Retinal Vascular Reactivity in Central Serous Chorioretinopathy

Felice Cardillo Piccolino,[1] Marco Lupidi,[1–3] Carlo Cagini,[2] Daniela Fruttini,[4] Massimo Nicolò,[1,5] Chiara Maria Eandi,[1,6] and Silvia Tito[1]

[1]Fondazione per la Macula Onlus, Di.N.O.G.Mi., University Eye Clinic, Genova, Italy
[2]Department of Biomedical and Surgical Sciences, Section of Ophthalmology, University of Perugia, S. Maria della Misericordia Hospital, Perugia, Italy
[3]Centre de l'Odéon, Paris, France
[4]Department of Internal Medicine, University of Perugia, S. Maria della Misericordia Hospital, Perugia, Italy
[5]Clinica Oculistica Università di Genova DINOGMI, Ospedale Policlinico San Martino, Genova, Italy
[6]Department of Surgical Sciences, Eye Clinic, University of Torino, Torino, Italy

Correspondence: Felice Cardillo Piccolino, Fondazione per la Macula Onlus, Di.N.O.G.Mi., University Eye Clinic, Viale Benedetto XV 5, Genova 16132, Italy; felice.cardillopiccolino@gmail.com.

FCP and ML contributed equally to the work presented here and should therefore be regarded as equivalent authors.

Submitted: April 1, 2018
Accepted: August 6, 2018

Citation: Piccolino FC, Lupidi M, Cagini C, et al. Retinal vascular reactivity in central serous chorioretinopathy. *Invest Ophthalmol Vis Sci*. 2018;59:4425–4433. https://doi.org/10.1167/iovs.18-24475

Purpose. To investigate the retinal vascular response to the isometric exercise in patients with central serous chorioretinopathy (CSCR) by using optical coherence tomography angiography (OCT-A).

Methods. This was a multicenter case-control study including 35 CSCR patients and 25 age-matched healthy controls. All subjects underwent macular OCT-A scans in resting conditions and during a handgrip isometric exercise. Hemodynamic data, such as systolic blood pressure (SBP), diastolic blood pressure (DBP), mean arterial pressure (MAP), and ocular perfusion pressure (OPP), were recorded at baseline and during the stress test. Qualitative and quantitative assessments of the retinal superficial capillary plexus (SCP) and deep capillary plexus (DCP) were performed on OCT angiograms. The results obtained in CSCR patients were then compared with those of healthy subjects.

Results. At baseline and during the isometric exercise, SBP, DBP, MAP, and OPP were significantly higher ($P < 0.05$) in CSCR patients than controls. Under stress conditions, the hemodynamic values significantly increased both in patients and controls. The qualitative and quantitative analyses of OCT angiograms evidenced an increased blood flow during exercise only in CSCR patients. Baseline vascular perfusion density (VPD) values of SCP and DCP were significantly lower ($P < 0.05$) in CSCR cases than in healthy subjects. A significant increase ($P < 0.05$) of VPD values was obtained during the exercise in CSCR patients and not in controls.

Conclusions. Unlike healthy subjects, retinal blood flow in patients with CSCR seems affected by rapid increases in BP and OPP. Our study suggests that the autoregulatory mechanisms controlling retinal microcirculation are not entirely able to counteract overperfusion in patients with CSCR.

Keywords: central serous chorioretinopathy, OCT-angiography, retinal blood flow, CSCR

Central serous chorioretinopathy (CSCR) is an idiopathic disease characterized by serous detachment of the neurosensory retina and/or the retinal pigment epithelium (RPE) at the posterior pole of the eye.[1,2] It is usually a benign disorder; however, there are chronic manifestations of the disease, leading to severe deterioration of central vision associated with foveal atrophy.[3–7] The nosographic history of CSCR (the current term used) includes a variety of other labels, such as central serous retinopathy,[5] central serous choroidopathy,[4] and diffuse retinal pigment epitheliopathy,[1] each of which focuses on the tissue mainly considered involved in the disease.

Indocyanine green angiography (ICGA) in the 1990s showed a series of choroidal findings in patients with CSCR, favoring general consensus on a primary involvement of the choroid in the pathophysiology of the disease.[8–11] Leakage from the inner choroid, areas of choriocapillaris (CC) filling delays, and venous congestion detected bilaterally in active and inactive disease by ICGA testify to basic changes of the choroidal circulation in patients affected by CSCR.[8–12]

The concept of CSCR as a choroidal disease was consolidated by studies using spectral-domain OCT with enhanced depth imaging and swept-source OCT, which have evidenced a thickened choroid, dilated choroidal vessels, and other structural alterations associated with the disease.[13–15] OCT angiography (OCT-A), a recent label-free imaging modality able to provide information on the chorioretinal blood flow, has revealed areas of impaired flow signal, or flow-voids, at the CC layer in patients with CSCR.[16–18] A dysfunction of local mechanisms regulating choroidal blood flow also has been demonstrated by laser doppler flowmetry in this disease.[19] By using OCT-A, performed during an isometric exercise with handgrip test (HGT), we recently have observed a defective choroidal vascular response to systemic hemodynamic changes in CSCR.[20] Using the same methodology and the same group of patients, in the present study we turned the attention to the

retinal microcirculation, whose functionality in CSCR has been disregarded in the past. We investigated the response of retinal blood flow to an abrupt increase of the systemic blood pressure (BP) in CSCR, with the aim to better understand the pathophysiological background of this disease.

Methods

Study Design

This study was held at the Fondazione per la Macula Onlus (Genova, Italy) and at the Eye Clinic, S. Maria Della Misericordia Hospital (Perugia, Italy). It was a prospective case-control study in which patients and controls underwent OCT-A before and during HGT, which is able to produce a rapid increase of BP. We evaluated the impact of the increased ocular perfusion pressure (OPP) on the retinal microvascular hemodynamics. The study was performed in accordance with the Declaration of Helsinki and approved by the Genova and Perugia Institutional Ethics Committees. Informed written consent was obtained from patients and controls before the ophthalmologic examination and the HGT.

