Peripapillary choroidal thickness change of polypoidal choroidal vasculopathy after anti-vascular endothelial growth factor

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Peripapillary choroidal thickness change of polypoidal choroidal vasculopathy after anti-vascular endothelial growth factor

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I would like to express my hearful thanks to my parents, wife's parents for their endless support and unwavering love. I dedicate this research to my soul wife, my adorable daughter

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ABSTRACT

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PURPOSE: To investigate peripapillary choroidal thickness (PCT) of polypoidal choroidal vasculopathy (PCV) and exudative age-related macular degeneration (AMD), and to evaluate their responses to anti-vascular endothelial growth factor (VEGF).

METHODS: Thirty eyes with PCV and 25 eyes with exudative AMD who were treatment naïve were included in the study. PCT and subfoveal choroid thickness (CT) were evaluated before and after intravitreal anti-VEGF.

RESULTS: The initial mean PCT of PCV (153.78 ± 56.23 μm) was thicker than that of exudative AMD (88.77 ± 23.11 μm, $P < 0.001$). Temporal, superior, nasal, and inferior PCT of PCV were all thicker than exudative AMD (all, $P < 0.05$). After anti-VEGF, the mean PCT of PCV was significantly reduced (134.17 ± 41.66 μm, $P < 0.001$) but not in exudative AMD (86.87 ± 22.54 μm, $P = 0.392$). PCT in each quadrant showed a similar tendency.

CONCLUSIONS: PCV exhibit a thick choroid overall in both the peripapillary and macula regions. Both regions decrease in thickness after anti-VEGF in PCV, but not in exudative AMD. In exudative AMD, subfoveal CT decreased but the peripapillary region did not.

Key words : Age related macular degeneration, polypoidal choroidal vasculopathy, choroid

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I. INTRODUCTION

Polypoidal choroidal vasculopathy (PCV) was originally introduced as a retinal disorder characterized by abnormalities of the choroidal vasculature, including the inner branching vascular networks terminating in polypoidal lesions that can be seen on indocyanine green angiography. (ICGA).[1] PCV has been considered a variant of exudative age-related macular degeneration (AMD) because of their similarities in phenotypic features,[2] but PCV and exudative AMD have differences in ethnic prevalence, natural histories, and treatment responses.[3-5] These differences suggest that PCV and exudative AMD are two distinct diseases, with PCV being a primary abnormality of the choroid.[6]

It is increasingly being known that PCV has a thick subfoveal choroid.[7-9] Recently, several studies have reported that the subfoveal choroid is thicker in eyes with PCV than in eyes with typical exudative AMD,[7-9] and that the subfoveal choroid is thicker in eyes with PCV with choroidal vascular hyperpermeability, suggesting different pathological mechanisms in PCV and exudative AMD.[10] It has been proposed that pachychoroid neovasculopathy, including pachychoroid pigment epitheliopathy, central serous chorioretinopathy, and PCV are caused by

a pachychoroid-driven process involving choroidal congestion and choroidal hyperpermeability manifested by choroidal thickening and dilated choroidal vessels.[11,12]

However, current studies on the choroidal thickness (CT) of PCV have been limited to the choroid of the macular region. Therefore, it is unclear whether the increased CT in patients with PCV is a general characteristic of the choroid or a localized phenomenon limited to the macula. Because the choroid is supplied by various capillary arteries according to their regional distribution, the CT outside the macula, especially the peripapillary region, may reflect a different PCV pathophysiology. We hypothesize that PCV has a different peripapillary choroidal thickness (PCT) and anti-vascular endothelial growth factor (VEGF) response, compared to exudative AMD. In the following study, we retrospectively investigated PCT and its response to anti-VEGF in eyes with PCV and exudative AMD.

