

The evaluation of juvenile ocular hypertension by optical coherence tomography angiography

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Abstract

Background: We wish to evaluate the vessel density using optical coherence tomography angiography (OCTA) in juvenile ocular hypertension (JOHT). In addition, we investigate the potential risk parameters of intraocular pressure (IOP) and vertical cup/disc ratio (CDR) with OCTA for observing the development of JOHT.

Methods: We examined 86 eyes in 45 healthy subjects and 65 eyes in 34 patients with JOHT using OCTA at the glaucoma clinic of the Eye, Nose, and Throat Hospital of Fudan University. The vessel density (VD) of radial peripapillary capillaries (RPC) and perifoveal superficial vascular plexus (SVP) was compared between healthy and JOHT group. Other basic study factors such as: age, sex, blood pressure, best-corrected visual acuity, central corneal thickness, IOP, CDR, the thickness of retinal nerve fiber layer, ganglion cell complex, visual field mean deviation, and pattern standard deviation were also recorded.

Results: Temporal RPC-VD was negatively associated with IOP ($p=0.043$). Additional five sections of nasal, inferior-nasal, inferior-temporal, superior-temporal and superior-nasal of RPC-VD showed positive correlation with CDR. SVP-VD in superior and nasal regions were affected by high IOP ($p=0.023$ and $p=0.049$). No other difference was uncovered between healthy and JOHT subjects.

Conclusions: Peripapillary temporal perfusion had negative correlation with IOP in JOHT subjects. And regions were positively correlated with large CDR. Perfusion of perifoveal regions were only affected by IOP. We conclude that OCTA could be used as an effective technique to monitor the development of JOHT.

Background

Ocular Hypertension (OHT) is defined as intraocular pressure (IOP) higher than 21 mmHg with normal optic disc structure/function and no previous history of angle closure. Approximately 5% of OHT patients develop glaucoma after 5 to 7 years follow up [1]. Glaucoma is the leading cause of irreversible blindness including both adult-onset disease (occurring after 40 years of age) and juvenile-onset disease (occurring between the ages of 3 and 40 years old), and the IOP of juvenile-onset patients are often extremely high with a more aggressive clinical course [2 3]. Thus, OHT in juveniles (JOHT) should be given more attention when considering long-term follow up. However JOHT presents few ocular symptoms and little disturbance of visual acuity which makes the diagnosis and management a difficult clinical challenge [4]. Evidence provided by previous studies concerning OHT focuses on people more than 40 years old in accord with traditional diagnostic standards [1]. Currently, there is no consensus in the literature that offers guidance to the clinician in determining of whom in JOHT should be treated. The ocular hypertension treatment study (OHTS) established that medically treating ocular hypertension is efficacious in delaying or preventing the onset of glaucoma while the European Glaucoma Prevention Study (EGPS) failed to demonstrate the significance of reducing IOP preventing the onset of the disease [5 6]. The effects of lowering IOP in JOHT subjects were ambiguous. Moreover, JOHT individuals are

being identified with the prevalence of optical screening and some of them are even with large vertical cup/disc ratio (CDR). This is considered a good qualitative predictor for the onset of POAG in JOHT, though this correlation has not been empirically verified [7]. The index of CDR has long been used in the assessment of JOHT, while the wide range of CDR values in the normal population from 0.00 to 0.87 limits its utility [8 9]. Thus, decisions regarding the therapy of JOHT can be difficult, especially for those with large CDR [10 11]. New modalities should be considered to assess the progression of JOHT patients and how the predictors of CDR and IOP impact on the evaluation of the disease.