Study Population

Patients with a documented history of CSCR and age-matched healthy controls were consecutively enrolled between February 2017 and January 2018. The diagnosis of CSCR was established on the basis of the presence of serous retinal detachment (SRD) associated with RPE leakage, choroidal vascular hyperpermeability, and choroidal thickening documented respectively by fluorescein angiography, ICGA, and OCT. Eyes with actual serous retinal detachment in the analyzed central area were not included in the study owing to the potential impact on segmentation strategies. In case of bilateral eligibility, the study eye was randomly selected. Condition of actual active (A) or quiescent (Q) disease (presence or absence of SRD outside the examined area) was considered for a subgroup analysis. Cases with arterial BP higher than 150 mm Hg or diastolic BP higher than 90 mm Hg at baseline were not included in the study for safety reasons. Further ocular or systemic exclusion criteria were as follows: refractive error of 3 diopters or more, peripapillary choroidal dystrophy and staphyloma, glaucoma, previous ocular surgery or laser photocoagulation, photodynamic therapy (PDT) in the previous 12 months, systemic steroidal therapy in the previous 6 months, or any evidence of chorioretinal disease that could interfere with the purpose of the study. Eyes with poor-quality images on OCT-A (quality index lower than 30) due to poor fixation or media opacities that could confound the quantitative assessment were also excluded. The control group consisted of healthy subjects with best-corrected visual acuity of 20/20 and no history or clinical evidence of chorioretinal or systemic diseases. Patients and controls underwent a complete ophthalmologic examination including intraocular pressure (IOP) measurement, and OCT-A, which was performed at baseline and during the isometric exercise.

Experimental Protocol

Hemodynamic baseline measurements of BP were taken in resting condition by using a portable electronic sphygmomanometer (Omron Model M6; Omron Europe B.V., Hoofddorp, The Netherlands). The automated oscillometric system allowed measurements between 0 and 300 mm Hg of BP and between 40 and 200 heartbeats. Test accuracy was approximately 3 mm Hg for BP and 5% for heartbeat, in accordance with the AAMISP10 auscultatory standard. The sphygmomanometer wrist was set at the level of the heart.

After pupil dilation with 1% tropicamide (Visumidriatic, Visufarma, Italy) patients underwent a baseline OCT-A examination. The HGT was then executed on the dominant side by using a Jamar hand dynamometer (Lafayette Instruments, Lafayette, IN, USA), following the American Society of Hand Therapist recommendation.[21] The enrolled subject was seated in a comfortable position with elbow flexed at 90°, shoulder adducted, and forearm and wrist in a neutral position. They were instructed to squeeze the handle maximally for three times, and a value equal to 30% of the mean maximal isometric handgrip strength was then computed. The handgrip exercise was then performed maintaining this isometric effort for 2.5 to 3 minutes. An OCT-A was performed in the examined eye starting from 1.5 minutes from the beginning of the exercise. BP and heart rate were measured at the same time and its recovery was checked soon after the HGT. OPP at baseline and during the exercise was also computed on the basis of the following formula: OPP = 2/3 of mean arterial pressure (MAP) less IOP.[22]

OCT Angiography System Setup

The OCT-A was performed for each enrolled subject by using an 85-kHz spectral-domain OCT (Spectralis OCT2; Heidelberg Engineering, Heidelberg, Germany). The OCT-A scanning pattern was a high-resolution 15° × 10° volume scan centered in the central macula. Each of the 261 cross-sectional scans composing the volume (11-μm distance between two consecutive cross-sectional scans) was the result of an averaging process of 35 frames. The in-built software (Heyex Software Version 1.9.201.0; Heidelberg Engineering) provides en face or cross-sectional angiograms. An automated segmentation algorithm based on the capability to distinguish different levels of reflectivity between the inner retinal layers allows en face images to be obtained. In the current study the retinal capillary network was simplified into two vascular structures: the superficial capillary plexus (SCP) and the deep capillary plexus (DCP). The SCP is a multilayered vascular structure located at the level of the ganglion cell layer. It was imaged with an en face section starting at the inner border of the ganglion cell layer to the inner border of the inner plexiform layer in macular area. The DCP brackets on either side the inner nuclear layer. En face image of the DCP was obtained by segmenting from the inner boundary of the inner plexiform layer to the outer boundary of the outer plexiform layer.[23]

The SCP and DCP en face OCT angiograms were quantitatively analyzed by the custom-built software AngiOCTool (version 4.0; Lupidi M, Coscas G, Centre de l'Odeéon, Paris, France). Technical details on the automated quantification of vessels' metrics have been previously described.[23] Vascular perfusion density (VPD) values were computed in each layer as the ratio between the number of decorrelated pixels and the total number of pixels in the examined area. The magnification associated with axial length variation was considered and data were corrected accordingly.[24] Quantitative data were achieved on a 10° × 10° area corresponding to 3 × 3 mm (original image 15° × 10° area corresponding to 4.5 × 3 mm) in order to minimize the effects of artifacts at the edges of the en face OCT angiogram. We assumed that changes in the number of decorrelated pixels on HGT OCT-angiograms could reflect changes in vascular perfusion with respect to baseline.

A qualitative assessment of the SCP and DCP on baseline and HGT OCT-angiograms was also performed. The sites of potential retinal capillary perfusion changes occurring during the stress test were evidenced by using the subtraction protocol in the image calculator tool of a free imaging software

Investigative Ophthalmology & Visual Science

TABLE 1. Hemodynamic Findings in CSCR Patients and in Healthy Controls at Baseline and During the Isometric Handgrip Exercise and Their Absolute and Relative Differences: Comparison Between CSCR and Control Data and Their Variation From Baseline to Under-Stress Values

