Choroidal Hemodynamic Changes during Isometric Exercise in Patients with Inactive Central Serous Chorioretinopathy

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PURPOSE. Imaging studies suggest that the choroidal vasculature may be altered in central serous chorioretinopathy. Little is known, however, about the regulation of ocular blood flow in patients with central serous chorioretinopathy (CSC). The hypothesis for the present study was that choroidal blood flow changes during an increase in ocular perfusion pressure induced by isometric exercise may be altered in CSC.

METHODS. An observer-masked, two-cohort study was performed in 14 nonsmoking patients with chronic-relapsing but inactive CSC and in 14 healthy nonsmoking volunteers. Both groups were matched for age and sex. Subfoveal choroidal blood flow (CBF) was assessed with laser Doppler flowmetry, and ocular perfusion pressure (OPP) was calculated from mean arterial pressure (MAP) and intraocular pressure (IOP). Changes of CBF during isometric exercise over a period of 6 minutes were measured.

RESULTS. Whereas the increase of MAP, the pulse rate, and the OPP were comparable between the two study groups, subfoveal CBF increased significantly more in the group of patients with CSC (P < 0.001). IOP remained unchanged in both groups during isometric exercise. At an 85% increase in OPP, subfoveal CBF was approximately twice as high in the patients with CSC compared with the healthy control group.

CONCLUSIONS. The data indicate an abnormal subfoveal CBF regulation in patients with relapsing CSC compared with age-matched, nonsmoking, healthy volunteers during isometric exercise. (Invest Ophthalmol Vis Sci. 2005;46:4717–4721) DOI:10.1167/iovs.05-0268

Central serous chorioretinopathy (CSC) is a frequently occurring macular disease that predominantly affects young to middle-aged men. Usually, resolution of the serous exudation is followed by a marked restoration of central vision. Mental stress2–4 and hypercortisolism5–9 are factors associated with the precipitation or aggravation of this disease. In animal experiments, repeated injections of catecholamines induced a condition similar to CSC.10,11 Studies of fundus angiography, especially with indocyanine-green dye, revealed vascular patterns, such as choroidal hyperpermeability, localized choroidal filling delays, and venous congestion.12–17 Despite the biophysical and technical limitations in choroidal angiography, these observations raise the question of whether the choroidal vasculature is involved in the pathophysiology of CSC.

Vascular autoregulation is a crucial factor in the integrity of the peripheral circulation in many organs and is defined as the ability of a vascular bed to maintain constant blood flow during changes of perfusion pressure. At present, isolated changes of perfusion pressure cannot be induced and investigated in humans. However, in the human choroid, a nonlinear pressure-flow relationship has been found during experimental changes in perfusion pressure.18–23 Because some patients with CSC tend to have a chronic relapsing course with irreversible vision loss, we raised the question of whether a persistent abnormal regulatory response is involved in the pathogenesis of chronic CSC. Laser interferometric measurements of ocular fundus pulsation in patients with newly diagnosed active CSC provided evidence that choroidal perfusion in the macular region may be abnormal.24 This recent study focused our interest on the choroidal vascular bed in chronic inactive CSC and its reaction to mild physical activity during isometric exercise.

In the present study we compared choroidal blood flow (CBF) responses at the avascular fovea between asymptomatic patients with chronic CSC and healthy volunteers. During an experimental increase of perfusion pressure as provoked by isometric exercise, a net choroidal vasoconstriction is necessary to keep blood flow constant. Numerous mediators may be involved in this vasoconstrictor response, because blood flow in the choroid is controlled by several hormonal, neural, and paracrine regulatory systems.25 We hypothesized that this vasoconstrictor response may be altered in patients with chronic CSC compared with age-matched control subjects. The results of our study may add knowledge to our understanding of the pathophysiologic background of this peculiar ocular disease that has the potential to cause serious vision problems.