II. MATERIALS AND METHODS

This retrospective, comparative series was approved by the Institutional Review Board of Yonsei University, Seoul, South Korea. Informed consent was obtained from all patients, and all study protocols adhered to the tenets of the Declaration of Helsinki. All data were collected from the Department of Ophthalmology, Severance Hospital, and all subjects underwent a comprehensive ophthalmic examination, including measurement of best-corrected visual acuity, a dilated fundus examination, fundus fluorescein angiography (FAG), and ICGA with a spectral domain optical coherence tomography (SD-OCT; Spectralis OCT, version 1.5.12.0; Heidelberg Engineering, Heidelberg, Germany).

We retrospectively reviewed the medical records of patients with PCV and exudative AMD from January 2012 to June 2014. Inclusion criteria were the following: 1) treatment of naïve PCV or exudative AMD, 2) more than 6 month follow-up periods with anti-VEGF treatment (three consecutive monthly injections followed by a pro re nata protocol), and 3) OCT scan images of the peripapillary and macula regions at the initial visit and at the 6 month

follow-up visit. Exclusion criteria included the presence of refractive errors > ± 3.0 diopters, amblyopia, significant cataract, obscuration of choroidal images by existence of significant media opacity or thick subfoveal hemorrhage, central geographic atrophy, a history of ocular inflammation, a history of retinal detachment, previous vitrectomy, intraocular surgery (including cataract surgery) in the study eye within 1 year, a history of ocular trauma, and glaucoma in the study eye. Eyes that underwent photodynamic therapy were also excluded.

PCV was diagnosed primarily on the basis of ICGA findings, branching vascular networks, and terminating polypoidal lesion(s). Diagnosis of exudative AMD was based on a combination of fundus FAG and ICGA according to hyperfluorescense with late leakage associated with pigment epithelial detachment in the macular region, serous retinal detachment, subretinal exudation, and hemorrhage.[13]

1. Measurement of Peripapillary and Macular Choroidal Thickness

The peripapillary area was defined as the area within 3.4 mm from the center of the optic disk. Choroidal thickness was defined as the vertical distance from the hyperreflective line of Bruch's membrane to the innermost hyperreflective line of the sclerochoroidal interface. A 360°, 3.4 mm diameter circular OCT scan used the standard protocol for retinal nerve fiber layer assessment. Each sector was measured 90° from the temporal area, clockwise in the right eye and counter clockwise in the left eye. (Figure 1.) Thus, the 0° area of both eyes indicated the temporal peripapillary area and the 90°, 180°, and 270° areas corresponded to the superior, nasal, and inferior PCT, respectively. PCT was measured using a previously reported method.[14] Briefly, using the modification tool in the OCT image viewer program, the segmentation line indicating the retinal pigment epithelium (RPE) was modified to the sclerochoroidal junction by the investigator. With this modification, the chorioretinal thickness between the internal limiting membrane and the sclerochoroidal junction was measured. The CT was calculated by subtraction of the retinal thickness from the chorioretinal thickness at each quadrant. (Figure 1) Measurement of subfoveal CT on the line scan image was performed manually with a built-in

caliper tool of the OCT viewer program. Subfoveal CT was measured at the center of the fovea. If the RPE line was not clearly defined because of pigment epithelial detachment or other abnormalities, Bruch's membrane was used as the inner margin of the choroid. If a hyporeflective band representing a suprachoroidal layer was seen on OCT, it was not included in the CT.[15] In cases of poorly-defined chorioscleral junctions, the outer choroidal margin was defined as the line connecting the outer margin of the large choroidal vessel layer. Peripapillary and subfoveal OCT images were obtained at the time of initial presentation and 6 months after anti-VEGF treatment. All measurements were performed by two independent observers (S.H.K and J.M.L.) in a masked fashion, and the mean of these observations was used for analyses.