	CSCR Patients					Healthy Controls							
	Baseline, Mean ± SD	Under Stress, Mean ± SD	*P* Value Paired Data	Absolute Difference, Δ, Mean ± SD	Relative Difference, Δr, Mean ± SD	Baseline, Mean ± SD	Under Stress, Mean ± SD	*P* Value Paired Data	Absolute Difference, Δ, Mean ± SD	Relative Difference, Δr, Mean ± SD	*P* Value CSCR vs. Controls Baseline	*P* Value CSCR vs. Controls Under Stress	*P* Value CSCR vs. Controls Absolute Difference, Δ	*P* Value CSCR vs. Controls Relative Difference, Δr
SBP	126.94 ± 11.62	165.57 ± 16.41	<0.0001	38.63 ± 15.28	31.0% ± 13.3%	112.20 ± 7.70	143.44 ± 10.95	<0.0001	31.24 ± 9.21	28.0% ± 8.3%	<0.0001	<0.0001	0.0541	0.3880
DBP	83.4 ± 7.91	105.60 ± 10.68	<0.0001	22.26 ± 8.94	27.2% ± 11.7%	75.12 ± 5.35	97.24 ± 7.12	<0.0001	22.12 ± 6.00	29.7% ± 8.4%	<0.0001	0.0059	0.7354	0.2749
HR	70.29 ± 8.61	87.94 ± 11.15	<0.0001	17.66 ± 11.61	26.3% ± 17.9%	69.68 ± 6.79	92.08 ± 10.99	<0.0001	22.40 ± 9.59	32.5% ± 14.0%	0.8929	0.1011	0.0733	0.0795
MAP	97.88 ± 8.60	125.59 ± 11.46	<0.0001	27.71 ± 10.43	28.8% ± 11.8%	87.48 ± 5.89	112.64 ± 7.71	<0.0001	25.16 ± 6.57	29.0% ± 7.8%	<0.0001	<0.0001	0.4903	0.7997
OPP	56.24 ± 5.92	74.72 ± 7.53	<0.0001	18.48 ± 6.95	33.6% ± 14.3%	48.59 ± 4.69	65.36 ± 5.38	<0.0001	16.77 ± 4.38	35.0% ± 9.8%	<0.0001	<0.0001	0.4700	0.5411

HR, hearth rate.

(FIJI, an expanded version of ImageJ, version 1.51h, Wayne Rasband; provided in the public domain by the National Institutes of Health, Bethesda, MD, USA). The two OCT-A sessions (baseline and during HGT) were performed by the same experienced operator (ML) within a single visit. All scans were independently reviewed by two investigators (FCP and ML) to ensure sufficient image quality and correct segmentation.

Statistical Analysis

The quantitative variables were described by their mean, standard deviation (SD), and absolute (Δ) and relative (Δr, ratio of absolute difference and baseline value) differences between baseline and under stress conditions. To check whether the sample came from a normally distributed population the Shapiro-Wilk test was applied. Based on the statistical distribution, comparisons of means of independent variables were performed by using the Student's *t*-test or the Mann-Whitney test. The paired *t*-test or Wilcoxon–Mann-Whitney test were used to compare paired data. The Pearson's "*r*" or Spearman's rank correlation coefficient was used to measure the statistical dependence of quantitative variables. A *P* value of <0.05 was considered as statistically significant. All statistical analyses were performed with the SAS System for Windows (release 9.4; SAS Institute, Inc., Cary, NC, USA).

RESULTS

Study Population

Thirty-five eyes of 35 patients with an established diagnosis of CSCR and 25 eyes of 25 age-matched healthy controls were enrolled in the study. All subjects were Caucasian. The mean age of CSCR patients was 48.6 ± 7.6 years (range, 34–66 years) and the mean age of controls was 43.2 ± 8.3 years (range, 26–60 years). Two females were in the CSCR group (5.7%), and in the control group (8%). Mean IOP values were 13.4 ± 1.8 mm Hg in the CSCR group and 14.7 ± 1.7 mm Hg in the control group. Patients with CSCR had symptoms lasting for more than 6 months. Among the included eyes 14 had active disease, with subretinal fluid outside the examined area. Fourteen patients (40%) had a previous history of PDT followed by reactivation of the disease. Twenty (57%) had received in the past a systemic steroidal therapy and 6 (17%) had a well-controlled systemic hypertension. The control subjects were not assuming or had not assumed in the past any significant systemic therapy. No adverse events were observed in any subject during the examination and the handgrip exercise.

Hemodynamic Data

Hemodynamic data (mean, SD, Δ, and Δr) at baseline and during the isometric exercise are shown in Table 1. Baseline and under-stress values were significantly higher ($P < 0.05$) in CSCR patients than controls. Following the exercise, a significant increase ($P < 0.05$) of the basal values was obtained both in CSCR and healthy subjects. The Δ and Δr between baseline and under-stress data were not significantly different in the two groups (Table 1).

Qualitative Imaging Analysis

In an overall observation, the basal network of retinal microvasculature, both in the SCP and the DCP, was better defined in the control group than in CSCR patients (Figs. 1, 2). In patients with CSCR the capillary network appeared better outlined in the HGT OCT-angiogram than in the baseline

Table 2. Quantitative OCT-Angiography Assessment of Vascular Perfusion Density in CSCR Patients and Healthy Controls at Baseline and During the Isometric Handgrip Exercise

	CSCR Patients			Healthy Controls				
	Baseline, Mean ± SD	Under Stress, Mean ± SD	*P* Value Paired Data	Baseline, Mean ± SD	Under Stress, Mean ± SD	*P* Value Paired Data	*P* Value CSCR vs. Controls Baseline	*P* Value CSCR vs. Controls Under Stress
SCP VPD	25.2% ± 2.2%	26.7% ± 2.6%	<0.0001	26.7% ± 2.2%	26.6% ± 2.3%	0.0875	0.0163	1
DCP VPD	24.5% ± 2.7%	26.2% ± 2.8%	<0.0001	26.7% ± 2.7%	26.7% ± 2.7%	0.3639	0.0047	0.4838

angiogram. Differences between the two examinations were not noted in the control group (Fig. 3). The differential image obtained by the subtraction of the baseline from the HGT OCT-angiogram highlighted the occurring retinal microvascular changes. During the stress condition, retinal vascular tracts, which were not well visible at the baseline examination, were shown, and focal increases in vessel caliber were also appreciated (Figs. 1, 2). Areas of retinal thinning and photoreceptor atrophy in longstanding CSCR cases showed an intact microvasculature.

Quantitative Imaging Analysis

Results of the quantitative assessment of the SCP and DCP are reported in Tables 2 through 4. A statistically significant increase ($P < 0.05$) of VPD was noted in these vascular layers in CSCR patients under stress conditions. Moreover, the baseline values were significantly lower ($P < 0.05$) in CSCR cases than controls. No statistically significant differences were shown among baseline and under-stress VPD values in the control group, as well as between the two groups when considering under-stress data. Absolute and relative VPD variations (ΔVPD SCP, ΔVPD DCP) between baseline and under stress conditions were significantly higher in CSCR patients than in healthy subjects (Table 3). A significantly higher variation ($P < 0.0001$) of SCP and DCP VPD in CSCR patients than in controls was also detected in a post hoc analysis (Table 4) where we considered subsets of CSCR cases (19 patients) and healthy subjects (16 controls) without a statistically significant difference of under-stress OPP (mean OPP: 69.2 ± 3.5 mm Hg for the CSCR group versus 68.9 ± 2.8 mm Hg in healthy controls, $P = 0.68$).

