Vascular Dysregulation in the Choroid of Subjects With Acral Vasospasm

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Objective: To assess the relationship between ocular perfusion pressure and blood flow in the choroid in subjects with acral vasospasm.

Patients and Methods: Twenty otherwise healthy subjects with acral vascular dysregulation and 55 age-matched nonvasospastic healthy volunteers were recruited. After a 20-minute rest in a sitting position, intraocular pressure and choroidal blood flow were determined by means of applanation tonometry and choroidal laser Doppler flowmetry, respectively. The laser Doppler flowmetry variables velocity, volume, and flux were assessed. The correlations between mean ocular perfusion pressure \( \left( \frac{2}{3} \times \left( \frac{1}{3} \times \text{diastolic blood pressure} + \frac{2}{3} \times \text{systolic blood pressure} \right) \right) - \text{intraocular pressure} \) and blood flow measures were determined by means of the Pearson linear correlation factor. The \( t \) test was used to evaluate differences between normal subjects and patients with vasospasm.

Results: Apart from a slight difference in systolic blood pressure (mean±SD, 113.70±11.88 mm Hg in the vasospastic group and 121.09±14.58 mm Hg in the control group; \( P=0.05 \)), the 2 study groups were completely comparable. Velocity and flux correlated significantly with the mean ocular perfusion pressure (\( r=0.76, P<.001; r=0.64, P=0.002 \), respectively) in vasospastic subjects. Such correlations did not occur in the control group, and the difference between vasospastic patients and control subjects with regard to these correlations was statistically significant (\( P<.001 \) and \( P=0.003 \), respectively).

Conclusions: Choroidal blood flow seems, to some degree, to be independent of perfusion pressure, but not in subjects with acral vasospasm.

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GLAUCOMA is a progressive optic neuropathy involving characteristic structural changes of the optic nerve and characteristic visual field defects. The level of intraocular pressure (IOP) is the risk factor most often associated with glaucomatous optic neuropathy. However, the substantial number of cases of open-angle glaucoma that continue to progress in damage despite therapeutically lowered IOP as well as the existence of patients who develop glaucoma with normal IOP has prompted the search for risk factors other than increased IOP. In addition to neurotoxicity, reduced ocular blood flow, ocular vascular dysregulation, and systemic blood pressure alterations have been suggested as possible contributing factors to the pathogenesis of glaucoma.

Among the vascular factors, vascular dysregulation or a lack of autoregulation, leading to transient vasoconstrictions or to a lack of appropriate vasodilation, has recently been proposed as a more likely contributor to glaucomatous damage than frank ischemia. The etiology or the pathophysiology of vascular dysregulation is not clear. There is some evidence that vascular endothelial dysfunction might play an important role. The most typical clinical manifestation is a history of frequent cold hands, often associated with vasospastic reactions to cold in the nailfold capillaries as assessed by nailfold capillaroscopy. Some parallelism between finger and ocular blood flow has also been suggested. Vasospasms in the ocular circulation, namely the retinal vessels, have been observed in association with unstable primary angina and with migraine. Furthermore, vascular dysregulation has been described in the retrobulbar circulation of otherwise healthy subjects with vasospasm and patients with glaucoma who have progressive damage despite lowered IOP.

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PATIENTS AND METHODS

Seventy-five healthy subjects were included in this study. A notification in the University Eye Clinic Basel (Basel, Switzerland) informed potential volunteers (collaborators, students, and parents and friends of patients) of the opportunity to participate in a scientific research project.

After informed consent was obtained, subjects were screened for ocular and systemic diseases. A detailed medical and ophthalmic history was recorded, including a questionnaire containing queries about complaints of cold hands, and all subjects completed an ophthalmologic examination. Subjects were not included if they had a history of ocular or systemic disease, a family history of glaucoma, a history of eye surgery, any chronic systemic or topical medication, a best-corrected visual acuity worse than 20/25, an applanation IOP of 20 mm Hg or more, or any pathologic finding on ophthalmologic examination, including slit-lamp biomicroscopy and funduscopy.