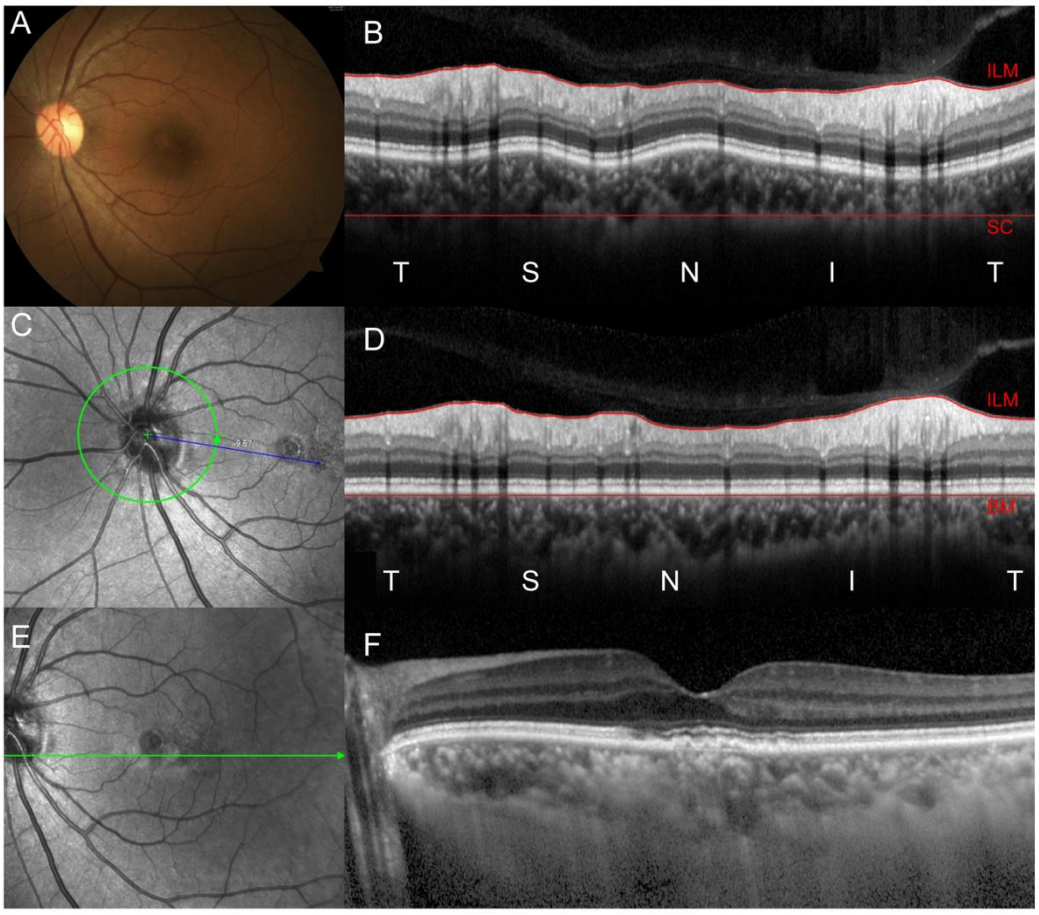

Fig 1. Measurement of peripapillary choroidal thickness (PCT) and subfoveal choroidal thickness (CT). (A) Fundus photography of 56 years old female with polypoidal choroidal vasculopathy (C) A 360° 3.4 mm diameter circle scan around the disc were performed to obtain

retinal and choroidal thickness. We measure the PCT by subtraction the retinal thickness (D) from the chorioretinal thickness obtained by manual modification of retinal pigment epithelium line (B). Subfoveal CT (F). ILM = internal limiting membrane; SC = sclerochoroidal junction; BM = Bruch's membrane

2. Statistical Analyses

The baseline characteristics between PCV and exudative AMD were compared with chi-square tests for categorical variables and independent *t*-tests for continuous variables. All comparisons between PCV and exudative AMD were adjusted by age using ANCOVA. The paired *t*-test was used to compare results before and after anti-VEGF treatment in each group. The one-way ANOVA test was used to determine possible differences between each sector of the PCT. All comparisons between PCV and exudative AMD were adjusted by age using ANCOVA. All statistical analyses were performed using SPSS, version 20.0 for Windows (SPSS, Chicago, IL, USA). $P < 0.05$ was considered significant.

