

Choroidal vascular sublayers in Chinese pre-eclampsia and healthy pregnancy

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Research Article

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Abstract

Background: Using spectral-domain optical coherence tomography (SD-OCT) to investigate choroidal vascular sublayers in Chinese pre-eclampsia (PE) and healthy pregnancy.

Methods: This was an observational, cross-sectional study, including 20 normal subjects, 23 healthy pregnancy and 37 patients with PE. Using SD-OCT, subfoveal choroidal thickness (SFCT) at 750µm nasal and temporal to the fovea, 1500µm nasal and temporal to the fovea at T1500, T750, SFCT, N750, N1500 and sublayers (choriocapillaris/Sattler layer and Haller layer) were measured.

Results: There was no significant difference in mean age, spherical equivalent among the three groups ($P=0.532$). Additionally, no significant difference in the gestational age between the healthy pregnancy and PE group was found ($P=0.783$). Significant differences were seen in large choroid vessel thickness (LCVT), medium choroidal vessel thickness (MCVT) and choroidal thickness (CT) at 5 locations among three groups ($P<0.05$). There was significant increase in healthy pregnancy group than in normal subjects at N1500-CT, N750-CT, SFCT, T750-CT and MCVT ($P<0.05$), while no significant difference was observed at T1500CT and LCVT ($P>0.05$). Meanwhile, significant increase was detected in PE group than in healthy pregnancy group at N1500-CT, N750-CT, SFCT, T750-CT, T1500CT and LCVT ($P<0.05$), whereas no significant difference was observed at MCVT ($P=0.709$).

Conclusion: Our study revealed the variation of choroidal vascular sublayers during pregnancy and PE.

Key words: Pre-eclampsia, subfoveal choroidal thickness, choroidal sublayers, optical coherence tomography

Background

Pre-eclampsia (PE) is one of the main causes of maternal, fetal and neonatal mortality and morbidity [1]. It is a multi-systemic disorder, including thrombocytopenia, elevated levels of liver transaminases, renal insufficiency, pulmonary edema and visual or cerebral disturbances.

To date, optical coherence tomography (OCT) has been proven valuable for observing changes in choroid. By using SD-OCT, numerous studies have focused on measuring the thickness of the choroid and its association with the pathophysiology of many diseases, such as age-related macular degeneration, polypoidal choroidal vasculopathy, central serous chorioretinopathy (CSC), and high myopia [2-4].

In previous studies, PE has been demonstrated to result in increased choroidal thickness [5, 6]. Furthermore, quantitative assessment of choroidal vascular sublayers, including large choroid vessel thickness (Haller layer, LCVT) and medium choroidal vessel thickness (choriocapillaris/Sattler layer, MCVT), has provided new insight into the role of the choroid in patients with CSC and myopic eyes [7, 8].

Nowadays, the changes of the thickness in different choroidal sublayers are poorly understood in PE patients. Therefore, the aim of this investigation is to analyze different locations of CT, subfoveal LCVT and MCVT of patients with PE.

Methods

We performed this observational, cross-sectional study at Beijing Anzhen Hospital, Capital Medical University. This study complied with the tenets of the Declaration of Helsinki and was approved by the local ethics committee. Written informed consent was obtained from the participants before the study began. The study enrolled 20 eyes of 20 normal subjects (normal group), 23 eyes of 23 healthy pregnant women (healthy pregnancy group) and 37 eyes of 37 patients with PE (PE group). It was conducted to compare choroidal thickness at the fovea and in the locations of 750 μ m/1500 μ m temporal/nasal to the fovea (T1500, T750, SFCT, N750, N1500), choriocapillaris/Sattler layer (MCVT) and Haller layer (LCVT). All the subjects were from Chinese Han population, and they were recruited for this study from the Ophthalmology Clinics between May 2016 and October 2018.