METHODS

Subjects

The present study was performed in accordance with the Declaration of Helsinki and the Good Clinical Practice guidelines. After approval of the study protocol by the Ethics Committee of the Vienna University School of Medicine and after written informed consent was obtained, 28 male volunteers were enrolled in the study (14 patients with CSC, mean age 39.3 years; 14 healthy subjects, mean age 38.6 years). All study participants were between 28 and 47 years of age with a body mass index between the 15th and 85th percentiles.26 The patients were selected by the Department of Ophthalmology and Optometry. The healthy control subjects were selected by the Department of Clinical Pharmacology. All participating individuals had a negative history of actual or recent smoking or drug use. The included patients had to have a positive history (one or more relapses) of clinically definite chronic CSC confirmed by previous fluorescein and indocyanine angiography and a biomicroscopically inactive status of CSC.
without evidence of macular edema or appearance of exudative material at the time of study entry. Furthermore, the last episode of CSC had to have occurred 6 months to 2 years before study enrollment. All participants passed a prestudy screening 2 weeks before the study day. This screening test included a complete assessment of medical history, including the intake of pharmacologic agents such as steroids or catecholamines; measurement of body height and weight; systemic blood pressure and heart rate (supine and standing); and a complete ophthalmic examination including best corrected visual acuity, slit lamp examination, measurement of ocular pressure, fundus examination, and fluorescein- and indocyanine-green angiography.

Subjects were excluded if any clinically relevant abnormality was found as part of the prestudy screening. All subjects had to be drug free, including corticosteroids, in the 2 weeks preceding the study day. Subjects with moderate or severe systemic hypertension (defined as systolic blood pressure >150 mm Hg or diastolic blood pressure >90 mm Hg) either treated or untreated were not included in the study. In addition, subjects with ametropia of >3 D, anisometropia >1 D, IOP ≥19 mm Hg, visual acuity <20/25, or any evidence of eye disease that might interfere with the purpose of the trial were excluded. Subjects with anisometropia of >1 D were excluded, because they normally do not provide optimal results with the portable laser Doppler flowmetry (LDF) system.

Experimental Design

This study was of an observer-masked design in two cohorts. Subjects were asked to refrain from alcohol and caffeine for at least 12 hours before trial days. Dilatation of one pupil was obtained with 2 drops of tropicamide (5 mg/mL; Mydriaticum augentropfen; Agepha GmbH, Vienna, Austria).

After a 20-minute resting period, baseline measurements with confocal LDF were obtained with the subject in a sitting position. The measurements were continued without cessation during the squatting period of 6 minutes. This exercise was performed in a position in which the upper and the lower leg were as close as possible to a right angle. At the end of the squatting period, immediately before the cessation of squatting, IOP was measured again.

Systemic Hemodynamics

Systolic, diastolic, and mean arterial blood pressures (SBP, DBP, MAP) were measured on the upper arm by an automated oscillometric device. Pulse rate (PR) was automatically recorded from a finger-pulse oximeter (HP-CMS patient monitor; Hewlett-Packard, Palo Alto, CA). Systemic hemodynamics were measured in 1-minute intervals during squating periods and in 10-minute intervals during resting periods.

Applanation Tonometry and Ocular Perfusion Pressure

The intraocular pressure (IOP) was measured with a Perkins applanation tonometer (Clement Clarke, Edinburgh, UK). Oxybuprocaine hydrochloride was used to anesthetize the cornea. Ocular perfusion pressure (OPP) was calculated as 2/3MAP – IOP.27 This formula is based on evidence that the pressure in choroidal veins almost equals the IOP.28,29 At the end of the period of isometric exercise, we observed only small changes of IOP over baseline. Hence, we used a linear regression model to extrapolate the IOPs at the other time points during squating.

Laser Doppler Flowmetry

Continuous measurement of subfoveal CBF was performed with LDF.30 With this technique, the vascularized tissue is illuminated by coherent laser light. Light scattered by the moving red blood cells undergoes a frequency shift. In contrast, static tissue light-scattering cells do not change the light frequency, but lead to randomization of light directions, impinging on red blood cells. Hence, red blood cells receive light from numerous random directions. Because the frequency shift is dependent, not only on the velocity of the red blood cells, but also on the angle between the wave vectors of the incident and the scattered light, scattering of the light in tissue broadens the Doppler shift power spectrum. From this spectrum, the average velocity of red blood cells (Vel), the volume of red blood cells (Vol) and the CBF (Vel × Vol) can be determined based on a theory of light-scattering in tissue in relative units.31