III. RESULTS

Thirty eyes with PCV and 25 exudative eyes with AMD were included in the study. The mean age of the PCV patients was 6.63 years younger than that of the exudative AMD patients (67.17 ± 7.78 and 73.80 ± 8.06 years, respectively, $P = 0.038$). There was no difference in other baseline characteristics, such as history of diabetes mellitus or hypertension, sex, lens status, and refractive error between the PCV and the exudative AMD patients (Table 1).

Table 1. Baseline Characteristics of Patients with PCV and Exudative AMD

	PCV	Exudative AMD	*P* value
N (eyes)	30	25	
Age (years) (mean ± SD)	69.17 ± 7.78	73.80 ± 8.06	0.038
Sex (male: female)	16:14	10:15	0.419
Involved eye (OD:OS)	14:16	11:14	> 0.999
Lens (phakic)	25 (83.3%)	19 (76%)	0.521
DM	4 (13.3%)	3 (12%)	> 0.999
HTN	15 (50%)	16 (64%)	0.414
Refraction, SE (D) (mean ± SD)	0.15 ± 1.44	0.16 ± 1.35	0.997

PCV = polypoidal choroidal vasculopathy; AMD = age related macular degeneration; N = number; SD = standard deviation; DM = diabetes mellitus; HTN = hypertension; SE = spherical equivalent; D = diopters.

1. Peripapillary Choroidal Thickness

The initial PCT of PCV was thicker than that of exudative AMD. All quadrants showed a similar tendency (all, $P < 0.001$). The mean initial PCT of PCV was 1.73-fold thicker than those of exudative AMD, and the difference between PCV and exudative AMD was 65.01 μm ($P < 0.001$). The initial PCT difference was largest at the superior quadrant and lowest at the inferior quadrant (77.11 μm and 49.03 μm, respectively). The initial inferior PCT of PCV was thinner than the temporal and superior quadrants ($P = 0.018$, $P = 0.015$, respectively) but not thinner than the nasal quadrant ($P = 0.09$). The initial inferior PCT of exudative AMD was thinner than the superior and nasal quadrants ($P = 0.014$, $P = 0.012$, respectively) but not thinner than the temporal quadrant ($P = 0.105$) (Figure 2).

