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ARTICLE

Peripapillary and macular choroidal thickness before and after phenylephrine instillation

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Abstract

Objectives We investigated the effects of topical phenylephrine 2.5% instillation on choroidal thickness (CT), peripapillary choroidal thickness (pCT) and retinal nerve fibre layer (RNFL).

Methods Healthy control patients underwent enhanced depth imaging (EDI) by spectral-domain optical coherence tomography (OCT) before and 30 min after phenylephrine instillation, using eye-tracking and follow-up software. Changes in 14 different locations of CT, 2 locations of pCT and RNFL were assessed.

Results The study included 119 eyes of 62 patients (19 males and 43 females), with a mean age of 59.8 ± 15.3 years (range: 26-88 years). Within 30 min after instillation, the mean subfoveal CT both in vertical and horizontal scan were significantly thinned ($p = 0.005$ and $p = 0.018$, respectively). In total, 1500, 1000 and 500 µm temporal CT measurements showed also a significant thinning ($p = 0.021$, $p = 0.037$ and $p = 0.020$, respectively), as well as 500 µm both superior ($p = 0.045$) and inferior ($p = 0.009$). 1500, 1000 and 500 µm nasal CT, and 1500 and 1000 µm CT superior and inferior measurements showed no significant thinning after phenylephrine instillation. pCT was significantly thinned after phenylephrine in both superior ($p = 0.016$) and inferior ($p = 0.050$) measurements. RNFL analysis did not significantly change after phenylephrine instillation ($p = 0.209$).

Conclusions A significant thinning of CT and pCT occurred following phenylephrine instillation. Future studies analysing CT and pCT should detail if this mydriatic agent was used or not.

Introduction

The thickness of the human choroid has been related with eye diseases such as age-related macular degeneration (AMD) [1], degenerative myopia [2] and central serous retinopathy (CSC) [3], as well as systemic diseases like Alzheimer's Disease [4, 5], Parkinson disease [6] or systemic arterial hypertension [7] and other conditions such as smoking [8], caffeine intake [9], and time of day [10].

The choroid is a highly vascularized layer that supplies the outer retina with oxygen, nutrients and growth factors and serves as a heat diffuser that protects the photoreceptors [11]. As this layer is a tissue where the vascular component is essential, its thickness is determined by the course and branching pattern of the ciliary arteries [12]. For this reason, it might be thought that the choroidal thickness (CT) might decrease its thickness after using a mydriatic agent as phenylephrine 2.5%. However, conflicting results were reported in the literature. Some studies suggest no change [13, 14], although others showed a significant thinning of the CT after instillation of this drug [15, 16]. In this study, a larger number of eyes were included, and 10 different measurements of the CT, as well as 2 measurements of peripapillary choroidal thickness have been analysed, in order to solve this controversy. Besides, retinal nerve fibre layer (RNFL) was measured as well to find a possible change after phenylephrine instillation or a correlation with choroidal thickness.

Methods

Patients

All participants were recruited from the ophthalmology department of Valdecilla Hospital, from May 2017 to June

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2018. The study protocol was approved by the Ethics Committee of Valdecilla Hospital, and it was performed in accordance with the principles of the Declaration of Helsinki. Written consent forms were distributed to all the participants before the examinations.

All subjects were required to have a refractive error less than -6.0 diopters of sphere or 3 diopters of cylinder, no history of retinal diseases (for example, diabetic retinopathy, macular degeneration, optic neuritis).

Exclusion criteria included clinically relevant opacities of the optic media and low-quality images due to unstable fixation, or severe cataract (patients with mild to moderate cataract might be enrolled in the study, but only high-quality images were included).

Clinical assessment

All subjects underwent a thorough ophthalmic examination on the day of OCT imaging, including best-corrected visual acuity, refraction, intraocular pressure (IOP) measurement with GAT, slit lamp examination and fundus examination. The refractive error was recorded using an auto refractometer Canon RK-F1 (Canon USA Inc., Lake Success, NY, USA). Axial length (AL) and central cornea thickness were measured by Lenstar LS 900 (Haag Streit AG, Koeniz, Switzerland).