Inclusion criteria for pregnant women were a single pregnancy in the third trimester with spherical equivalent (SE) between -6 and 6 diopters(D). PE was defined as hypertension (BP \geq 140/90mmHg after 20 weeks of gestation) and new onset of proteinuria (\geq + on dipstick reading or \geq 0.3g/d by 24h urine collection). Inclusion criteria for normal subjects were: childbearing age (20-40 years); non-pregnancy; SE between -6D and 6D. Exclusion criteria were previous ocular surgeries, history of smoking, any systemic disease, such as chronic hypertension, diabetes mellitus, renal, rheumatologic, anemia or cardiovascular diseases.

All subjects underwent complete ophthalmic examinations, including a best corrected visual acuity(BCVA) test, noncontact tonometry (CT-80A computerized tonometer; Topcon, Tokyo, Japan), spherical equivalent refractive error using an Autorefractor (RK-F1; Canon, Tokyo, Japan), slit-lamp examination and SD-OCT (3D OCT-1000 Mark II; Topcon, Tokyo, Japan). We used the choroid mode to obtain images of the choroid. The 6mm single line scan was captured 50 times in the same position using eye tracking technology, then the software generated a high-resolution averaged image of the 50 B-scans. The definition of choroidal thickness was the vertical distance between the posterior edge of the hyper-reflective retinal pigment epithelium and the choroid/sclera junction. CT was measured at the fovea and in the locations of 750 μ m/1500 μ m temporal/nasal to the fovea. LCVT was defined as the thick layer of oval-shaped hyperreflective profiles with hyporefective cores in the outer choroid. It was measured perpendicularly from the inner border of the sclera to the innermost point of the selected large choroidal vessel as described previously [8, 9]. MCVT was defined as thickness of medium vessels and choriocapillaries, since the measurement of choriocapillaris is unreliable in cross-sectional SD-OCT. It was calculated by subtracting large vessel thickness from choroidal thickness at SFCT (fig.1). All participants took this OCT scans in the afternoon (1pm to 4pm). Two independent experienced specialists measured these parameters using a built-in caliper in the OCT software, and the average value of the data were

used for statistical analysis. Group identities remained anonymous to both examiners. One of the two eyes with good image quality was enrolled.

Statistical analysis

Statistical analysis was performed using a statistical software package (SPSS for Windows, version 23.0; Chicago, IL, USA). All values were reported as mean±standard deviation (SD). Kruskal-Wallis test was used to compare age, spherical equivalent, differences in choroidal thickness, LCVT and MCVT among three groups. The differences of age, spherical equivalent, gestational age, choroidal thickness, LCVT and MCVT between any two groups were compared using Mann-Whitney U-test. A P value ≤ 0.05 was considered statistically significant.

Results

Demographic Characteristics

The study included 80 subjects: 37 patients with PE, 23 healthy pregnancy and 20 normal subjects. There was no significant difference in mean age, spherical equivalent among the three groups. ($P=0.532, 0.415$, respectively) Additionally, no significant difference was found in the gestational age between the healthy pregnancy and PE group ($P=0.783$) (Table 1).

Choroidal measurements

LCVT, MCVT and CT at all locations in the three groups are listed in Table 1. Significant differences were seen in LCVT, MCVT and CT at all locations among three groups (all $P<0.05$).

1500 μ m nasal to the fovea (N1500-CT)

N1500-CT were $219.50\pm 62.06\mu\text{m}$, $257.61\pm 40.49\mu\text{m}$ and $292.08\pm 58.26\mu\text{m}$ in normal group, the healthy pregnancy group and the PE group respectively, with statistical significance among three groups ($P<0.05$), and also in pairwise comparison with statistical significance ($P<0.05$).

750 μ m nasal to the fovea (N750-CT)

N750-CT were $237.75\pm 65.24\mu\text{m}$, $280.96\pm 37.93\mu\text{m}$ and $314.81\pm 59.71\mu\text{m}$ in normal group, the healthy pregnancy group and the PE group respectively, with statistical significance among three groups ($P<0.05$), and also in pairwise comparison with statistical significance ($P<0.05$).