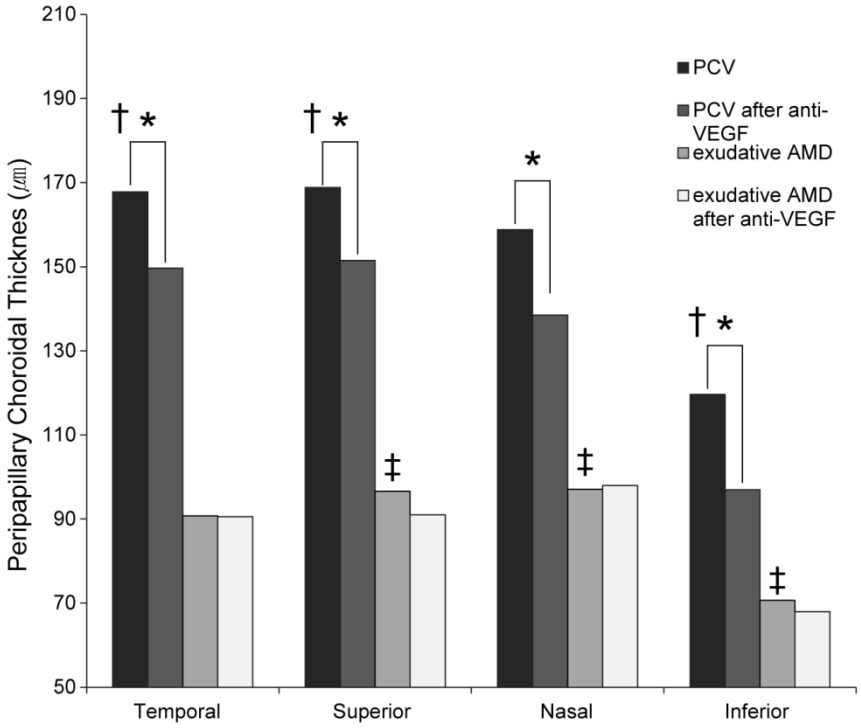

Fig 2. Change of peripapillary choroidal thickness (PCT) in polypoidal choroidal vasculopathy (PCV) and exudative age related macular degeneration (AMD). PCT of PCV was thicker than exudative AMD, before and after anti-vascular endothelial growth factor (VEGF). PCT was decreased after anti-VEGF in PCV (*P < 0.022) but not in exudative AMD. Inferior PCT was thinnest in both PCV and exudative AMD, before and after anti-VEGF. †*P* < 0.018 with post hoc analysis between each sector of PCV before treatment. ‡*P* < 0.014 with post hoc analysis between each sector of exudative AMD before anti-VEGF.

After anti-VEGF treatment, the mean PCT of the PCV decreased 12.75%, from 154.78 ± 56.23 μm to 134.17 ± 41.66 μm (*P* < 0.001). The PCT of the PCV after treatment of all quadrants showed a similar tendency (Figure 2). The PCT reduction in PCV was greatest at the inferior quadrant and lowest at the superior quadrant (18.94%, 22.67 μm; and 10.23 %, 17.27 μm, respectively). However, in exudative AMD, there was no statistically significant difference after anti-VEGF treatment. The mean PCT of exudative AMD after treatment decreased 2.14%,

from 88.77 ± 23.11 μm to 86.87 ± 22.54 μm (P = 0.392). The PCT reduction in exudative AMD was largest at the superior quadrant and lowest at the nasal quadrant, but all differences in quadrants were not significant (P = 0.23–0. 948) (Table 2). Although the PCT of PCV decreased more than exudative AMD after treatment, the mean PCT of PCV was still thicker (1.53-fold) than that of exudative AMD, and the difference between PCV and exudative AMD was 47.3 μm (P < 0.001). The inferior PCT was thinner than the other quadrants in both PCV and exudative AMD after treatment (P = 0.03 to < 0.001).

2. Subfoveal Choroidal Thickness

The initial subfoveal CT of PCV was 128.35 μm, and thicker (1.75-fold) than that of exudative AMD (P < 0.001). After anti-VEGF treatment, both the subfoveal CT of PCV and exudative AMD were reduced (P < 0.001, P = 0.021, respectively). However, the percentage reduction was greater in PCV than in exudative AMD (59.56 μm, 19.85% and 15.56 μm, 9.06 %, respectively). The difference also decreased; the mean subfoveal CT of PCV after treatment was still thicker (1.54-fold) than that of exudative AMD, and the difference between PCV and exudative AMD was 84.35 μm (Table 2).