Optical coherence tomography procedure

Methodology for measurement of CT

Prior to the administration of the phenylephrine eye drops (pre-treatment) and 30 min after complete mydriasis, choroidal scans were obtained of patient's eyes using an enhanced depth image (EDI) combined spectral-domain OCT (Spectralis HRA + OCT, Heidelberg Engineering, Heidelberg, Germany; wavelength for scan: 870 nm).

A single, well-trained ophthalmologist (ALE) performed all OCT examinations in random order to prevent any fatigue bias. The EDI image was averaged over 100 scans using the automatic averaging mode. The follow-up acquisition mode, unique to this SD-OCT device, was used to perform the second measurement, as it automatically placed follow-up scans in precisely the same anatomic location as previous scan.

CT was measured by a masked and experienced investigator (JG), who was blinded to phenylephrine status. The border of CT was defined as extending from the outer portion of the hyperreflective line (corresponding to the RPE) to the inner surface of the sclera. CT was measured at 10 different locations on the retina (Fig. 1): at the fovea (with horizontal and vertical scan: F_H and F_V, respectively), and at 500, 1000 and 1500 μm from the fovea in the nasal (N500μm, N1000μm and N1500μm, respectively), temporal (T500μm, T1000μm and T1500μm, respectively), superior (S500μm, S1000μm and S1500μm, respectively), and inferior (I500μm, I1000μm and I1500μm, respectively) quadrants.

Methodology for measurement of peripapillary choroidal thickness (pCT)

A vertical scan was taken through the optic nerve, using an EDI high-definition scan protocol, bisecting the optic nerve into approximately equal halves. The scan should allow that the visibility of the anterior LC surface was complete (excluding the main vessels) was selected from the baseline EDI images. Same experienced investigator (JG) analysed pCT. Measurements were made close to the optic nerve at 500 μm distal (superior and inferior) to the beginning of the retinal pigment epithelium (RPE): 500 μm superior pCT_S and 500 μm inferior pCT_I. Each thickness measurement was made perpendicular to the RPE going from the posterior RPE edge to the choroid-scleral junction.

Methodology for RNFL imaging

Cross-sectional imaging of the peripapillary area was performed using Spectralis OCT, which simultaneously captures infrared fundus and SD-OCT images at 40,000

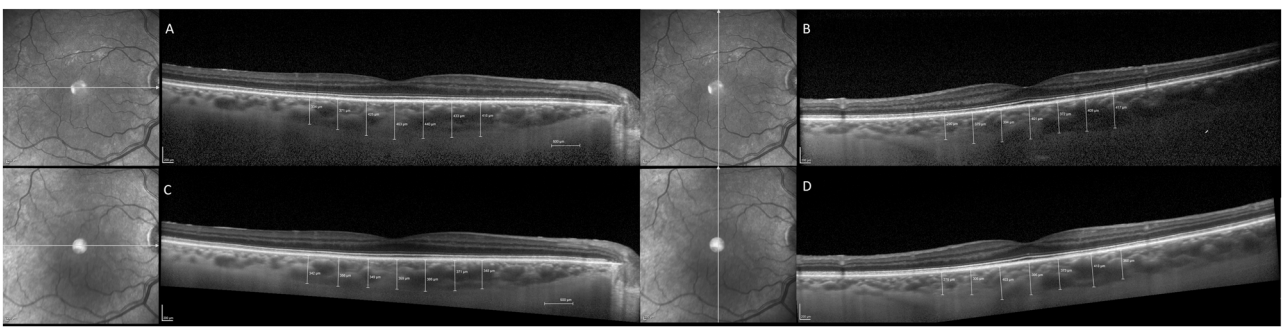

Fig. 1 Choroidal thickness (in μm) in horizontal scans (**a**: pre- phenylephrine, **c**: post- phenylephrine) and in vertical scans (**b**: pre- phenylephrine, **d**: post- phenylephrine), showing a choroidal thinning 30 minutes after phenylephrine 2.5% instillation

A-scans per second. A real-time eye-tracking system measures eye movement and provides feedback to the scanning mechanism to stabilise the retinal position of the B-scan. The instrument uses 1024 A-scan points from a 3.45 mm circle centred on the optic disc. The examiner is required to manually place the scan around the optic disc.