Subjects were classified as vasospastic if they related a clear history of frequent cold hands (answering “yes” to the questions, “Do you have always cold hands, even during summertime?” and “Do other people tell you that you have cold hands?”) and as normal if they denied such a history. Subjects describing sometimes cold hands were excluded from the present analysis. Because a simple assessment of a clear history of cold hands has been suggested to be better at distinguishing ocular features supposedly related to vascular dysregulation than the more complex determination of vasospasm by methods such as finger laser Doppler flowmetry (LDF), no objective assertion of acral vasospasm was performed.

All subjects underwent choroidal blood flow assessment by means of choroidal LDF. In brief, a continuous laser light is projected into the fovea and the back-scattered light is then analyzed. The back-scattered laser light contains 2 components: light scattered by the relatively stationary structures, such as vessel walls and tissue, and light scattered by moving blood cells. Most of the light is back-scattered without shift of the frequency. Moving particles, however, cause a Doppler shift on scattered light in proportion to the velocity of the moving particle. The interference of these 2 wave components leads to an alternating signal at the photodetector. This signal is subjected to a fast Fourier transform algorithm to obtain the power spectrum of the multiple frequency shift components. From this spectrum, variables called flux, volume, and velocity, which are related to blood flow, are computed by means of an algorithm based on Bonner and Nossal’s photodiffusion theory. These flow variables are related to each other through the following relationship: flux = constant * volume * velocity. Each variable is linear with respect to changes. For the present experiments, a new compact confocal (local plane thickness of approximately 300 µm) laser Doppler flowmeter (Choroidal Blood Flowmeter-ChBF; IRO, Sion, Switzerland) was used.

The subjects were asked to fixate on a diode laser beam (wavelength, 811 nm; 95 mW at the cornea) delivered to the undilated eye. The diameter of the beam at the fundus of the emmetropic eye is about 10 to 20 µm. Light scattered in the tissue volume sampled by the incident laser beam is

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RESULTS

Among the 75 volunteers, 20 subjects (15 women and 5 men) had a history of acral vasospasm and 55 (20 women and 35 men) did not. The difference in sex distribution was statistically different between the experimental groups (Fisher exact test: P = .003). The mean (±SD) age was 46 ± 15 years for the 20 vasospastic subjects and 48 ± 12 years for the 55 control subjects (P = .56). Hemodynamic variables such as SBP, DBP, MABP, OAP, and MOPP, as well as IOP, are outlined in Table 1. These variables were comparable between the 2 experimental groups except for SBP, which was statistically significantly lower in vasospastic subjects (P = .05). The choroidal LDF variables in the left eye of the vasospastic group and the control group are shown in Table 2. These variables were statistically comparable between the vasospastic subjects and the control group (Table 2).

The correlation between the MOPP and the choroidal LDF variables velocity, volume, and flux among the 2 experimental groups are shown in Figures 1, 2, and 3. In the vasospastic group, the MOPP correlated statistically significantly with the choroidal LDF variables velocity (Figure 1) and flux (Figure 3), but not volume (Figure 2). The correlation factors for velocity, volume, and flux were 0.76 (P < .001), 0.30 (P = .20), and 0.64 (P = .002), respectively, among the vasospastic subjects. None of these correlations was statistically significant in the control group. For the control group, the respective correlation factors for velocity, volume, and flux were 0.02 (P = .90), 0.04 (P = .76), and 0.03 (P = .84). The difference between vasospastic patients and control subjects with regard to the correlation between MOPP and LDF variables (divergence of the regression lines) was statistically significant.
detected at the fundus image plane of the camera by a fiber-bundle photodetector system organized with 6 fibers arranged circularly around the central fixation point, all within the avascular zone of the fovea, favoring measurement of choroidal blood flow. For all subjects, the left eye was chosen arbitrarily as the experimental eye. During a measurement, the subject’s head was comfortably placed in a slitlamp head rest. Care was taken to keep the direct current component of the signal as constant as possible during the recording, which lasted at least 20 seconds. Data points were averaged in phase with the heart pulse, which was continuously recorded. All data points with the same phase delay after the start of the pulse were averaged together, and this procedure was repeated for all phase delays, producing an average waveform representative of each flow variable. A mean value during the heart cycle was computed for each variable.