In the present study, a compact laser Doppler flowmeter, which has been described in detail previously, was used for the measurements of CBF.32 Briefly, a polarized laser source (λ = 785 nm, 100 μm) is relayed with a 1:1 optical system (laser beam at the cornea: width, 1.3 mm; power, 90 μW) and focused on the subject’s retina (nominal spot in the retinal image plane: 12 μm in diameter; actual spot on the retina: 50–100 μm in diameter, optical thickness of confocal layer: 300 μm). The point laser source, the point of illumination of the fovea, and the detecting optical fiber are located in conjugated planes. The scattered light is collected by an optical system organized with six fibers arranged circularly around the central fixation point along a circle of 180 μm diameter (within the avascular zone of the fovea). All measurements were performed in the fovea, by asking the subject to fixate directly the beam, which appears as a small red dot. The fovea was chosen because the retina is avascular in this region. For statistical analysis, only the portions of the signal that were within 15% of the baseline direct current (DC) were taken for analysis. Compared with previous fundus camera-based systems for the assessment of CBF,30 the new system offers two major advantages: Adjustment of the detector relative to the measurement on the retina is omitted, because the system uses confocal optics, and the system is portable, which facilitates measurements during isometric exercise.

Data Analysis

All statistical analyses were performed on computer (Statistica, ver. 4.5; StatSoft Inc., Tulsa, OK). All outcome variables were calculated for each subject individually and then averaged. The effect of exercise on the outcome parameters was assessed with repeated-measures ANOVA. Probabilities were calculated as the interaction between groups (CSC versus control) and time. The relative change in hemodynamic parameters induced by isometric exercise was calculated. To gain information on the pressure–flow relationship, we sorted relative change the light frequency, but lead to randomization of light direction, impinging on red blood cells. Hence, red blood cells receive light from numerous random directions. Because the frequency shift is dependent, not only on the velocity of the red blood cells, but also on the angle between the wave vectors of the incident and the scattered light, scattering of the light in tissue broadens the Doppler shift power spectrum. From this spectrum, the average velocity of red blood cells (Vel), the volume of red blood cells (Vol) and the CBF (Vel × Vol) can be determined based on a theory of light-scattering in tissue in relative units.31

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RESULTS

No adverse events were detected during this study, and the squatting procedure was well tolerated by all participating subjects. None of the subjects reported any change in visual acuity during isometric exercise, and a slit lamp examination immediately after the squatting period did not reveal any changes in fundus appearance. There were no significant differences between the baseline values in the two groups (Table 1).

As depicted in Figure 1, 6 minutes of isometric exercise induced a significant increase in MAP, PR, OPP, and CBF in patients with CSC and healthy control subjects (P < 0.001, each). The increase in MAP, PR, and OPP was comparable between groups (MAP: P = 0.69; PR: P = 0.13; OPP: P = 0.61). The increase of CBF was significantly more pronounced in the
CSC group than in the healthy control group ($P < 0.001$). IOP immediately before cessation of isometric exercise did not change in both groups. At the end of the squatting period, the IOP was 13.7 ± 0.8 and 13.4 ± 0.6 mm Hg in the healthy control and CSC groups, respectively. Approximately 30 minutes after subjects ceased squatting, the return of MAP, PR, and CBF to baseline was verified.

The pressure–flow relationship during the squatting periods is presented in Figure 2. The fitted curves and their mathematical expression are also shown. In the CSC group, CBF increased at changes in OPP smaller than in the control group. At an increase in OPP of 85%, the calculated increase in CBF was twice as high in the group of patients with CSC, compared with the healthy control group (CSC group: 20%, healthy control group: 10%).

**DISCUSSION**

In the present study LDF was chosen, to gain insight into CBF regulation in patients who have asymptomatic chronic CSC. In this study, 14 consecutive patients with inactive CSC were compared to an equal-sized control group of healthy volunteers, to assess the subfoveal CBF regulation during isometric exercise. The results of this study clearly indicate that subfoveal CBF regulation in patients with a history of chronic CSC is impaired. Furthermore, the choroidal dysregulation in these patients with so-called “inactive” disease, most of them with substantial functional restoration, seem to pertain at least 6 months past the last episode.