Statistical Analysis

Statistical analysis was performed using IBM SPSS Statistics V.20.0 (International Business Machine Corporation, Armonk, NY, USA).

A 1-sample Kolmogorov-Smirnov test was used to verify the normality of the data distribution. The CT, pCT and RNFL before and after phenylephrine 2.5% instillation were compared using paired Student's t-test. Pearson correlation analysis was performed to assess the relationship between AL, age and spherical equivalent (SE) with RNFL, CT and pCT. The sample size calculation for this study was based on chi-test used by Yuvaci et al. [16]. A study with a change of 25.72 ± 32.66 before and after phenylephrine instillation and a power of 95% will require a total sample of 98 eyes to test the association at 5% levels using two tailed test. The power calculation was carried out using Gpower 3.1.7. The level of statistical significance was set at $P < 0.05$.

Results

Overall, 119 eyes of 62 patients (19 males and 43 females) were included in the study. The mean age was 59.8 ± 15.3 years (age range: 26−88 years). The mean SE was measured as −0.64 ± 0.79 diopters. Mean AL was 23.1 ± 1.01 mm (range, 21.3–25.8 mm). All included eyes were phakic. Mean IOP was 14.5 ± 3.5 mmHg (IOP range 9−21 mmHg).

Figure 2 shows the pre-phenylephrine thickness of CT at different locations. After 30 min of phenylephrine instillation, we found a significant thinning of the CT in the horizontal scans in temporal and subfoveal thickness: T1500 µm 262.1 ± 94.2 pre-phenylephrine and 254.4 ± 89.3 post- phenylephrine ($p = 0.021$), T1000 µm (276.4 ± 102.8 and 271.4 ± 100.3 µm, $p = 0.037$), T500 µm (283.4 ± 109.2 and 277.1 ± 105.6 µm, $p = 0.020$), F_H (292.8 ± 113.1 and 282.2 ± 111.5 µm, $p = 0.005$). However, nasal scans of CT did not show a significant change after phenylephrine: N500 µm (284.4 ± 114.7 and 277.8 ± 109.8 µm, $p = 0.088$), N1000 µm (271.8 ± 108.9 and 265.3 ± 109.5 µm, $p = 0.126$) and N1500 µm (248.0 ± 109.3 and 243.3 ± 101.8 µm, $p = 0.195$).

Similarly, we found a significant thinning of the CT in the vertical scans only in subfoveal CT and adjacent superior and inferior CT: S500 µm (286.6 ± 99.6 and 278.8 ± 101.7 µm, $p = 0.045$), F_V (285.7 ± 103.6 and 274.7 ± 108.3 µm, $p = 0.018$) and I500 µm (277.4 ± 103.9