The entire experimental procedure was standardized. After the presence or absence of vasospasticity was established, the subjects rested for 20 minutes in a sitting position. Before choroidal LDF, the IOP was measured by means of applanation tonometry after 1 drop of 0.4% benoxinate hydrochloride was applied and the tearfilm was stained with a strip of fluorescein sodium. Afterward, LDF variables were obtained from the choroid. All LDF measurements were performed by the same experienced technician (H.V.), who was masked to the history regarding cold hands of the subjects and was not allowed to shake hands with them. Before as well as immediately after choroidal blood flow measurement, systemic blood pressure and heart rate were recorded by means of an automatic device (Profilomat; Roche, Basel, Switzerland). This device measures blood pressure automatically, on the same principle as the conventional mercury sphygmomanometer, with a cuff and a microphone. Subjects with marked variations in blood pressure during the examinations were excluded. The average of the 2 measurements was considered for blood pressure and pulse rate for further analysis.

The blood pressure readings for systolic blood pressure (SBP) and diastolic blood pressure (DBP) obtained during choroidal LDF were used to calculate the mean arterial blood pressure (MABP) according to the following formula: MABP=(2/3 × DBP) + (1/3 × SBP). The ophthalmic artery pressure (OAP) was calculated according to the following formula: OAP=(2/3 × MABP. The mean ocular perfusion pressure (MOPP) was calculated as MOPP = OAP – IOP.

The correlation between MOPP and the choroidal blood flow variables velocity, volume, and flux was assessed by means of the Pearson linear correlation factor in both experimental groups. To evaluate differences in these correlations between vasospastic patients and control subjects, the interaction by the covariates velocity, volume, or flux (parallelism of regression lines) was computed in a covariance analysis model comparing MOPP between the experimental groups. Differences in hemodynamic variables such as SBP, DBP, MABP, OAP, and MOPP, as well as IOP and choroidal LDF variables velocity, volume, and flux, between the group of vasospastic subjects and the control group were assessed by means of the t test for unpaired variables. Sex distribution in the experimental groups was compared by means of Fisher exact test. P values less than .05 were considered statistically significant.

| Table 1. Systemic Hemodynamic Variables and Intraocular Pressure (IOP)* |
|-----------------------------|-----------------------------|-----------------------------|
|                             | Patients With Vasospasm     | Patients Without Vasospasm  |
|                             | SBP (mm Hg)                  | DBP (mm Hg)                  |
|                             | 113.70 ± 11.88               | 74.25 ± 10.29               |
|                             | 121.09 ± 14.58               | 77.36 ± 16.17               |
|                             | MABP (mm Hg)                 | OAP (mm Hg)                 |
|                             | 87.40 ± 10.36                | 58.27 ± 6.90                |
|                             | 91.94 ± 9.92                 | 61.29 ± 6.61                |
|                             | MOPP (mm Hg)                 | IOP (mm Hg)                 |
|                             | 43.55 ± 7.20                 | 14.72 ± 2.46                |
|                             | 46.33 ± 5.99                 | 14.96 ± 2.97                |

*Unless otherwise indicated, data are given as mean ± SD millimeters of mercury. SBP indicates systolic blood pressure; DBP, diastolic blood pressure; MABP, mean arterial blood pressure; OAP, ophthalmic artery pressure; and MOPP, mean ocular perfusion pressure.

Corporately significant for velocity (F = 13.71, P < .001) and flux (F = 9.85, P = .003), but not for volume (F = 1.69; P = .20).