Statistically significant correlations between the degree of hemodynamic changes and variations of OCT-A quantitative parameters were not observed. However, a negative linear correlation between the baseline IOP and the absolute and relative VPD variations both at the level of the SCP and DCP was shown in CSCR patients (Fig. 4). Subgroup analysis showed that age, sex, previous corticosteroid therapies or previous PDT, and activity (A) or quiescence (Q) of the disease were not influencing factors for the hemodynamic or OCT-A quantitative results.

Discussion

In the current study, OCT-A was used to investigate the retinal vascular response to systemic hemodynamic changes induced by an isometric exercise in patients with CSCR. An increase of the retinal blood flow was observed in these patients, while a similar response was not seen in a control group of healthy subjects. Our findings suggest that the physiological mechanisms controlling the retinal microcirculation may be dysregulated in CSCR.

In a previous study with OCT-A in the same group of patients we have examined the behavior of CC blood flow to an experimental elevation of BP.[20] The results of that study support the concept of an impaired regulation of choroidal blood flow in patients with CSCR and are consistent with those obtained by Tittl et al.[19] using laser doppler flowmetry and squatting exercise.

In the present study, we extended our attention to the retinal microcirculation in CSCR, exploiting the peculiarities of OCT-A, which allows to simultaneously analyze both the choroidal and retinal vascular areas with the same macular volume scan. Appropriate OCT-A segmentation strategies offer a detailed imaging of the retinal capillaries and a clear distinction of the SCP and the DCP.[25] We examined with qualitative and quantitative analyses both these microvascular layers at baseline and during the isometric effort with HGT, in CSCR patients and in healthy controls.

Likewise using OCT-A, with a qualitative evaluation of the retinal angiograms, Costanzo et al.[16] have observed an abnormal (not better defined) blood flow in the outer retina of 9 (27.3%) of 24 eyes with CSCR. Furthermore, in a quantitative OCT-A study, Nelis et al.[26] report an increased central retinal VPD and a reduced foveal avascular zone in affected eyes, as well as in fellow eyes of CSCR patients. They interpret these findings as a compensatory vasodilatory response of the foveal vessels to primary CSCR changes in the CC and RPE. Conversely, our quantitative OCT-A evaluation showed a reduced VPD at baseline in both retinal capillary plexuses of the central macula in CSCR patients compared to normal subjects. The lower baseline values of SCP and DCP VPDs appeared to be due to a diffuse attenuation of the decorrelation signal coming from the capillary networks that

Table 3. Absolute and Relative Differences Between Baseline and Under-Stress Values in Terms of Vascular Perfusion Density in CSCR Patients and Healthy Controls

	CSCR Patients		Healthy Controls			
	Absolute Difference, Δ, Mean ± SD	Relative Difference, Δr, Mean ± SD	Absolute Difference, Δ, Mean ± SD	Relative Difference, Δr, Mean ± SD	*P* Value CSCR vs. Controls, Δ	*P* Value CSCR vs. Controls, Δr
SCP VPD	0.02 ± 0.02	6.3% ± 7.6%	0.00 ± 0.00	−0.7% ± 1.9%	<0.0001	<0.0001
DCP VPD	0.02 ± 0.02	7.3% ± 7.7%	0.00 ± 0.00	0.1% ± 0.8%	<0.0001	<0.0001

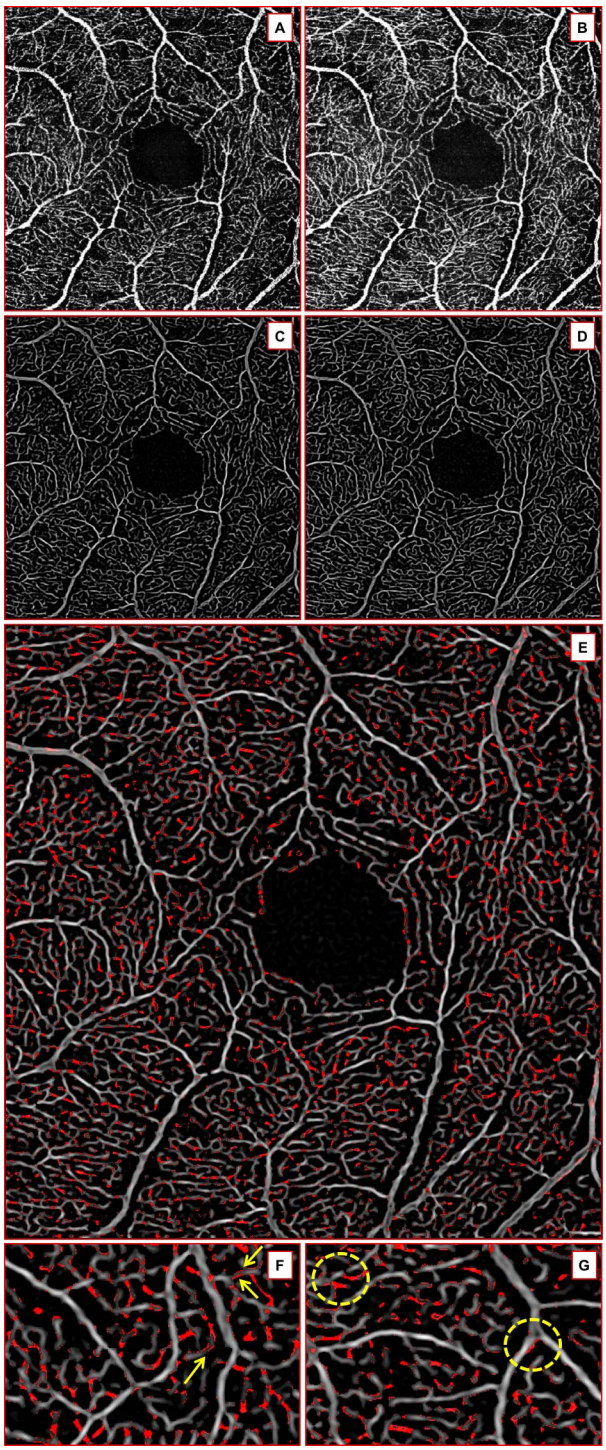

FIGURE 1. (**A**–**G**) En face OCT angiography in a CSCR case. Assessment of the SCP at baseline and during the HGT and comparative analysis. (**A**, **B**) High-resolution OCT angiograms of the SCP at baseline (**A**) and during the HGT (**B**). (**C**, **D**) Contrast-enhanced images of the SCP after "vesselness" filtering (obtained by FIJI, an expanded version of ImageJ, version 1.51h) at baseline (**C**) and during the HGT (**D**). (**E**) Differential OCT angiogram: the *gray* component of the vascular network represents the SCP at baseline, while the *red* one shows the amount of vascular perfusion increase during the HGT. (**F**, **G**) an additional decorrelation signal is shown in proximity of the vessel walls (**F**, *yellow arrows*) and in correspondence to vascular crossings or branching (**G**, *yellow dashed lines*) during the HGT.