SFCT

SFCT were $263.45\pm 69.66\mu\text{m}$, $309.39\pm 39.71\mu\text{m}$ and $346.87\pm 66.49\mu\text{m}$ in normal group, the healthy pregnancy group and the PE group respectively, with statistical significance ($P<0.05$), and also in pairwise comparison with statistical significance ($P<0.05$).

750µm temporal to the fovea T750-CT

T750-CT were $248.75 \pm 60.16 \mu\text{m}$, $287.91 \pm 40.36 \mu\text{m}$ and $312.76 \pm 54.88 \mu\text{m}$ in normal group, the healthy pregnancy group and the PE group respectively, with statistical significance ($P < 0.05$), and also in pairwise comparison with statistically significance ($P < 0.05$).

1500µm temporal to the fovea T1500-CT

T1500-CT were $239.20 \pm 46.97 \mu\text{m}$, $264.52 \pm 32.79 \mu\text{m}$ and $294.35 \pm 46.41 \mu\text{m}$ in normal group, the healthy pregnancy group and the PE group respectively, with statistical significance ($P < 0.05$).

Significant difference was detected only between the healthy pregnancy group and the pre-eclampsia group ($P = 0.012$).

LCVT

LCVT were $188.25 \pm 60.88 \mu\text{m}$, $214.13 \pm 43.57 \mu\text{m}$ and $252.35 \pm 70.19 \mu\text{m}$ in normal group, the healthy pregnancy group and the PE group respectively, with statistically significance ($P < 0.05$).

Significant difference was found only between the healthy pregnancy group and the pre-eclampsia group ($P = 0.016$).

MCVT

MCVT were $75.20 \pm 33.65 \mu\text{m}$, $95.26 \pm 18.73 \mu\text{m}$ and $94.51 \pm 26.85 \mu\text{m}$ in normal group, the healthy pregnancy group and the PE group respectively, with statistically significance ($P < 0.05$).

Significant difference was detected only between normal group and the healthy pregnancy group ($P = 0.007$).

Discussion

The choroid contains more than 85% of the blood flow in the eye, which supplies the outer retina. Abnormal choroidal blood volume or hemodynamic changes may lead to retinal photoreceptor dysfunction and death [10]. Therefore, the choroid plays a fundamental role in the pathophysiology of many disease, including age-related macular degeneration (AMD), central serous chorioretinopathy and diabetic retinopathy [3, 11, 12].

CT is a significant indicator in different kinds of retinopathy. Prior studies have investigated CT in healthy pregnant women. Liu et al. [13] found that CT in healthy pregnant women is greater than that in normal nonpregnant women. In another study, SFCT was shown to be significantly increased in pregnant women than in healthy women, which may be resulted from physiological hemodynamic changes during

pregnancy, such as increased cardiac output, arterial compliance, and decreased total vascular resistance [14]. However, Takahashi et al. and Benfca et al. [15, 16] demonstrated that no statistically difference in CT between healthy non-pregnant women and healthy pregnant women in the third trimester. In our study, there were significant increase at N1500-CT, N750-CT, SFCT, T750-CT and MCVT in healthy pregnancy group than in normal subjects (all $P < 0.05$), while no significant differences were observed at T1500-CT and LCVT (all $P > 0.05$). To the best of our knowledge, this is the first investigation having measured total CT, Haller layer thickness and medium vessel CT in pregnant in vivo.