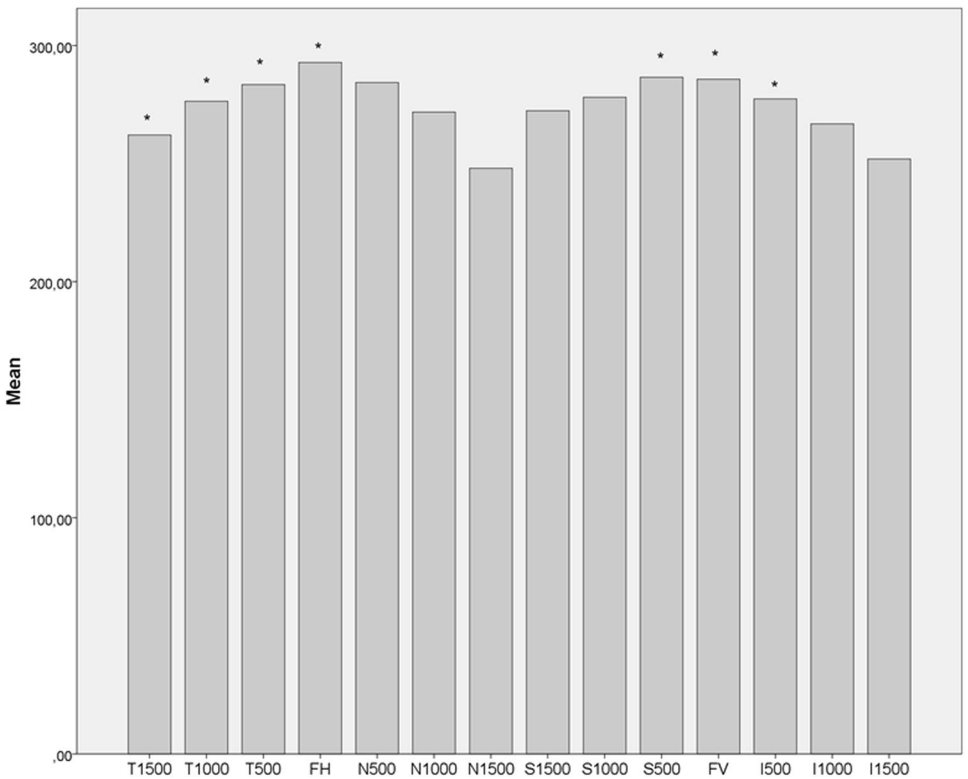

Fig. 2 Pre-phenylephrine mean of different locations of choroidal thickness. T (temporal), N (nasal), S (superior), I (inferior), FH (subfoveal choroidal thickness in horizontal scan), FV (subfoveal choroidal thickness in vertical scan). 500, 1000 and 1500 are the µm that locations are away from subfoveal measurement. *$P < 0.05$ if significant differences with paired Student's *t*-test were found

Table 1 Choroidal thickness before and 30 min after phenylephrine instillation

	Baseline. Mean ± SD (μm)	30 min post phenylephrine. Mean ± SD (μm)	*P*-value
CT T1500 μm	262.1 ± 94.1	254.3 ± 89.3	0.021*
CT T1000 μm	276.4 ± 102.8	271.4 ± 100.3	0.037*
CT T500 μm	283.4 ± 109.2	277.0 ± 105.5	0.020*
F_H	292.83 ± 113	282.1 ± 111.5	0.005*
CT N500 μm	284.3 ± 114.7	277.8 ± 109.7	0.088
CT N1000 μm	271.8 ± 108.9	265.3 ± 109.5	0.126
CT N1500 μm	248 ± 109.2	243.2 ± 101.8	0.195
CT S1500 μm	272.3 ± 96.4	264.7 ± 92.7	0.153
CT S1000 μm	278.1 ± 101.3	274.1 ± 98	0.409
CT S500 μm	286.5 ± 99.5	278.8 ± 101.7	0.045*
F_V	285.7 ± 103.6	274.6 ± 108.2	0.018*
CT I500 μm	277.4 ± 103.9	267.0 ± 104.2	0.009*
CT I1000 μm	266.8 ± 102.9	261.0 ± 103.3	0.126
CT I1500 μm	251.9 ± 96.5	247.5 ± 98	0.192
pCT_S	126.3 ± 46.5	120.0 ± 42.3	0.016*
pCT_I	112.9 ± 58.3	104.6 ± 39.7	0.050*
RNFL	98.9 ± 9.9	98.7 ± 9.7	0.209

CT Choroidal thickness, *T* temporal, *N* nasal, *S* superior, *I* inferior, F_H subfoveal choroidal thickness in horizontal scan, *FV* subfoveal choroidal thickness in vertical scan, pCT_S peripapillary choroidal thickness 500 μm superior, pCT_I peripapillary choroidal thickness 500 μm inferior

*P value is <0.05

Table 2 Pearson correlation of axial length (AL), age and spherical equivalent (SE) with retinal nerve fibre layer (RNFL), choroidal thickness (CT) and peripapillary choroidal thickness (pCT), as well as with their changes after phenylephrine, showing that significant relationship was found with basal measurements, but not with their changes after the mydriatic agent

	AL		SE		Age	
	r	*p*-value	*r*	*p*-value	*r*	*p*-value
RNFL	−0.133	<0.001*	−0.089	0.001*	−0.065	0.005*
CT F_H	−0.090	0.001*	−0.047	0.019*	−0.150	<0.001*
CT F_V	−0.065	0.005*	−0.046	0.021*	−0.131	<0.001*
pCT_S	−0.002	0.606	−0.006	0.421	−0.070	0.004*
pCT_I	−0.004	0.476	−0.005	0.449	−0.104	<0.001*
Changes in RNFL	0.007	0.360	0.007	0.360	0.009	0.314
Changes in CT F_H	0.008	0.319	0.003	0.559	0.001	0.706
Changes in CT F_V	0.007	0.358	0.001	0.767	0.002	0.673
Changes in pCT_S	0.005	0.462	0.016	0.186	0.011	0.252
Changes in pCT_I	0.001	0.755	0.001	0.767	0.012	0.237