COMMENT

Choroidal LDF measurements were obtained in 20 vasospastic, otherwise healthy subjects and in 55 age-matched controls. Mean ocular perfusion pressure and choroidal LDF variables were statistically comparable between the 2 groups. A linear parametric regression analysis disclosed significantly lower choroidal blood flow variables (flux and velocity, but not volume) in vasospastic subjects with lower ocular perfusion pressure. Similar correlations did not occur in the control group. The difference between vasospastic patients and control subjects with regard to the correlation between MOPP and choroidal blood flow was statistically significant for the LDF variables flux and velocity. These observations suggest that, in contrast to normal subjects, choroidal blood flow is low in vasospastic subjects when ocular perfusion pressure is low, suggesting an altered vascular regulation in the choroidal circulation of vasospastic subjects.

The choroid plays an important role in the supply of nutrients to the outer retina in humans, particularly in the avascular region of the fovea. A high flow rate–low oxygen extraction system has been considered to be necessary for the choroid, with the argument that choriocapillaris P O 2 must be kept high to maintain normal photoreceptor oxidative metabolism. The essential factor controlling the requirement for high flow rate seems

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to be the distance between the choroid and the photoreceptor inner segments. The relatively long diffusion distance requires a high PO2 at the choroid so that there is a steep enough oxygen gradient (high enough flux) between the choroid and the inner segment layer. A sufficient supply, however, will depend on adequate adjusting mechanisms, counteracting the negative effects of external perturbations. A number of regulatory systems and factors, such as circulating hormones, as well as metabolic, myogenic, and neurogenic factors, participate in the regulation of the vascular tone.\textsuperscript{36} Blood flow through an organ such as the eye depends on the arterial and venous pressure difference, ie, the perfusion pressure. A decrease in perfusion pressure produces a decrease in flow, unless this decrease is counteracted by a similar decrease in vascular resistance. Autoregulation is said to occur when the effect of the decrease in perfusion pressure is compensated for by a decrease in vascular resistance; the flow remains constant, and, thus, within certain limits, local perfusion remains largely independent of the local perfusion pressure. In various vascular systems, this is accomplished in two principal ways, metabolic and myogenic mechanisms.\textsuperscript{37} Myogenic responses may require several minutes to induce stable vessel diameters after an acute intravascular pressure change.\textsuperscript{38,39} On the other hand, in the rabbit’s brain circulation, for example, autoregulatory responses, probably driven by metabolic mechanisms, seem to occur within approximately 3 to 13 seconds after a steep decrease in MABP, depending on the severity of hypotension.\textsuperscript{40}

Vascular autoregulation applies to various vascular systems, including that of the heart, the brain, the retina, and the optic nerve. In the choroidal circulation, however, studies pertaining to the effect of increased IOP on choroidal blood flow have suggested a linear relationship between choroidal blood flow and perfusion pressure in animal eyes, failing to show evidence of autoregulation in this vascular bed.\textsuperscript{41,42} More recently, investigations in rabbits in which systemic blood pressure had been manipulated demonstrated a nonlinear relationship between choroidal blood flow and perfusion pressure, suggesting that the choroid may well have some capability to autoregula-

**Figure 1.** Relationship between choroidal blood flow velocity and mean ocular perfusion pressure (MOPP) in normal subjects (A) and patients with vasospasm (B). Velocity correlated positively with ocular perfusion pressure in vasospastic patients ($r=0.76$, $P<.001$), but not in normal control subjects ($r=0.02$, $P=.80$). The difference between vasospastic patients and control subjects with regard to the correlation between MOPP and choroidal blood flow velocity (divergence of the regression lines) was statistically significant ($P<.001$).