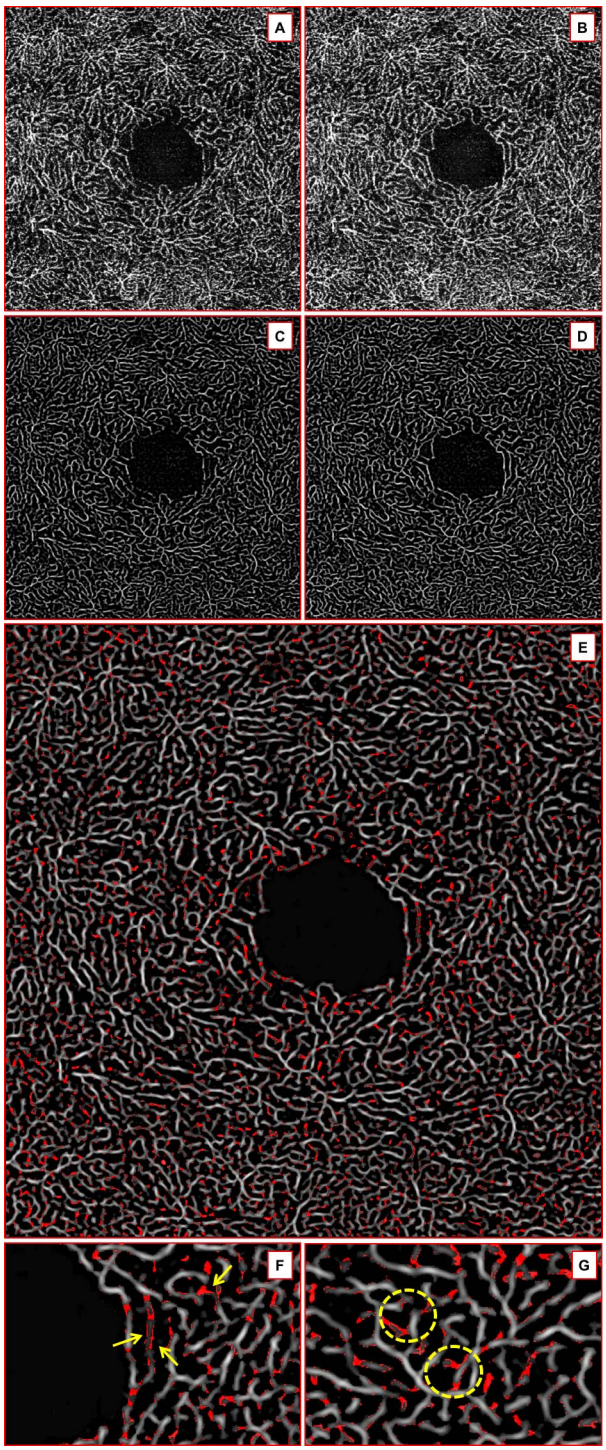

FIGURE 2. (**A**–**G**) En face OCT angiography in a CSCR case. Deep capillary plexus in resting conditions and during the HGT. (**A**, **B**) High-resolution OCT angiograms of the DCP in resting conditions (**A**) and during the HGT (**B**). (**C**, **D**) Contrast-enhanced images of the DCP after "vesselness" filtering at baseline (**C**) and during the HGT (**D**). (**E**) Differential OCT angiogram: the DCP at baseline is shown by the *gray* network, while *red tracts* represent the increase of blood flow during the HGT. (**F**, **G**) Details of the differential OCT angiogram: an increase of blood flow is shown at the border of vessel walls (*yellow arrows*) and at vascular crossings or branching (*yellow dashed lines*) during the HGT.

Investigative Ophthalmology & Visual Science

Table 4. Absolute and Relative Differences Between Baseline and Under-Stress Values in Terms of Vascular Perfusion Density in a Subset of CSCR Patients and Healthy Controls Without a Statistically Significant Difference in Terms of Under-Stress Ocular Perfusion Pressure

	CSCR Patients, $n = 19$		Healthy Controls, $n = 16$			
	Absolute Difference, Δ, Mean ± SD	Relative Difference, Δr, Mean ± SD	Absolute Difference, Δ, Mean ± SD	Relative Difference, Δr, Mean ± SD	*P* Value CSCR vs. Controls, Δ	*P* Value CSCR vs. Controls, Δr
SCP VPD	1.5% ± 1.9%	6.2% ± 7.4%	−0.1% ± 0.4%	−0.6% ± 1.6%	<0.0001	<0.0001
DCP VPD	1.5% ± 1.4%	6.6% ± 6.4%	0.0% ± 0.2%	0.0% ± 0.9%	<0.0001	<0.0001

was also perceptible in a qualitative analysis of the angiograms. However, absolute filling defects were not observed, either in areas of retinal thinning or photoreceptor atrophy due to a longstanding disease. Contrarily to the aforementioned studies we excluded eyes with central macular detachment, avoiding any risk of artefactual findings due to potential failures in the segmentation process, which substantially increase in case of evident changes of the macular profile.

Blood flow in the chorioretinal vessels is driven by the OPP, which depends on the systemic BP and the opposing force of the IOP. The isometric exercise produces a significant increase of BP by activation of muscle mechanoreceptors and stimulation of the sympathetic system.[27,28] The consequent increase of the OPP triggers neural and hormonal regulatory systems responsible to keep, by vasoconstriction, blood flow constant within the eye.[27–30] In all the enrolled subjects we obtained a significant increase in BP and OPP during the exercise. However, the response we detected with OCT-A was different in CSCR patients compared to controls. The quantitative analysis of OCT angiograms showed a significant increase of SCP VPD and DCP VPD during the HGT in CSCR cases, and not in healthy subjects.

