' Authenticity

All figures submitted have been created by the authors, who confirm that the images are original with no duplication and have not been previously published in whole or in part.

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