**Figure 2.** Relationship between choroidal blood flow volume and mean ocular perfusion pressure (MOPP) in normal subjects (A) and patients with vasospasm (B). Volume did not correlate with ocular perfusion pressure in vasospastic patients ($r=0.30$, $P=.20$) or in normal control subjects ($r=0.04$, $P=.76$). The difference between vasospastic patients and control subjects with regard to the correlation between MOPP and choroidal blood flow volume (divergence of the regression lines) was not statistically significant ($P=.20$). AU indicates arbitrary units.
Choroidal blood flow was assessed by means of LDF technology. Measurements of choroidal blood flow with the use of a fundus camera–based LDF system strongly suggested that the LDF signal originates predominantly from the choriocapillaris, rather than from the larger choroidal vessels behind this layer or the capillaries of the macular region of the retina. In the present study, the relative contribution of light scattered by the blood in the choriocapillaris compared with that scattered from the larger vessels should be even stronger, because the probing beam and detecting aperture were confocal with the level of the photoreceptors. With regard to the contribution from retinal capillaries, a recent study performed with this instrument demonstrated no detectable change in choroidal blood flow in response to breathing 100% oxygen, confirming the absence of a contribution from the retina. Indeed, studies assessing the response of choroidal blood flow to changes in ocular perfusion pressure, changes in arterial blood oxygen or carbon dioxide tensions, and the Valsalva maneuver support the assumption that choroidal LDF measures change in choroidal blood flow in the foveal region. The sensitivity of choroidal blood flow measurements, defined as the minimum change that can be detected on the basis of 11 subjects, was found to be approximately 6% with this device.

Only the LDF variables flux and velocity, but not volume, correlated with ocular perfusion pressure in vasospastic subjects. A mechanism that could have played a role in the maintenance of constant choroidal blood volume within the narrow physiologic range of IOP is a passive increase in volume of the choriocapillaris. This could be caused by a slight engorgement of this blood layer in response to the moderate increases in IOP as suggested by the positive correlation between IOP and choroidal blood volume observed in a previous study in healthy subjects. Furthermore, the present measurements provide only information on choroidal blood flow in the foveal region of the fundus. Other regions of the choroid could present completely different features, especially with regard to the relationship between perfusion pressure and blood flow. Regional differences in the responsiveness of the cat's choroidal circulation support the assumption that specific regulatory mechanisms may prevail in the foveal region. Indeed, a distinct dense nitric innervation, localized in the temporal-central portion of the choroid, has been described in humans but not in other species. This finding suggests that, especially in this region, in addition to intrinsic vascular mechanisms, neural mechanisms distinct from those seen elsewhere within the choroid may take a large part in local blood flow control. Neural regulatory mechanisms could, therefore, be the origin of autoregulatory behavior of the foveal choriocapillaris.

In the present study, choroidal blood flow correlated positively with MOPP in vasospastic subjects, suggesting that ocular blood flow might also decrease with decreasing perfusion pressure. Such a behavior was not observed in the control group, suggesting that blood flow–regulating mechanisms are different between vasospastic and nonvasospastic subjects. The findings of the present study demonstrate that blood flow alterations occur in the choroidal circulation or, more precisely, in the foveal region. However, the results of the present study suggest that the autoregulatory behavior of the foveal choriocapillaris is not identical in humans and in rabbits. Further studies are necessary to clarify the mechanisms responsible for the autoregulation of choroidal blood flow in the foveal region.

Figure 3. Relationship between choroidal blood flow flux and mean ocular perfusion pressure (MOPP) in normal subjects (A) and patients with vasospasm (B). Flux correlated positively with MOPP in vasospastic patients (r = 0.64, P = .002) but not in normal control subjects (r = 0.03, P = .84). The difference between vasospastic patients and control subjects with regard to the correlation between MOPP and choroidal blood flow velocity (divergence of the regression lines) was statistically significant (P = .003). AU indicates arbitrary units.
veal choriocapillaris of vasopastic subjects. Whether similar alterations exist in other ocular vessels, such as those feeding the anterior optic nerve, is not known. Indeed, vasopasms have been suggested to represent a risk factor for ophthalmic diseases such as glaucoma,24 anterior ischemic optic neuropathy,26 venous thrombosis in young individuals,25 or central serous chorioretinopathy:27 Consequently, whether subjects with such diseases present similar alterations in their choroidal circulation would be of utmost interest.

In summary, the present study demonstrated an altered vascular regulation in the choroidal circulation of vasopastic subjects. Such alterations might, hypothetically, render the eye susceptible to variations in IOP or systemic blood pressure.