Previous experimental and clinical investigations have provided evidence showing strong correlation between vascular dysregulation and glaucoma [12 13]. Recently, the rapidly evolving technology of optical coherence tomography angiography (OCTA), has been utilized to measure retinal local circulation without the need for dye infusion. The split-spectrum amplitude-decorrelation angiography (SSADA) algorithm can be used to quantify blood flow [14]. Radial peripapillary capillaries (RPC) comprise a network of capillary beds located within the retinal nerve fiber layer (RNFL) that supply the retinal ganglion cell (RGC) axons, and damage to RNFL and RGC are typical manifestations of glaucoma [15]. Thus OCTA could quantitatively characterize the microvasculature around the nerve head to find the perfusion changes of glaucoma. Previous studies using OCTA have shown that perfusion of RPC is significantly reduced in glaucoma and related to the severity of the disease [16 17]. Additionally, macular vessel density of superficial retinal vascular plexus (SVP) has also been investigated and a reduction in macula has been found [18]. However, the perfusion profile of JOHT remains unknown. Therefore, investigating the use of non-invasive and high-resolution OCTA techniques for JOHT subjects is an important research avenue to pursue.

The purpose of this study was to evaluate retinal blood flow in JOHT using OCTA and to examine the relevance of IOP and CDR to the perfusion profile.

Methods

Study participants

This was a cross-sectional study. Participants were recruited from Aug 1, 2017 to Jul 1, 2018 at the glaucoma clinic of the Eye, Ear, Nose and Throat Hospital of Fudan University of Shanghai, China. The study received approval from the Ethical Review Committee of the Eye, Ear, Nose and Throat Hospital and adhered to the tenets of the Declaration of Helsinki. All participants provided written informed consent before the examination.

Eligibility was determined by a complete ophthalmologic examination, including slit-lamp biomicroscopy, best-corrected visual acuity (BCVA), refractive error (RE) measured with an autorefractor (KR-890; Topcon, Tokyo, Japan), IOP measurement with Goldmann applanation tonometry, gonioscopy, axial length (AL) and central corneal thickness (CCT) A-scan ultrasound (A-scan Pachymeter, Ultrasonic, Exton, PA, USA), and dilated fundus examination. Standard automated perimetry (SAP) (30 – 2 Swedish Interactive Threshold Algorithm; Humphrey Field Analyzer II; Carl Zeiss Meditec, Inc., Dublin, CA), spectral-domain

optical coherence tomography (SD-OCT) (RTVue OCT; Optovue Inc., Toledo, OH) and OCTA (RTVue-XR Avanti, software version 2014.2.0.65; Optovue, Inc; Fremont, CA, USA) were also accomplished by operators. And OCTA scans were repeated at least twice and mean of the results were evolved in final analysis. Systematic information including age, sex, blood pressure (BP) and pulse rate (PR) were collected. BP was recorded as systolic blood pressure (SBP) and diastolic blood pressure (DBP). The mean arterial pressure (MAP) was calculated as the following formula: $MAP = 2/3DBP + 1/3SBP$. The mean ocular perfusion pressure (MOPP) was calculated by subtracting the IOP from two thirds of the MAP[19].

Inclusion criteria were (1) age > 3 years old and < 40 years old, (2) normal open-angles on gonioscopy, (2) BCVA \geq 12/20, (3) AL < 26.50 mm and RE < -6.0D, (4) average RNFL and GCC thickness within 99% confidence limits, (5) a minimum of two reliable normal visual fields (ie, false-positive errors < 15%, false-negative errors < 15% and fixation loss < 20%), defined as a pattern standard deviation (PSD) and mean deviation (MD) within 95% coincidence limits within six months. Exclusion criteria for all groups were previous intraocular surgeries, nonglaucomatous optic neuropathy, or secondary elevated IOP and other ocular diseases. Participants were also excluded if there was a diagnosis of such as hypothyroidism, diabetes mellitus, cardiovascular diseases and abnormal hemorheology [20].

Major inclusion criteria of control subjects (CON) include normal optic disc accord with ISNT rule, intact neuroretinal rim and IOP \leq 21 mmHg with no history of elevated IOP. JOHT are with untreated IOP of > 21 mmHg and < 32mmHg[1].