Normally, healthy individuals who undergo a 6-minute period of isometric exercise show only a mild increase in CBF, despite the pronounced increase in OPP. In the present study CBF reached a twofold increase in CSC patients compared with the control subjects during squatting indicating an inadequate vasoconstrictor response in the patients with CSC. Looking at the pressure-flow relationship depicted in Figure 2, it is interesting that CBF in asymptomatic patients with CSC increased at OPPs between 40% and 50% above baseline, whereas it was still within the regulatory range in healthy control subjects. We and others have shown that LDF measurements during isometric exercise employing the portable device used in the

<table>
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<th>TABLE 1. Baseline Values of Ocular and Systemic Hemodynamic Parameters</th>
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<td><strong>MAP (mm Hg)</strong></td>
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<td>Control Subjects</td>
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Data are presented as the means ± SD ($n = 14$, each). au, arbitrary units.

**FIGURE 2.** Pressure-flow relationship using the categorized OPP–CBF data during isometric exercise. The $n$ values indicated at each data point show the number of subjects from whom data were clustered in the respective OPP range. Relative data were sorted into groups of 12 values each, according to ascending OPPs. The means and the lower limits of the 95% confidence intervals are shown.
present study show adequate reproducibility, allowing the detection of pharmacological modifications of choroidal pressure-flow curves in the subfoveal region and modifications of the choroidal regulatory behavior in smokers and in subjects with vasospasm. To characterize in detail the reasons for altered subfoveal CBF regulation in patients with chronic CSC is beyond the scope of the present study. Several factors contributing to CBF regulation during changes in perfusion pressure have been described in experimental animals and humans, including the endothelial system, the arginine/nitric oxide system, and an unknown neural vasodilator.

An important aspect of blood flow regulation during isometric exercise is that isometric exercise induces a considerable stimulation of the sympathetic and parasympathetic nervous system. This is of interest, because patients with CSC exhibit an altered heart rate variability that indicates an abnormal sympathetic activity of the autonomic nervous system, well compatible with the association of the disease with type A behavior. Several other factors have been described as associated with CSC that could contribute to altered CBF regulation. Elevated psychological stress has been implicated in the etiology of CSC, inducing pronounced endothelial dysfunction. This is also compatible with the observation that patients with CSC are more likely to use psychopharmacological medications. In addition, it is known that the disease is associated with exogenous hypercortisolism and an abnormal endogenous cortisol profile. This does not rule out an involvement of the adrenergic system, because corticosteroids alter the expression and transcription of adrenergic receptor genes and potentiate, for example, the effects of adrenergic stimulation in rabbit ciliary processes. In addition, as mentioned before, several animal experiments have shown that repeated injections of epinephrine and corticosteroids mimic an ocular disease comparable to CSC.

Several imaging studies have shown that CSC may be associated with abnormal blood flow in the choroid. Fluorescein and indocyanine green angiographic studies are indicative of local alterations of blood flow in the choroid in the active and the chronic forms of the disease. We have shown, that active CSC is associated with increased fundus pulsation amplitudes and an abnormal local variability of fundus pulsation amplitudes, indicative of increased pulsatile CBF. Recently, it has been shown that patients with active CSC show lower LDF CBF levels than do healthy control subjects. This was not the case in our study population consisting of patients with inactive chronic CSC (Table 1). One needs to be careful, however, when comparing absolute LDF readings between different ocular diseases, because the morphologic changes associated with active CSC probably may influence the scattering properties of tissues. Accordingly, differences in LDF CBVs in baseline conditions may describe altered light-scattering rather than altered perfusion.

The present study does not finally answer the question of whether the observed choroidal vascular dysregulation is involved in the pathogenesis of the disease or merely a consequence of CSC. For a final answer to this question, a longitudinal study may be necessary, investigate CBF regulation during the natural course of CSC. In addition, one has to keep in mind that the results of the present study apply only to the choroid in the foveal avascular zone. Whether these results can be transferred to other regions of the choroid remains unclear. Direct measurement of CBF in the periphery is difficult, because retinal and choroidal contributions to the LDF signal cannot generally be discriminated with current technology.

In conclusion, the data of the present study indicate abnormal CBF regulation in patients with inactive chronic CSC. Whether choroidal perfusion abnormalities play a role in the pathogenesis of CSC or are a consequence of the disease remains to be shown.

References