Previous studies have already evaluated the CT between the patients with PE and the healthy pregnancy. Garg et al. assessed CT of 15 PE pregnant, 15 healthy pregnant, and 19 healthy non-pregnant women during the postpartum period in their study. They found that CT was significantly higher in PE women than in the other groups, which may be caused by increased vascular endothelial growth [6]. JW Kim et al. found that CT to be significantly increased in PE than in normal subjects or in healthy pregnancy. They observed PE did appear to result in increased CT, which suggests that additional unknown factors induce hyperpermeability in pregnant women [5]. However, no studies have investigated which layer of the choroid increased. Our study extends the previous findings and observes the thickness of the sublayers of the choroid. Interestingly, there were significant increase in PE group than in healthy pregnancy group at each location of CT and LCVT, while no significant differences were observed at MCVT. This suggests the increase of the CT is likely due to the thickening of the Haller layer.

As is known, PE is a disorder associated with hypertension that leads to maternal multiple organs failure and fetal compromise [17]. One of the main features in PE is hypovolemia, that is associated with an increased sympathetic activity [18]. Choroid contains large membrane-lined lacunae, non-vascular smooth muscle cells and intrinsic choroidal neurons, which receive sympathetic, parasympathetic and nitergic innervation [19]. Schrodler et al. [20] have hypothesized that the intrinsic choroidal neurons may act as intermediaries in the sympathetic system between the post-ganglionic neurons and the muscle, and increase smooth muscle tone. Additionally, nonvascular smooth muscle cells (NVSMC) may be associated with increased thickness of Haller layer in CSC [7]. Since pregnancy is one of the risk factors of CSC, especially in the third trimester [21], it can be suggested that the thickening of the choroid in PE is similar to the choroidal alterations in CSC.

Unlike Haller layer, MCVT is significantly different between normal group and healthy pregnancy group, while not between healthy pregnancy group and PE group. It is important to further understand the relationship between choroidal thickening and choroidal blood flow. The parasympathetic innervation has been shown to vasodilate and increase choroidal blood flow, whereas the sympathetic input vasoconstricts and decreases choroidal blood flow. In addition, the sensory input has been shown to both convey pain and thermal information centrally, then act locally to vasodilate and increase choroidal blood flow [22]. Yang et al. [23] suggest that normal pregnancy is associated with a facilitation of sympathetic regulation and an attenuation of parasympathetic influence, and such alterations are enhanced in preeclamptic pregnancy. Under these conditions, we hypothesized that the thickening of the Haller layer in

healthy pregnancy group may be prevented since thickening of medium choroidal vessel layer is due to the expansion of the stroma.

There are several limitations in our study. The first one is the small number of patients. In addition, these parasympathetic, sympathetic, and sensory fibers and their terminals tend to be localized to the walls of the arteries and veins of the choroid, while not to the choriocapillaries. However, it's difficult to separate choriocapillaries from medium vessel choroidal layer using SD-OCT. Therefore, we investigated choriocapillaries and medium choroidal vessel layer as a whole. Finally, we were not able to investigate PE patients after pregnancy to obtain longitudinal data. Large-scale and longitudinal studies are recommended to elucidate this problem in the future.

Conclusion

In conclusion, our study revealed the presence of a significant increase of 5 locations of CT and LCVT in PE group, and a significant increase of 4 locations of CT and MCVT in pregnancy group. The NVSMC and the adjustment of parasympathetic and sympathetic nervous may play a role in the variation of choroidal vascular sublayers during pregnancy and PE.

Abbreviations

BCVA: best corrected visual acuity; CSC: central serous chorioretinopathy; CT: choroidal thickness; LCVT: large choroid vessel thickness; MCVT: medium choroidal vessel thickness; NVSMC: nonvascular smooth muscle cells; PE: pre-eclampsia; SD: standard deviation; SD-OCT: spectral-domain optical coherence tomography; SE: spherical equivalent; SFCT: subfoveal choroidal thickness

Declarations

Funding

No funding was obtained for this study.

Availability of data and materials

The datasets used during the current study available from the corresponding author on reasonable request.