OCTA image acquisition and processing

All of the OCTA scans were acquired via a commercial spectral domain system. The system uses an A-scan rate of 70 kHz and has a light source centred on 840 nm and a bandwidth of 45 nm. Both eyes of each participant were operated and scanned within the same visit. The uses of two repeated B-scans at 304 raster positions allowed the acquisition of three-dimensional (3D) OCTA scans with each B-scan consisting of 216 A-scans. With a B-scan frame rate of 210 frames per second, each OCTA volume scan could be acquired in approximately 3 seconds. An en face retinal angiogram was created by projecting the flow signal internal to retinal pigment epithelium. All this processing could be achieved using the software included above. Motion artifacts were removed by 3D orthogonal registration and merging of the two scans. SSADA was described in previous publications and developed to overcome the pulsatile bulk motion noise in the axial direction [15].

OCTA was used to quantify the perfusion of both optic disc and macula. The peripapillary and perifoveal vessel density (VD) were calculated as the proportion of measured area occupied by flowing blood vessels as the pixels with decorrelation values over the threshold in SSADA. Scans were obtained over a 4.5×4.5 mm region centred at the optic nerve head and a 6.0×6.0 mm region centred at the fovea (Fig. 1). Retinal layer segmentation was analysed automatically to segment the inner limiting membrane (ILM) and the outer boundary of the inner plexiform layer (IPL) for both peripapillary and perifoveal scans (Fig. 1. B, D, F, H). RPC plexus from ILM to RNFL for peripapillary scans and SVP from ILM to IPL for

perifoveal scans were recorded and analysed, respectively. The peripapillary region was defined as a 700 µm wide elliptical extending outward from the boundary of optic disc. The peripapillary area was divided into six sectors as designated by Garway-Heath (Fig. 1. A, E) (N, nasal; I, inferior; T, temporal; S, superior) [21]. The perifoveal retinal perfusion was measured using a masking procedure. The masking overlay consisted of an annulus, defined by an inner diameter of 0.6 mm and an outer diameter of 6 mm, and the region was divided into four sectors according to the ETDRS regionalization (Fig. 1. C, G). The large vessels were excluded from the image in order to calculate only the capillary density while scans with low signal strength index of less than 48 or motion artefacts were also excluded[22].

Statistical analysis

Patients' characteristics between two groups were compared using two-sample t test or Kruskal-Wallis rank sum test when data was in accord with gaussian distribution or not. All the continuous variables are described as means ± standard deviation (SD). A chi-square test was used to analyse the frequency data on gender. Both of the eyes of participants up to inclusion criteria were selected for the analysis, thus a linear mixed model was used to detect the differences in eye-level covariates between control and JOHT due to within-subject correlation. Parameters of IOP > 21 mmHg or CDR > 0.6 were given the value of 1 while the opposite was assigned to 0 to assess the impact of the two factors on vessel density using a liner mixed model. As FD-OCT showed a higher sensitivity and lesser specificity in calculation of CDR, a ratio slightly higher than ophthalmoscopic standards was applied [23]. All analyses were performed by SAS software (v9.4, Inc, Cary, NC). A p-value less than 0.05 was considered statistically significant.

Results

86 eyes of 45 CON subjects and 65 eyes of 34 JOHT subjects who initially met the eligibility criteria were included in final analysis. Two groups' demographics and clinical characteristics are summarized in Table 1. They were comparable for age, gender, SBP, DBP, MAP, PR, BCVA, CDR, GCC thickness, visual field MD and PSD (Table 1). Parameters of AL, CCT, IOP and RNFL thickness were statistically different between healthy and JOHT subjects, thus IOP was further compared using a corrected formula as follows: Corrected IOP = Measured IOP - (CCT - 520) * 2.5 / 50 [24]. Corrected IOP of JOHT subjects were significantly higher than that of CON as designed ($p < 0.001$). RPC-VD and SVP-VD were adjusted for AL, CCT and RNFL differences in the post-hoc analysis to compare VD between JOHT and CON. Difference was found in NI and T peripapillary region ($p = 0.042$ and $p = 0.033$) while other regions showed no difference (Fig. 2).