The entire retinal capillary network in CSCR patients appeared better outlined during the HGT, indicating an increased perfusion associated with the increased BP. The OCT-angiogram differential images revealed new flow signals particularly at the edges of the vessel lumen and in correspondence to vascular branching, showing an increase of perfusion where the blood flow is basically slower (Figs. 1, 2). These findings suggest an ineffective retinal blood flow regulation in patients with CSCR, at least in the experimental conditions of the study, while confirming efficient retinal vascular regulatory mechanisms in healthy subjects (Fig. 3).

Using laser doppler velocimetry, Robinson et al.[22] have demonstrated an efficient retinal blood flow autoregulation in healthy subjects in response to the acute increase of BP produced by isometric exercise. They observed that there was no change in retinal blood flow until an average rise of 40% in mean BP. In our experiment, the rise of MAP during the HGT was significantly below this value (average increase of 28.8% in CSCR patients and 29% in healthy controls), nevertheless it was sufficient to produce blood flow changes in the retinal capillary plexuses of CSCR patients.

Furthermore, given that in these patients the baseline MAP tended to be higher and the IOP lower, compared to controls, the increase of blood flow could be explained by the OPP exceeding the upper limit of retinal blood flow autoregulation, which was not reached in the healthy controls. However, a significantly different retinal vascular response was still detectable when comparable subgroups for OPP were evaluated, suggesting an actual defective retinal blood flow regulation in CSCR. The increases in OPP following isometric exercise were not linearly associated with the increases of

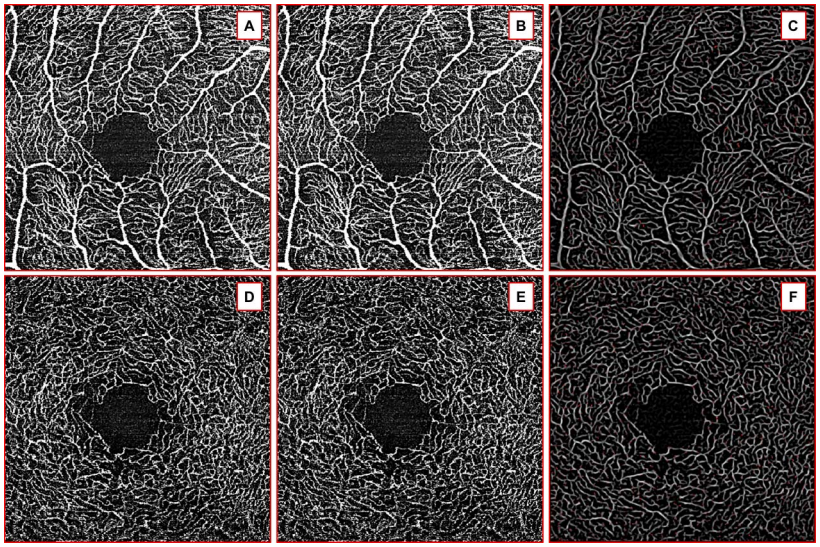

Figure 3. (**A**–**F**) En face OCT angiography in a healthy control subject. Assessment of the SCP and the DCP at baseline and during the HGT and comparative analysis. (**A**, **B**) High-resolution OCT angiograms of the SCP at baseline (**A**) and during the HGT (**B**). (**C**) Differential, contrast-enhanced OCT angiogram: the *gray* component of the vascular network represents the SCP at the baseline, while the *red* one shows the amount of vascular perfusion increase during the HGT. (**D**, **E**) High-resolution OCT angiograms of the DCP at baseline (**D**) and during the HGT (**E**). (**F**) Differential, contrast-enhanced OCT angiogram: the *gray* component of the vascular network represents the DCP at baseline, while the *red* one shows the amount of vascular perfusion increase during the HGT.