Authors' contributions

TTH and JW conceived and designed the study protocol. TTH and XM collected the data. XXG and XM were involved in the analysis. TTH wrote the first draft of the manuscript. XM, XXG and JW reviewed and revised the manuscript and produced the final version. All authors have read and approved the final manuscript.

Ethics approval and consent to participate

This study was performed in accordance with the Declaration of Helsinki and was approved by the Ethics Committee of Capital Medical University affiliated Beijing Anzhen Hospital. Written informed consent was obtained from all subjects after the aims of the study were explained to the participants.

Competing interests

The authors declare that they have no competing interests.

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Tables

Table 1. Demographic Characteristics and choroidal measurements among normal subjects, healthy pregnancy and patients with PE

Information	Normal group	Healthy pregnancy group	PE group	<i>P</i>	<i>P</i>	<i>P</i>
				Among the three groups	Normal group vs healthy pregnancy group	healthy pregnancy group vs PE group
Number	20	23	37			
Age[years]	31.20±4.30	30.52±4.56	31.68±3.90	0.532	0.346	0.324
SE(D)	-2.19±1.52	-2.57±1.55	-2.03±1.72	0.415	0.466	0.212
Gestational age[week]		33.52±5.58	33.16±4.92			0.783
N1500-CT(μm)	219.50±62.06	257.61±40.49	292.08±58.26	0.000	0.036	0.009
N750-CT(μm)	237.75±65.24	280.96±37.93	314.81±59.71	0.000	0.034	0.007
SFCT(μm)	263.45±69.66	309.39±39.71	346.87±66.49	0.000	0.024	0.010
T750-CT(μm)	248.75±60.16	287.91±40.36	312.76±54.88	0.001	0.031	0.037
T1500CT(μm)	239.20±46.97	264.52±32.79	294.35±46.41	0.000	0.064	0.012
LCVT(μm)	188.25±60.88	214.13±43.57	252.35±70.19	0.002	0.144	0.016
MCVT(μm)	75.20±33.65	95.26±18.73	94.51±26.85	0.015	0.007	0.709

PE=pre-eclampsia, SE= spherical equivalent, SFCT= Subfoveal choroidal thickness, LCVT= large choroid vessel thickness, MCVT= medium choroidal vessel thickness. $P>0.05$ shows no significant difference

Figures

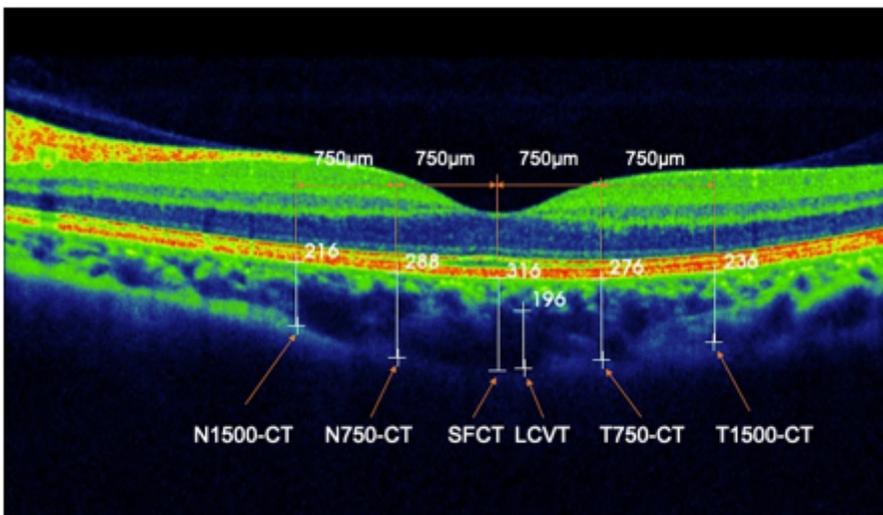


Figure 1

SD-OCT showing choroidal measurements including SFCT, LCVT, CT of temporal 750μm and 1500μm to the fovea.