Table 1 Demographic, clinical and ocular characteristics of the CON and JOHT subjects

	CON eyes (86 eyes of 45 subjects)	JOHT eyes (65 eyes of 34 subjects)	P value
Demographic characteristics			
Age (years)*	28.2±6.4	24.7±12.0	0.127
Gender (male%)†	30%	50%	0.064
Clinical characteristics			
SBP (mmHg)*	118.8±13.2	122.1±19.4	0.421
DBP (mmHg)*	74.1±9.8	74.1±12.8	0.983
MAP (mmHg)*	89.0±9.7	90.1±14.2	0.724
PR (bpm)*	74.1±14.2	78.5±12.7	0.141
Ocular characteristics			
BCVA (logMAR)	1.0±0.2	1.0±0.1	0.840
AL (mm)	24.5±1.1	24.9±1.0	0.049
CCT (µm)	535.2±33.7	565.2±31.8	<0.001
IOP (mmHg)	15.9±2.3	24.9±3.3	<0.001
MOPP (mmHg)	43.4±6.4	33.6±10.2	<0.001
Corrected IOP (mmHg)	15.2±2.2	22.7±4.5	<0.001
CDR (vertical cup/disc)	0.6±0.2	0.6±0.1	0.998
RNFL (µm)	107.3±9.4	104.0±10.0	0.044
GCC (µm)	95.4±6.6	93.2±6.6	0.050
MD (dB)	-1.3±1.1	-1.5±1.4	0.414
PSD (dB)	1.7±0.5	1.9±0.7	0.074

* Variables were analysed using two-sample t test or Kruskal-Wallis rank sum test due to data distribution.

† Variables of gender were compared using the chi-square test.

Unlabeled variables used a linear mixed model to adjust the eye-level factors.

CON, control; JOHT, juvenile ocular hypertension; SBP, systolic blood pressure; DBP, diastolic blood pressure; MAP, mean arterial pressure; PR, pulse rate; BCVA, best-corrected visual acuity; AL, axial length; CCT, central corneal thickness; IOP, intraocular pressure; MOPP, mean ocular perfusion pressure; RNFL, retinal nerve fiber layer; GCC, ganglion cell complex; MD, mean deviation; PSD, pattern standard deviation.

All data from CON and JOHT were included to evaluate the effect of IOP and CDR on RPC-VD. A eye-gender, CCT, AL and RNFL -adjusted linear mixed model showed that VD of inside disc was significantly lower in subjects with CDR more than 0.6 ($r=-13.304$, $p<0.001$; Table 2). RPC-VD of the T region was significantly influenced by IOP ($r=-1.329$, $p=0.043$; Table 2), while other regions showed no correlation with high IOP. Average RPC-VD, and N, IN, IT, ST, SN regions of RPC-VD were strongly correlated positively with CDR >0.6 ($r=2.621$, $p<0.001$; $r=4.425$, $p<0.001$; $r=3.110$, $p<0.001$; $r=2.153$, $p=0.001$; $r=1.642$, $p=0.019$; $r=2.463$, $p=0.006$, respectively). Of the six regions in RPC-VD, only the T region showed no correlation with CDR. ($r=0.926$, $p=0.152$)

Linear mixed model adjusted by CCT,AL, GCC and eye-gender also showed that perfusion of SVP had negative correlation with CDR, while IOP were not. S of SVP-VD was affected by IOP ($r=-1.877$, $p=0.023$; Table 2) while the N region was also influenced by the factor of IOP ($r=-1.693$, $p=0.049$; Table 2). Besides, parafovea and hemi-S SVP-VD was found to be statistically distinct with IOP ($r=-1.530$, $p=0.041$; $r=-1.570$,

p=0.037; Table 2). Unmentioned parameters were not found significant differences between positive and negative value of IOP or CDR in SVP-VD (all p>0.05, Table 2).