AL axial length, *SE* age and spherical equivalent, *RNFL* retinal nerve fibre layer, *CT* choroidal thickness, *pCT* peripapillary choroidal thickness, F_H subfoveal choroidal thickness in horizontal scan, F_V subfoveal choroidal thickness in vertical scan, pCT_S peripapillary choroidal thickness 500 μm superior, pCT_I peripapillary choroidal thickness 500 μm inferior

*P-value is <0.05

and 267.0 ± 104.2 μm, $p = 0.009$). However, the analysis of the other scans-changes did not show a significant change ($p > 0.126$) (Table 1).

Interestingly, peripapillary CT also showed a significant thinning after phenylephrine instillation: pCT_S and pCT_I 126.3 ± 46.6 and 112.9 ± 42.3 μm pre-phenylephrine and 120.0 ± 42.3 and 104.6 ± 39.8 μm post- phenylephrine; $p = 0.016$ and $p = 0.050$, respectively.

Although we found a thinning of average RNFL after drug administration, there were no significant changes between pre- and post-phenylephrine RNFL (98.9 ± 9.9 and 98.7 ± 9.7 μm, $p = 0.209$).

As showed in Table 2, a significant correlation was found between AL and RNFL ($p < 0.001$), as well as AL and pre-phenylephrine CT ($p < 0.005$). However, no significant correlation was found between AL and neither superior pCT_S ($p = 0.606$) nor inferior pCT_I ($p = 0.476$). Changes in RNFL, CT and pCT after phenylephrine did not correlate with AL ($p > 0.319$). Similarly, a significant correlation was found between SE and RNFL ($p = 0.001$), as well as SE and CT ($p < 0.021$). However, no significant correlation was found between SE and neither superior pCT_S ($p = 0.421$) nor inferior pCT_I ($p = 0.449$). Changes in RNFL, CT and pCT after phenylephrine did not correlate with SE ($p > 0.186$). Age was found to be significantly related with RNFL ($p = 0.005$), with CT in each location ($p < 0.001$) as well as pCT_S and pCT_I ($p < 0.004$). However, no significance was found between age and changes in RNFL ($p = 0.314$), CT ($p > 0.673$) and pCT ($p > 0.237$).

Discussion

Phenylephrine is a mydriatic agent used commonly by ophthalmologists to induce pupil dilation. However, this drug might modify also CT. The mechanism by which CT is changed by phenylephrine has been proposed in different studies [13, 15]. It is a α-agonist with sympathomimetic effects that may promote the contraction of nonvascular smooth muscle cells that are innervated by sympathetic input and the contraction of the choroidal vascular bed due to vasoconstricting effects. In addition, other mydriatic agents such as cyclopentolate and tropicamide have anti-muscarinic (parasympatholytic) effects and might act also by inducing a posterior movement of the ciliary muscle and decreasing mechanical traction after cycloplegia [16]. In the

present study, we use phenylephrine alone to better analyse its influence in CT, which depends only in the contraction of both choroidal vascular bed and nonvascular smooth muscle cells.

Previous studies have investigated the effect of phenylephrine on CT with different results. In agreement with the present study, Yuvacj et al. [16], Kara et al. [15] and Li et al. [17] reported a significant thinning in CT after using single phenylephrine in the first two studies or a combination of tropicamide and phenylephrine in the last study. However, Sander et al. [14] and Kim et al. [13], using phenylephrine alone or in combination with tropicamide, respectively, reports no significant variation in CT. This controversy might depend on the number of patients included, as the studies that found a significant change of CT ranged 29–39 eyes [15–17] and the others that did not find a significant change ranged 14–29 eyes [13, 14]. In the present study, we included 119 eyes trying to solve this controversy. Although there were less important differences in mean ages in these publications (11.9–39 years and 27.9–33.2 years in significant and no significant studies, respectively), we included a bigger range of ages (26–88 years) to analyse if age could have an influence on CT response after phenylephrine that might explain these previous results, finding no significant correlation ($p > 0.252$).