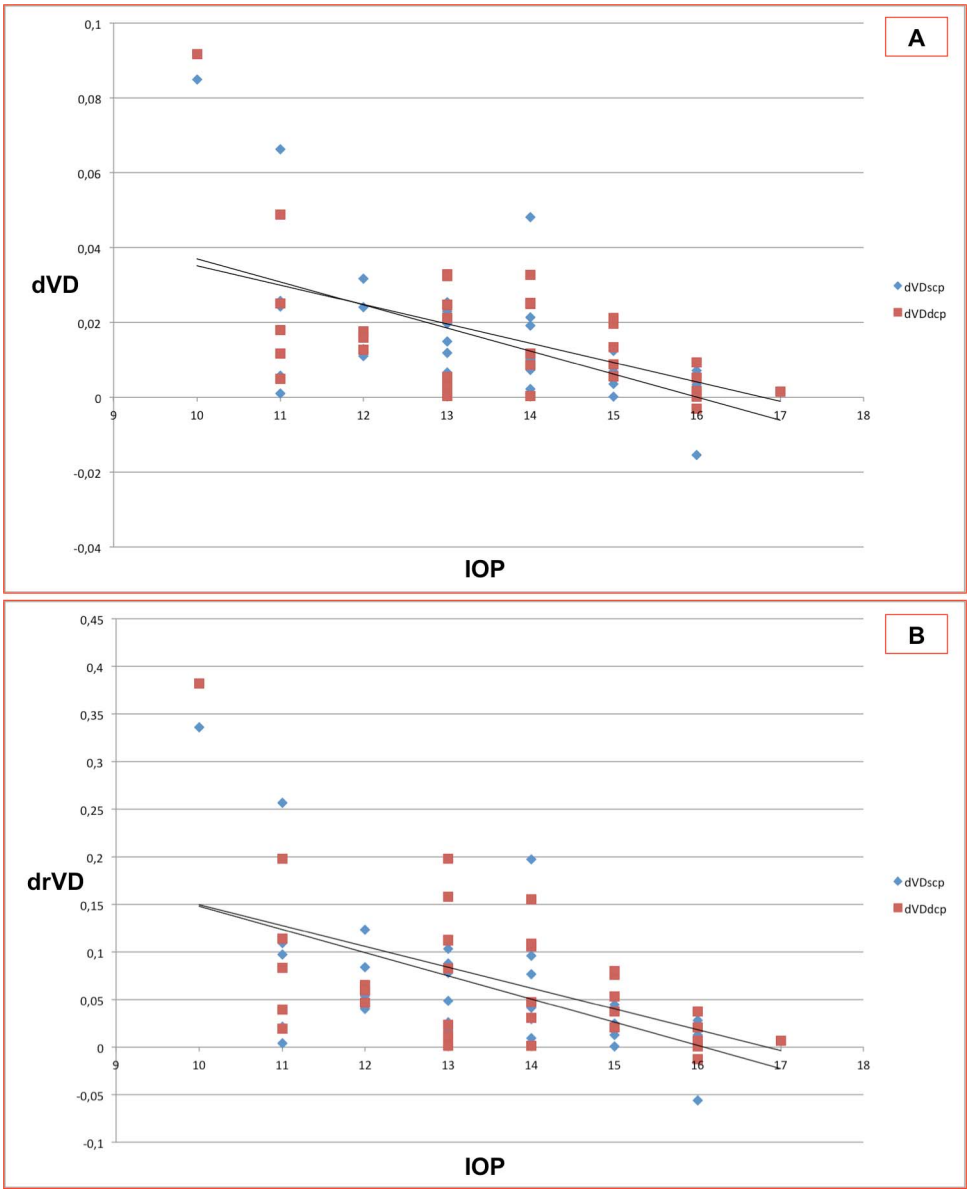

FIGURE 4. Correlation between IOP and absolute (**A**) or relative (**B**) vascular perfusion density variations (dVPD). A negative linear correlation between IOP and dVPD is shown, both at the level of the superficial (SCP) and deep (DCP) capillary plexuses. These correlations indicate that lower values of IOP are associated with higher variations of retinal blood flow.

retinal VPDs, indicating a residual degree of functioning in autoregulatory mechanism of retinal blood flow.

The concept of a choroidal vascular dysregulation for CSCR is easy to conceive of, considering the cumulating observations by multimodal imaging studies supporting a primary choroidal involvement in this disease.[8–15] From the present study, a local defect of blood flow regulation seems to be common to the retina and the choroid in CSCR. The different impact of this dysfunction on the two vascular areas may be explained by the greater vulnerability of the CC compared to the retinal capillaries. In the CC, which has a fenestrated endothelium sustained by few pericytes,[31] the impact of a bloodstream coming perpendicularly from the precapillary arterioles can easily produce leakage of fluid from the vessels. Instead, in the retinal capillaries, whose endothelium is not fenestrated and is protected by an exceptionally large number of pericytes (1:1 ratio to endothelial cells),[32] the hemodynamic shear stress should be better tolerated and not produce blood-retinal barrier decompensation.

Retinal circulation, except for the prelaminar segment of the central retinal artery, does not have an intrinsic sympathetic innervation that, conversely, the choroidal vessels have.[33,34] The maintenance of a constant blood flow in the retina seems to be ensured by local autoregulatory mechanisms of myogenic and metabolic nature, as well as by endothelial-derived vasoactive substances and by the pericytes themselves.[29,30,35] The relative contributions of these mechanisms in the homeostasis of retinal circulation are ill defined, and the locus of the potential vascular dysregulation in CSCR remains to be elucidated. It could be a primary defect, or instead an end-organ alteration possibly due to systemic hypertension, a recognized risk factor for the disease. In the current study, despite the fact that hypertensive subjects were excluded, the values of SBP and DBP at baseline were significantly higher in CSCR patients, and during the HGT they reached values

definitely in the range of hypertension (mean SBP, 165.6 mm Hg; mean DBP, 105.6 mm Hg). Furthermore, patients with CSCR, characterized by a type A personality and a high sympathetic tone,[36] may be easily exposed to systemic hemodynamic variations that worsen the target organ damage of hypertension.[37] The resulting effect on the retina could be the inadequate vascular response that we detected in the present study.

By getting less efficient local regulatory mechanisms, blood flow in the retinal microcirculation could be affected also by the compressing force exerted by the IOP.[33] This is consistent with the negative linear correlation observed in our CSCR cases between the IOP and the VPD variations of SCP and DCP during the isometric exercise.

The subgroups analysis did not reveal a significant difference in retinal blood flow reactivity for active or inactive CSCR, showing that the retinal vascular dysregulation is a constant condition characterizing patients affected by CSCR. The pathophysiologic relevance and the possible clinical impact of this lack of local retinal blood flow adjustment deserve to be further investigated. We cannot exclude a potential role in the progression of the disease in terms of neuroepithelial damage and development or persistence of posterior cystoid retinal degeneration in longstanding cases.

Limitations of the present study were basically related to the intrinsic limits of the technology used for imaging retinal blood flow, and to the assumption that changes in number of decorrelated pixels on HGT OCT-angiograms reflect the change in vascular perfusion induced by the stress test. Our findings need to be confirmed and could be better characterized by studies including a larger number of patients with different disease stages.

In conclusion, we used OCT-A to evaluate the retinal vascular reactivity to the systemic hemodynamic changes induced by isometric exercise in patients with CSCR. The findings of the present study indicate that mechanisms regulating blood flow in the retinal vessels might not be entirely able to counteract conditions of overperfusion in CSCR. This retinal vascular functional abnormality is an ancillary sign that has not been previously considered in CSCR. Its easy detection using OCT-A and HGT could contribute in the recognition and better characterization of affected people or subjects predisposed to CSCR.

Acknowledgments

Supported by Fondazione per la Macula Onlus, Genova, Italy.

Disclosure: **F.C. Piccolino**, None; **M. Lupidi**, None; **C. Cagini**, None; **D. Fruttini**, None; **M. Nicolò**, None; **C.M. Eandi**, None; **S. Tito**, None