Table 2 Regression coefficient of IOP and CDR in assessment of VD				
	r (IOP)	P value	r (CDR)	P value
Inside disc	-1.377	0.358	-13.304	<0.001***
Fovea	0.895	0.466	0.942	0.418
RPC-VD				
Avg	-0.887	0.122	2.621	<0.001***
N	-0.599	0.545	4.425	<0.001***
IN	-0.727	0.409	3.110	<0.001***
IT	-1.240	0.074	2.153	0.001**
ST	-0.978	0.181	1.642	0.019*
SN	-0.598	0.520	2.463	0.006**
T	-1.379	0.043*	0.926	0.152
SVP-VD				
Parafovea	-1.530	0.041*	0.905	0.625
Hemi-S	-1.570	0.037*	0.950	0.180
Hemi-I	-1.449	0.064	0.936	0.204
T	-1.235	0.116	1.330	0.075
S	-1.877	0.023*	0.177	0.818
I	-1.236	0.209	1.389	0.137
N	-1.693	0.049*	0.883	0.276

IOP, intraocular pressure; CDR, cup/disc ratio; VD, vessel density; RPC, radial peripapillary capillaries; SVP, superficial vascular plexus; T, temporal; I, inferior; N, nasal; S, superior.

Variables were analysed using lineal mixed model with IOP>21mmHg or CDR>0.6 defined as 1 while the opposite defined as 0.

* p-value <0.05; ** p-value <0.01; *** p-value <0.001.

Discussion

In this study, we reported the RPC-VD and SVP-VD between CON and JOHT subjects. IN and T of RPC-VD were higher in JOHT than in CON subjects. Risk factors of CDR and IOP were further taken into consideration in the assessment of VD. A positive correlation between CDR and RPC-VD in six regions except for T was established. T region of RPC-VD was significantly decreased with IOP more than 21 mmHg while its impact on S and N of SVP-VD was also observed. All of these data suggest that results of OCTA scans showed correlation with CDR and IOP and exhibit useful advantages in long-term follow-up of JOHT.

Capillary blood flow of glaucoma patients, OHT and CON subjects has been evaluated using scanning laser doppler flowmetry images in the past [25]. Subsequent research used OCTA to compare the similar parameters between CON and OHT subjects and agreed with our first findings of no obvious alterations in SVP-VD (Fig. 2) [16 22]. However, IN and T of RPC-VD showed statistical significance between CON and JOHT although the p-value was closed to 0.05. The average age of the subjects involved in previous

studies was more than forty years old, substantially different from the JOHT subjects we desired to target. Moreover, the CDR of the CON they used accorded with the inclusion criteria of less than 0.4 by ophthalmoscope while subjects of high CDR were sometimes considered as glaucoma suspects or OHT when the IOP was above 21 mmHg. Regarding the wide range of CDR values in the normal population varying from 0.00 to 0.87, grouping was different from previous studies in our research. This contradiction made further analysis of IOP and CDR necessary therefore the linear mixed model was applied to analyse these two factors separately.

Using the linear mixed model to study the risk factor of IOP higher than 21 mmHg, T RPC-VD exhibited significant reduction in JOHT subjects. Although no statistical correlation was found in the IT region, a consistent trend was observed throughout the comparison. Kerr and associates reported reduced blood flow in the temporal neuroretinal rim of the optic nerve, thus the decrease of RPC-VD in our study respected the patterns of early glaucomatous changes[26]. Meanwhile, sectors of superior and nasal SVP-pfVD also exhibited decreases matching the patterns of peripapillary regions. It should be noted that we did not actually measure blood flow of retina using OCTA, but the imaging technique could be a useful tool to show the vascular changes by the index of VD. Hence our results of reduction in both RPC- and SVP-VD could be explained by decrease of MOPP according to the formula which leads to a drop in ocular perfusion and microvascular networks are of primary interest in glaucoma [19]. On the other hand, high-level evidence has shown that treatments decreasing IOP improve the retinal circulation and reduce the risk of development of glaucoma in OHT [27]. It validates the effects of high IOP on ocular perfusion. Besides, individuals with high IOP are more likely to suffer from venous collapse, and this would exacerbate impaired blood flow. OCTA proves the difference of capillary VD caused by high IOP in JOHT subjects and could serve as a precise method to monitor disease development; although longitudinal data are still needed to fully evaluate this possibility.