There were also differences in the number of locations analysed. Yuvacj et al. analysed three different locations (subfoveal, nasal and temporal, with no detailed number of μm of separation from the subfoveal scan) [16], Kara et al. analysed just the subfoveal thickness [15] and Li et al. performed nine measurements of CT [17]. On the other hand, studies that did not find a significant thinning of CT analysed 13 [13] and 7 [14] measurements of CT. As there was a discrepancy here, we analysed CT at 14 locations (2 of subfoveal thickness in 2 different scans) and 12 more separated 1500, 1000 and 500 μm from these subfoveal locations. For these reasons, this study brings evidence that thinning of CT might be significant at least in subfoveal location ($p < 0.018$). Interestingly, this study showed that differences were significant, in addition to subfoveal CT, in 1500, 1000 and 500 μm temporal locations ($p < 0.037$), as well as 500 μm superior and 500 μm inferior ($p = 0.045$ and $p = 0.009$ respectively). Although Kara et al. [15] measured only subfoveal region, comparing to previous reports, Yuvacj et al. [16] found a significant thinning in both temporal and nasal locations, but with more difference in temporal location (18.7 vs 16.5 respectively). But our results were similar as published by Li et al. [17], since they found significant changes in close 1000 μm superior, inferior, temporal and nasal locations ($p < 0.021$), but 3000 μm away from subfoveal location their results were significant for temporal and nasal locations ($p = 0.034$ and $p = 0.049$), and no significant for superior nor inferior locations ($p > 0.271$). Actually, if a real change is made by phenylephrine, it could be depicted in subfoveal location. Moreover, 500 or 1000 μm adjacent to subfoveal location might reveal a significant thinning too. As long as more separated locations are analysed, CT is thinner, as could be appreciated in Fig. 2, that might explain that the result is significant or not.

Since the landmark study by Spaide et al. on the clinical use of EDI software for imaging of the choroid [18, 19], some other studies started to measure the CT in normal eyes and eyes with various retinal and retinochoroidal diseases [20–25]. As many of them obtained statistically significant results or at least CT changes, and it is an easy, fast and cheap measure to be taken, there are many articles that report CT abnormalities in eyes with different retinal disorders, such as central serous chorioretinopathy [3], polypoidal choroidal vasculopathy [22], exudative age-related macular disease [1] and high myopic eyes [2]. Even more, there are some systemic diseases that also induce an effect in choroid (thickening or thinning) like Alzheimer's disease [4, 5], Parkinson disease [6], and systemic arterial hypertension. For instance, it is reported that CT decreases in patients with systemic arterial hypertension [7]. Daily activities can modify CT, such as smoking [8], caffeine intake [9], and time of day [10]. Nevertheless, this article shows that phenylephrine drops instillation might modify CT, as there is a significant thinning of the CT in the horizontal scans in temporal and subfoveal thickness and in the vertical scans in subfoveal CT and adjacent superior and inferior CT 30 min after the administration. Therefore, this is an important limitation to some already published studies. Imamura et al., Kuroda et al. and Brandl et al., found CT changes in patients with central serous chorioretinopathy [20–22]. The first one demonstrates by EDI OCT a very thick choroid in patients with CSC and suggests this finding provides additional evidence that CSC may be caused by increased hydrostatic pressure in the choroid [20]. Kuroda et al. concluded that, in patients with CSC, the average choroidal thickness not only demonstrates a significant thickening at baseline, but also showed a marked decrease after 3 months, yet not reaching normal levels [21]. Both articles described that pupils were dilated for fundus examination as they wrote in the method paragraph, but none give specific details about how the pupil is dilated. Brandl et al. asserted the subfoveal CT in eyes with CSC is significantly greater than that in the control eyes, but they do not even indicate if fundus examination was effectuated, but in return, they practiced other eye's test (such as fluorescein angiography) in which mydriasis is needed [22]. On the other hand, Jost et al. did not get significant statistic results: AMD, neither in its nonexudative form or exudative form, was associated with a marked thinning or thickening of the choroid in the foveal and parafoveal region [25]. But