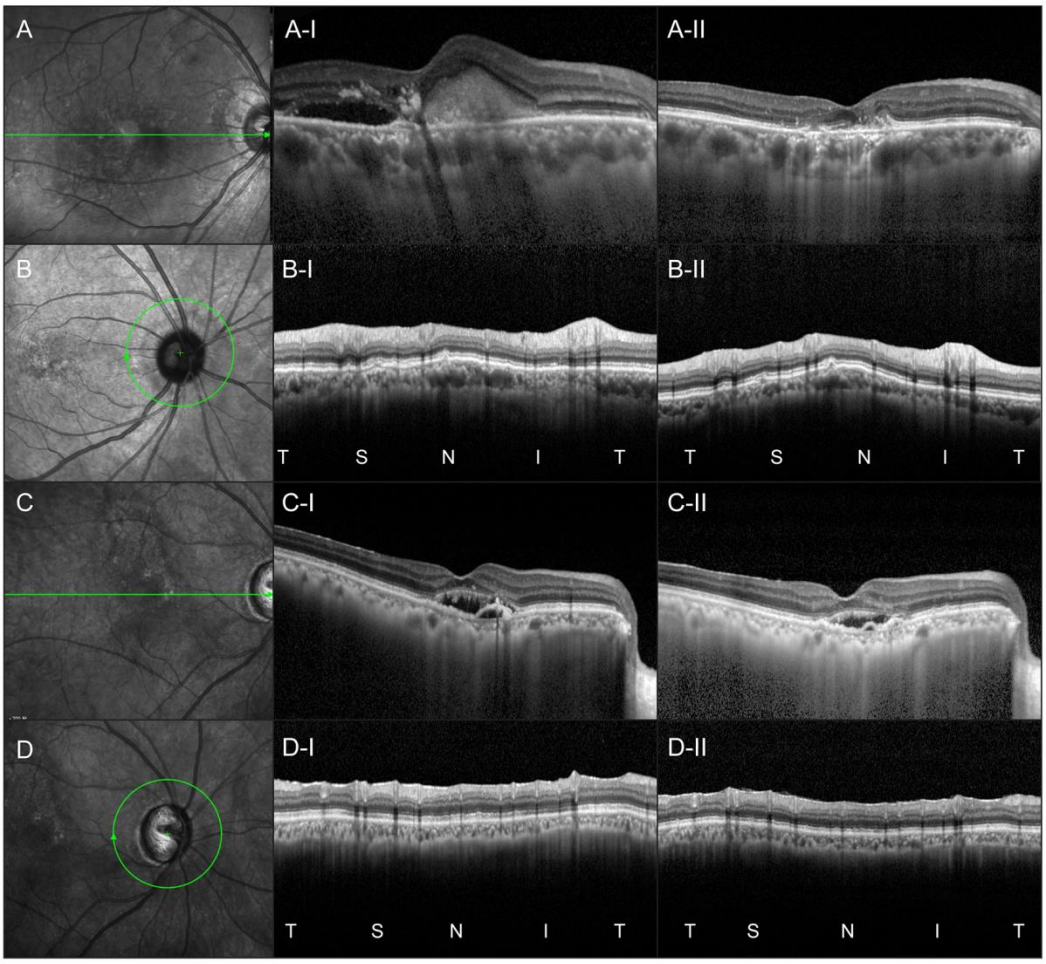

Fig 3. Representative case of peripapillary choroidal thickness (PCT) change after anti vascular endothelial growth factor (VEGF) in polypoidal choroidal vasculopathy (PCV) and exudative age related macular degeneration (AMD). (A, B) Seventy years old female with PCV (A-I, II) Subfoveal choroidal thickness (CT) decreased from 407 μm to 303 μm. (B-I, II) Mean PCT was 198 μm and decrease to 150 μm after anti-VEGF (25 %). (C, D) Seventy seven years old female with exudative AMD (C-I, II) Subfoveal CT decreased from 190 μm to 175 μm (D-I, II) Mean PCT was 119 μm and 114 μm before and after anti-VEGF, respectively.

Table 2. Comparison of PCT between PCV and Exudative AMD before and after anti-VEGF Treatment

	Before Treatment			After Treatment			
	PCV	Exudative AMD	*P* value	PCV	Exudative AMD	*P* value	
						PCV	Exudative AMD
Mean PCT (μm)	153.78 ± 56.23	88.77 ± 23.11	<0.001	134.17 ± 41.66	86.87 ± 22.54	<0.001	0.392
Temporal PCT (μm)	167.83 ± 70.69	90.72 ± 27.16	<0.001	149.70 ± 57.29	90.52 ± 29.64	0.022	0.948
Superior PCT (μm)	168.80 ± 59.05	96.64 ± 38.19	<0.001	151.53 ± 46.31	91.04 ± 32.34	0.006	0.231
Nasal PCT (μm)	158.83 ± 64.43	97.08 ± 28.61	<0.001	138.47 ± 52.94	98.00 ± 28.54	<0.001	0.79
Inferior PCT (μm)	119.67 ± 49.67	70.64 ± 20.92	<0.001	97.00 ± 38.26	67.92 ± 20.90	<0.001	0.302
Subfoveal (μm)	300.03 ± 108.00	171.68 ± 56.92	<0.001	240.47 ± 41.66	156.12 ± 64.56	<0.001	0.021