The RPC-VD of all six regions, except for the T sector, showed increase with CDR > 0.6. No statistical difference was found in perifoveal areas. CDR has been shown to be positively related to optic disk size and the number of nerve fibres revealed consistency with optic disk size with the macula unaffected [28 29]. RPC comprises a network of capillary beds located within the RNFL carrying metabolites to nerve fibres thus it should be correlated with the total number of nerve fibres. The positive relationship between CDR and RPC-VD in our study further clarifies this vascular structure of blood supply. However, the T sector showed no correlation with CDR. One reason for this could be that the T peripapillary region shares the thinnest RNFL according with ISNT rules. Taking application into consideration, CDR used as an individual risk factor for OHT development with a wide normal range makes it confusing in distinguishing large optic disc subjects with glaucoma suspects. OCTA quantifies these changes more precisely which could aid the evaluation of the early perfusion alterations in JOHT subjects.

The main limitation of our study is small sample size, especially JOHT subjects exhibiting both high IOP and normal CDR, and more data will allow us to estimate clinical efficacy more precisely for this group. Additionally, IOP has always been normalized in the majority of juveniles over adolescence with long-term follow-up that why medical terminology of 'adolescence IOP fluctuation' or 'adolescence ocular

hypertension' is used. We only used IOP as a factor directly, and in future we could test whether IOP alone, or corrected IOP can exhibit more powerful correlation with VD of JOHT subjects [30]. As explained above, more research concerning disc size, CDR and VD is necessary. There is no long-term follow-up done to support the value of the clinical implications in OCTA of CDR or IOP [4]. In addition, we still are unclear how IOP fluctuations accompany, for example, seasonal changes, and this is a further target for the group to study.

Conclusions

The current study demonstrated negative relationship between T RPC-VD and high IOP in JOHT, while CDR has the opposite outcome. Perfusion of perifoveal regions were affected by IOP but not by CDR. The results suggest that both factors of IOP and CDR should be considered and analysed separately when clinicians assess the test results of OCTA scans in JOHT. RPC-VD, especially in the temporal region might be an effective index to evaluate the development of JOHT.

Abbreviations

AL: axial length; BCVA: best-corrected visual acuity; BP: blood pressure; CON: control subjects; CCT: central corneal thickness; CDR: cup/disc ratio; DBP: diastolic blood pressure; EGPS: European glaucoma prevention study; I: inferior; ILM: inner limiting membrane; IOP: intraocular hypertension; IPL: inner plexiform layer; JOHT: juvenile ocular hypertension; MAP: mean arterial pressure; MD: mean deviation; MOPP: mean ocular perfusion pressure; N: nasal; OCTA: optical coherence tomography angiography; OHT: ocular hypertension; OHTS: ocular hypertension treatment study; PSD: pattern standard deviation; RE: refractive error; RGC: retinal ganglion cell; RNFL: retinal nerve fiber layer; RPC: radial peripapillary capillaries; S: superior; SAP: standard automated perimetry; SBP: systolic blood pressure; SD-OCT: spectral-domain optical coherence tomography; SSADA: split-spectrum amplitude-decorrelation angiography; SVP: superficial vascular plexus; T: temporal; VD: vessel density

Declarations

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Authors' contributions

XC and XW contributed equally to this work. XC, XW and XS conceived of and designed the experiments. XC, XW and XH performed the experiments. XC analyzed the data. XC, XW and XS wrote the manuscript. All authors read and approved the final version to be published.

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Availability of the data and materials

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Ethics approval and consent to participate

This study was approved by the Ethics Committee of the Eye, Ear, Nose and Throat Hospital of Fudan University. The committee's reference number was 2014043. All patients were informed previously about the study and signed informed consent forms in accordance with the tenets of the Helsinki Declaration, including minors (under age 18), from their parents/guardians.

Consent for publication

Nat applicable.

Competing interests

The authors declare that they have no competing interests.