the results would be questioned even if they were statistically significant because the mydriatic eye drop drug is not specified. The group of Chung studied the CT differences between eyes with polypoidal choroidal vasculopathy (PCV) and exudative AMD. They demonstrated a significant thickening of choroid in the eyes with PCV, in contrast with choroidal thinning depicted in eyes with AMD. The article showed no information in the section "materials and methods" about mydriasis for eye examination, in spite of its quite obvious performance to be included in its study, all subjects were required to undergo a comprehensive ophthalmologic examination [24]. In the same hand, Fujiwara et al., do not give specific details in the method paragraph if the dilatation was carried out. This group assured that the choroid in highly myopic eyes is very thin and experimented further thinning with increasing age and degree of myopia and also, suggested that abnormalities of the choroid might play a kind of role in the pathogenesis of myopic atrophy [23].

Neuro-ophthalmology studies did not detail if phenylephrine drops were used. For instance, in Parkinson's disease studies, Eraslan et al. propound EDI technique as an additional modality in the diagnosis and follow-up of patients with PD because their results assert choroid and lamina cribrosa suffer atrophy and volume loss [26]. The study included funduscopy examination. There is not information about the mydriasis procedure, as well as Garcia-Martin et al. report, where they avouch an increased peripapillary CT and also, they come up with OCT uses in clinical practice [27]. Similarly, it has been published a CT thinning in Alzheimer's disease (AD) [4, 5, 28], suggesting that CT could represent a biomarker for the diagnosis and follow-up of this disease. However, none of these reports detailed if phenylephrine drops were used. As these studies analysed differences between these diseases and healthy patients, we might suppose that these differences are real, as phenylephrine drops, if used, they were used in all the groups equally. Nevertheless, from now on, we suggest that these studies should describe if mydriasis was done, and how.

On the other hand, this study showed no differences before and after phenylephrine instillation in RNFL measurements. Although its use could be detailed in future studies, the findings of the reports that have been already published associating, for instance, a thinning of RNFL in patients with AD [29–32], could be less affected for the use of this mydriatic agent.

Herein, peripapillary CT was analysed as Ho et al. [33]. They found this method accurate, as they analysed intraclass coefficient, and they reported that the inferior peripapillary choroid was significantly thinner than all other quadrants. However, information about mydriatic agents were used could not be found in this article. As we found differences in this pCT after using phenylephrine, we encourage future studies of CT or pCT to detail this information in methods part of the article.

Several limitations are present in this study. First, two singles vertical and horizontal scan, and one single vertical optic nerve scan was chosen for the morphometric analysis, while the remaining peripheral scans were not evaluated. However, these scans might represent the CT in a large area, as we analysed 16 different points of CT and pCT.

Secondly, we analysed the changes only 30 min after phenylephrine drops instillation. Li et al. [17] analysed changes 0, 30 and 60 minutes after drop instillation. However, similar changes were depicted in 30 and 60 min measurements. We analysed differences in a single 30 minutes post-instillation examination as may be convenient for clinical practice due to its simplicity.

Thirdly, the effect of age or AL, which are shown to be associated with CT, might skew the analysis. However, although both factors have been confirmed to be associated with both CT and pCT ($p < 0.001$), changes in both structures have been proved not to be related with age ($p > 0.256$) nor AL ($p > 0.319$).

Finally, although eye fixation locates the scan in the centre of the fovea for CT analysis, peripapillary scans should be manually placed, avoiding blood vessels. This fact might be a variable in pCT measurements; however, we reduce this bias as software of OCT allowed to perform the post-phenyleprhine scan to be located in the same situation of the previous one due to the eye-tracking system.

Summary

What was known before

- Mydriatic agents used before performing Optical coherence tomography might thin choroidal thickness (CT).
- If so, studies analysing CT should detail if phenylephrine is used or not, and if this mydriatic agent is used, it should be used in control and case eyes.
- Previous articles settled controversial results.

What this study adds

- Herein it is consistently proved that phenylephrine thin choroidal thickness and peripapillary choroidal thickness.
- However, no significant changes were found in retinal nerve fibre layer after phenylephrine.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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