PCT = peripapillary choroidal thickness; PCV = polypoidal choroidal vasculopathy; AMD = age related macular degeneration; VEGF = vascular endothelial growth factor

IV. DISCUSSION

Our results showed that all quadrants of PCT in PCV are larger than those of exudative AMD, and were reduced after anti-VEGF treatment. The PCT of exudative AMD showed no difference after anti-VEGF treatment. Inferior PCT was thinner than other quadrants in both PCV and exudative AMD, before and after anti-VEGF treatment. The initial mean PCT was 1.73-fold thicker in PCV than exudative AMD. These differences decreased after anti-VEGF treatment to 1.53-fold. The mean PCT of PCV decreased 12.75% after anti-VEGF treatment ($P < 0.001$), but that of exudative AMD decreased 2.14% ($P = 0.392$). The results suggest that choroidal thickening in eyes with PCV is not a localized phenomenon limited to the macular area, but is rather a general characteristic extending to the peripapillary area outside the macula.

The choroid is supplied by various capillary arteries in a distinctive pattern. The nasal choroid is supplied by the medial posterior ciliary artery (PCA), whereas the lateral PCA supplies the area of the choroid not supplied by the medial PCA.[16] The posterior choriocapillaries in the peripapillary and submacular regions are supplied by short PCAs. The PCA from the ophthalmic artery supplies the choroid around the optic nerve head and also supplies the choroid up to the equator.[16] Usually, the temporal half of the choroid is supplied by the lateral PCA, and the nasal half of the choroid is supplied by the medial PCA.[16] The branches of the PCA consist of long PCAs and short PCAs (SPCAs). The temporal SPCAs, SPCAs that come from the lateral PCA, enter the eyeball in the macular region and supply the macular choroid.[16] Because there are no anastomoses between the long PCAs and the short PCAs, there are watershed zones between the areas that are supplied by both.[16-19] They have a segmental distribution without anastomosis and supply a well-defined sector of the choroid.[17,19,20]

Our results suggest that the pathophysiology of PCV is related to the entire blood supply to the choroid, rather than being only confined to the focal choroidal vascular abnormality. In addition, the pathogenesis of exudative AMD may be relatively confined to the macular area and focal chorioretinal abnormalities, because thickening of the choroid may be associated with the anatomy and circulatory characteristics of the eye.[21-23] The choroid in the

macula is somewhat different from the choroid of other areas. The blood supply to the choroid of the macula has two origins involving branches of the short PCAs and a recurrent branch of the long PCA.[24] The presence of very short posterior ciliary arteries (VSPCA), selectively directed to the macular region, has been confirmed by previous studies.[24] The presence of VSPCA may contribute to subfoveal CT and is thought to be related with the development of PCV.

Our finding that the CT decreases in the peripapillary region after anti-VEGF treatment may be another indication of the diffuse choroidal abnormality of PCV. PCV, as compared to exudative AMD, has been reported to occur in patients with thick subfoveal choroids.[11,12] Yamazaki et al. [25] examined the changes in subfoveal CT after intravitreal injections of ranibizumab for unilateral exudative AMD and PCV. The results suggested that intravitreal injections of ranibizumab have a pharmacological effect not only on the neovascular lesion but also on the thickened underlying choroid. Other studies have also reported that an abnormally thickened choroid decreased after anti-VEGF treatment.[26,27] In contrast to PCV, PCT of exudative AMD did not change after anti-VEGF treatment, suggesting that diffuse choroidal thickening is associated with pathogenesis of PCV and that choroidal thinning, such as vortex decompression, may help to reduce polyp development.