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Figures



Figure 1

Measurement points of OCTA scans. (A-D) OCTA scans of healthy subjects. (A) Peripapillary retinal perfusion centers on the nerve head. And the ring-shape region of interest is divided into six parts automatically as nasal (N), inferior nasal (IN), inferior temporal (IT), temporal (T), superior temporal (ST), superior nasal (SN). Signals inside of the inner circle are defined as perfusion of inside disc. Pixels of large blood vessels will be excluded during analysis. (B) The boundaries used for segmentation is indicated by the green line (inner plexiform layer, IPL) and the red line (inner limiting membrane, ILM). Radial paripapillary (RPC) plexus from ILM to retinal nerve fiber layer (RNFL) is analysed in the scans of nerve head. The arrow represents the direction of nasal. (C) Perifoveal retinal perfusion centers on the macula showing the superficial retinal vascular plexus (SVP). The area inside of the inner circle including the foveal avascular zone (FAZ) is excluded from the analysis. The ring-shaped region of interest is automated separated as hemi-superior (Hemi-S), hemi-inferior (Hemi-I), nasal (N), inferior (I), tempo (T) and superior (S). (D) SVP from ILM to IPL is analysed. The red line and the green line possessed the same definition as the lines in image (B). (E-H) Images of JOHT subjects.

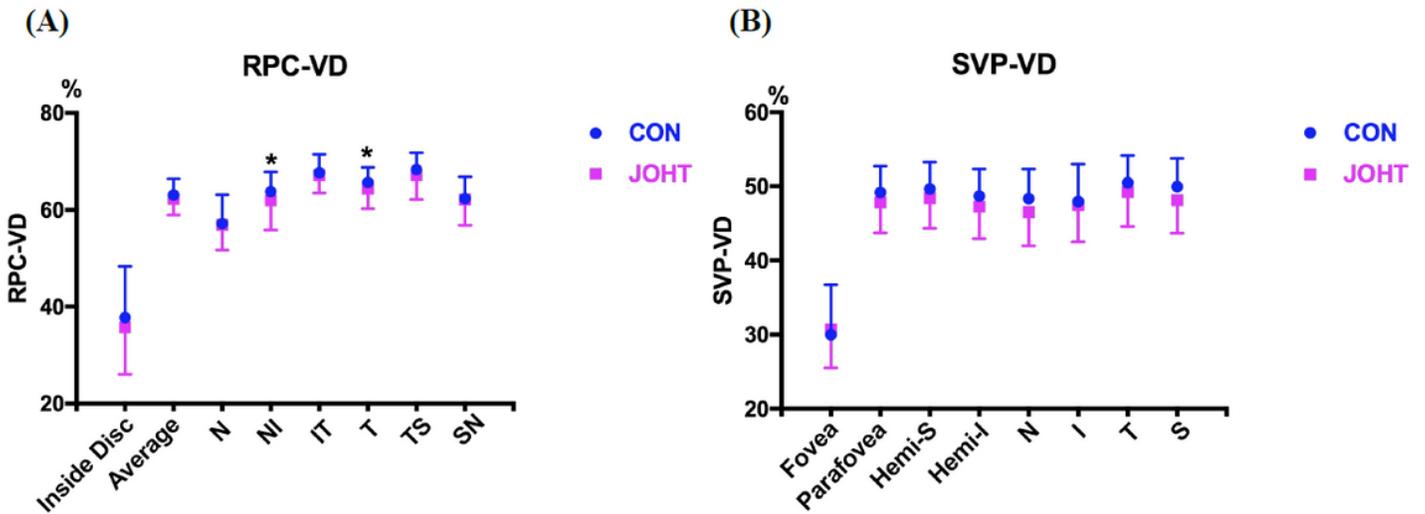


Figure 2

Peripapillary (A) and perifoveal (B) perfusion of both CON and JOHT subjects. Only NI and T of RPC-VD had significant difference between CON and JOHT ($p=0.042$ and $p=0.033$, * p -value <0.05). Data was shown as mean with error bars of SD. N, nasal; I, inferior; T, temporal; S, superior; RPC, radial peripapillary capillaries; SVP, supervisual vascular plexus; VD, vessel density; CON, control; JOHT, juvenile ocular hypertension.