References

1. Gass JDM. Pathogenesis of disciform detachment of the neuroepithelium, II: idiopathic central serous choroidopathy. *Am J Ophthalmol*. 1960;63:587–615.
2. Yannuzzi LA, Gitter KA, Shatz H. *The Macula: A Comprehensive Text and Atlas*. Baltimore: Williams & Wilkins; 1982:145–165.
3. Gilbert CM, Owens SL, Smith PD, et al. Long-term follow-up of central serous chorioretinopathy. *Br J Ophthalmol*. 1984;68:815–820.
4. Yannuzzi LA, Shakin JL, Fisher YL, et al. Peripheral detachments and retinal pigment epithelial atrophic tracts secondary to central serous pigment epitheliopathy. *Ophthalmology*. 1984;91:19.
5. Castro-Correia J, Coutinho MF, Rosas V, et al. Long-term follow-up of central serous retinopathy in 150 patients. *Doc Ophthalmol*. 1992;81:379–386.
6. Cardillo Piccolino F, Rigault de la Longrais R, Ravera G, et al. The foveal photoreceptor layer and visual acuity loss in central serous chorioretinopathy. *Am J Ophthalmol*. 2005;139:87–99.
7. Eandi CM, Chung JE, Cardillo Piccolino F, et al. Optical coherence tomography in unilateral resolved central serous chorioretinopathy. *Retina*. 2005;25:417–421.
8. Scheider A, Nasemann JE, Lund OE. Fluorescein and indocyanine green angiographies of central serous chorioretinopathy by scanning laser ophthalmoscopy. *Am J Ophthalmol*. 1993;115:50–56.
9. Guyer DR, Yannuzzi LA, Slakter JS, et al. Indocyanine green videoangiography of central serous chorioretinopathy. *Arch Ophthalmol*. 1994;112:1057–1062.
10. Cardillo Piccolino FC, Borgia L. Central serous chorioretinopathy and indocyanine green angiography. *Retina*. 1994;14:231–242.
11. Prunte C, Flammer J. Choroidal capillary and venous congestion in central serous chorioretinopathy. *Am J Ophthalmol*. 1996;121:26–34.
12. Piccolino FC, Borgia L, Zinicola E, et al. Indocyanine green angiographic findings in central serous chorioretinopathy. *Eye*. 1995;9:324–332.
13. Imamura Y, Fujiwara T, Margolis R, et al. Enhanced depth imaging optical coherence tomography of the choroid in central serous chorioretinopathy. *Retina*. 2009;29:1469–1473.
14. Yang L, Jonas JB, Wei W. Choroidal vessel diameter in central serous chorioretinopathy. *Acta Ophthalmol*. 2013;91:358–362.
15. Ferrara D, Mohler KJ, Waheed N, et al. En face enhanced-depth swept-source optical coherence tomography features of chronic central serous chorioretinopathy. *Ophthalmology*. 2014;121:719–726.
16. Costanzo E, Cohen SY, Miere A, et al. Optical coherence tomography angiography in central serous chorioretinopathy. *J Ophthalmol*. 2015;2015:134783.
17. Shinojima A, Kawamura A, Mori R, et al. Findings of optical coherence tomographic angiography at the choriocapillaris level in central serous chorioretinopathy. *Ophthalmologica*. 2018;236:108–113.
18. Chan SY, Wang Q, Wei WB, et al. Optical coherence tomographic angiography in central serous chorioretinopathy. *Retina*. 2016;36:2051–2058.
19. Tittl M, Maar N, Polska E, et al. Choroidal hemodynamic changes during isometric exercise in patients with inactive central serous chorioretinopathy. *Invest Ophthalmol Vis Sci*. 2005;46:4717–4721.
20. Cardillo Piccolino F, Lupidi M, Cagini C, et al. Choroidal vascular reactivity in central serous chorioretinopathy. *Invest Ophthalmol Vis Sci*. 2018;59:3897–3905.
21. Mathiowetz V, Weber K, Volland G, et al. Reliability and validity of grip and pinch strength evaluations. *J Hand Surg Am*. 1984;9:222–226.
22. Robinson F, Riva CE, Grunwald JE, et al. Retinal blood flow autoregulation in response to an acute increase in blood pressure. *Invest Ophthalmol Vis Sci*. 1986;27:722–726.
23. Lupidi M, Coscas F, Cagini C, et al. Automated quantitative analysis of retinal microvasculature in normal eyes on optical coherence tomography angiography. *Am J Ophthalmol*. 2016;169:9–23.
24. Huang D, Chopra V, Lu AT, et al.; for the Advanced Imaging for Glaucoma Study-AIGS Group. Does optic nerve head size variation affect circumpapillary retinal nerve fiber layer

thickness measurement by optical coherence tomography? *Invest Ophthalmol Vis Sci*. 2012;53:4990–4997.

25. Spaide RF, Klancnik JM, Cooney MJ. Retinal vascular layers imaged by fluorescein angiography and optical coherence tomography angiography. *JAMA Ophthalmol*. 2015;133:45–50.
26. Nelis P, Clemens CR, Alten F, et al. OCT angiography reveals changes in foveal vessel architecture and foveal flow in central serous chorioretinopathy. *Acta Ophthalmol*. 2017;95:e802–e803.
27. Riendl AM, Robert WG, Reinke JA, et al. Cardiovascular response of human subjects to isometric contractions of large and small muscle groups. *Exp Biol Med*. 1977;154:171–174.
28. Krzeminski K, Cybulski A, Ziemba A, et al. Cardiovascular and hormonal responses to static handgrip in young and older healthy men. *Eur J Appl Physiol*. 2012;112:1315–1325.
29. Riva CE, Grunwald JE, Petrig BL. Autoregulation of human retinal blood flow. *Invest Ophthalmol Vis Sci*. 1986;27:1706–1712.
30. Luo X, Shen Y, Jiang M, et al. Ocular blood flow autoregulation mechanisms and methods. *J Ophthalmol*. 2015;2015:864–871.
31. Cavallotti C, Balacco Gabrielli C, Feher J. The human choriocapillaris: evidence for intrinsic regulation of endothelium. *J Anat*. 2005;206:243–247.
32. Walshe TEW, Connell P, Cryan L, et al. The role of pulsatile flow in controlling microvascular retinal endothelial and pericyte cell apoptosis and proliferation. *Cardiovasc Res*. 2011;89:661–670.
33. Lutty GA, Bhutto I, McLeod DS. Anatomy of the ocular vasculatures. In: Schmetterer L, Kiel J, eds. *Ocular Blood Flow*. Berlin, Heidelberg: Springer-Verlag; 2012:3–21.
34. Laties AM. Central retinal artery innervation: absence of adrenergic innervation to the intraocular branches. *Arch Ophthalmol*. 1967;77:405–409.
35. Kiel JW. Local determinants. In: Schmetterer L, Kiel J, eds. *Ocular Blood Flow*. Berlin, Heidelberg: Springer-Verlag; 2012:211–241.
36. Yannuzzi LA. Type A behavior and central serous chorioretinopathy. *Trans Am Ophthalmol Soc*. 1986;84:799–845.
37. Rothwell PM, Howard SC, Dolan E, et al. Prognostic significance of visit-to-visit variability, maximum systolic blood pressure, and episodic hypertension. *Lancet*. 2010;375:895–905.

Investigative Ophthalmology & Visual Science