Our results confirmed the asymmetrical distribution of the PCT. The mean PCT showed regional differences, being thickest in the superior region and thinnest in the inferior region in both PCV and exudative AMD. These results are similar to previous OCT studies in normal eyes which have consistently shown the inferior region to be thinner than other regions.[28-30] The thinner choroid in the inferior region makes this area more vulnerable to retinal and choroidal diseases. Several studies have hypothesized that the thinnest peripapillary choroid in the inferior quadrant may involve an area of lower blood supply that may predispose the inferior region of the optic nerve to glaucomatous ischemic damage, supporting a possible explanation for the well-known observation that glaucoma typically first affects the inferior

optic nerve region.[28,31]

To the best of our knowledge, this is the first study that investigated the PCT in PCV and exudative AMD, and the effects of anti-VEGF treatment in the peripapillary region. However, this study has several limitations. First, it was a retrospective study, a comparison with a normal control group was not conducted, and diurnal variations of the CT were not considered.[32] Second, although we compared two groups adjusted for age, the baseline characteristics, types, and numbers of anti-VEGF treatments were not controlled. Third, because the peripapillary choroid was thin, and the measurement of the CT was performed manually, the accuracy of measurements was limited. Fourth, previous studies on choroidal hyperpermeability in PCV eyes reported that choroidal thickening might depend on choroidal vascular hyperpermeability.[10] An additional study is needed to investigate the relationship between increased CT and choroidal hyperpermeability.

V. CONCLUSION

Eyes with PCV exhibit a thick choroid overall in both the peripapillary and macula regions. Both regions decrease in thickness after anti-VEGF treatment in PCV, but not in eyes with exudative AMD. In eyes with exudative AMD, subfoveal CT decreased but the peripapillary region did not. The results of this study increase our understanding of the pathogenesis of PCV, and may provide the basis for the development of new treatments for this disorder.

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ABSTRACT(IN KOREAN)

결절성맥락막혈관병증에서 항혈관내피세포성장인자 치료 후 시신경주변 맥락막 두께의 변화

<지도교수 고 형 준>

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목적: 결절성 맥락막 혈관병증과 나이관련 황반변성에서의 시신경 주변부 맥락막 두께의 차이와 항 혈관내피세포 형성인자 안구내 주사술시 각 질환에서 시신경주변부 맥락막 두께 변화의 차이를 알아본다.
방법: 새로 진단받고 치료를 시작한 결절성 맥락막 혈관병증 30안과 나이관련 황반변성 25안을 대상으로 항 혈관내피세포 형성인자 주사술 전후 시신경 주변맥락막 두께와 망막중심두께를 측정하였다.
결과: 주사술 전 평균 시신경 주변 맥락막 두께는 결절성 맥락막 혈관병증(153.78 ± 56.23 μm)에서 나이관련 황반변성(88.77 ± 23.11 μm, $P < 0.001$)보다 두꺼웠다. 이 경향은 모든 사분면에서 동일하였다. (86.87 ± 22.54 μm, $P = 0.392$) 항 혈관내피 세포형성인자 안구내 주사술 후 시신경 주변 맥락막 두께는 결절성 맥락막병증에서는 의미 있게 감소하였으나(134.17 ± 41.66 μm, $P < 0.001$) 나이관련 황반변성에서는 그렇지 않았고(86.87 ± 22.54 μm, $P = 0.392$) 모든 사분면에서 동일한 경향을 보였다.
결론: 결절성 맥락막혈관병증에서 맥락막 두께는 시신경주변과 망막중심부 모두에서 나이관련 황반변성보다 두꺼웠다. 두 영역 모두 항 혈관내피세포 형성인자 안구내 주사술 후 의미 있게 두께가 감소하였다. 나이관련 황반변성에서는 망막 중심부 맥락막 두께는 주사술 후 줄어들었으나 시신경주변부는 그렇지 않았다.

핵심되는 말 : 나이관련황반변성, 결절성맥락막혈관병증, 맥락막