Choroidal Laser Doppler Flowmetry in Healthy Subjects

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Objective: To evaluate normal choroidal blood flow and its relationship with various factors such as age, systemic blood pressure, and intraocular pressure (IOP).

Methods: A total of 70 healthy subjects were recruited. Choroidal blood flow was assessed using a method based on laser Doppler flowmetry (LDF) technique. The LDF parameters of velocity, volume, and flux were obtained. The influence of age, mean systemic blood pressure, IOP, smoking, and sex on choroidal hemodynamic parameters was assessed in a multiple linear regression model. The correlations between interocular difference in IOP and interocular differences in the LDF parameters were assessed by means of the Pearson linear correlation factor.

Results: Velocity decreased significantly ($P = .03$) with advancing age of the subjects and volume increased significantly ($P = .02$) with increasing IOP. Mean blood pressure, smoking, and sex had no influence on the choroidal LDF parameters. Interocular difference in IOP correlated significantly with interocular difference in volume ($R = 0.34, P < .005$).

Conclusion: Choroidal blood flow velocity decreased with increasing age of the subjects, while the volume of moving erythrocytes decreased with lower IOP.


The choroidal circulation plays an important role in maintaining adequate function of the outer retina. Foveal choroidal blood flow has been suggested to decrease with advancing age in healthy individuals. In patients with eyes in nonexudative stages of age-related macular degeneration, choroidal blood flow was even more markedly decreased when compared with age-matched controls. Could, hypothetically, alterations in choroidal blood flow even precede degeneration of the neurosensory retina? If yes, perturbation of choroidal blood flow might represent a modifiable risk factor in age-related maculopathy. Indeed, several cardiovascular risk factors, including smoking, systemic hypertension, a previous diagnosis of a vascular event, high serum cholesterol levels, or high intake of saturated fat and cholesterol, and an increased body mass index have been found to have a statistically significant association, or, by their effect on choroidal circulation, have been hypothesized as possible pathogenetic factors for the development of age-related maculopathy. Consequently, a thorough understanding of choroidal blood flow is warranted. The present study evaluated the statistical distribution and the interocular differences in choroidal blood flow values, as well as the relationship of choroidal blood flow with age, sex, systemic blood pressure, smoking habits, and intraocular pressure (IOP) in a healthy population.

RESULTS

A total of 70 subjects (36 females and 34 males) satisfied the inclusion criteria (history and eye examination) and were examined by means of choroidal LDF. Their mean ± SD age was 37.5 ± 16.1 years (range, 13-70 years).

DESCRIPTIVE STATISTICS

For the descriptive analysis of the choroidal hemodynamic parameters (velocity, volume, and flux), one randomly selected eye per subject was included. The mean ± SD IOP for 70 eyes was 16.5 ± 2.8 mm Hg; systolic blood pressure, 116.5 ± 16.1 mm Hg; and diastolic blood pressure, 73.2 ± 12.5 mm Hg. These values did not differ significantly from a normal distribution (Shapiro-Wilks W test, $P > .20$).

The mean values; minima; maxima; 2.5th, 50th, and 97.5th percentiles; and the SDs for the choroidal hemodynamic parameters are listed in **Table 1**. The choroidal hemodynamic parameters (velocity, volume, and flux) were not normally distributed (Shapiro-Wilks $W$ test, $P < .03$, $P < .007$, and $P < .005$, respectively), and all 3 distribution curves showed a skew toward the right (**Figure**).
SUBJECTS AND METHODS

Subjects between 13 and 70 years of age were recruited for the present study. The protocol had been approved by the Institutional Ethical Committee and each subject signed an informed consent form prior to any examination. Subjects were screened for ocular and systemic diseases. A detailed medical and ophthalmic history was recorded, including queries about age, sex, diabetes, high levels of blood lipids, systemic or ocular circulatory diseases, ocular diseases and surgery, medication, drugs, and alcohol and smoking habits. Subjects were excluded if they had a history of ocular or systemic disease, a family history of eye disease or eye surgery, any long-term systemic or topical medication use, or drug or alcohol abuse. Subjects included after examination of the medical history completed an ophthalmologic examination and their blood pressure was measured. Subjects were excluded if they had a sphygmomanometrically recorded systolic blood pressure above 140 mm Hg or a diastolic blood pressure above 90 mm Hg, a best-corrected visual acuity worse than 20/25, high ametropia (spherical equivalent less than −5 diopters [D] or greater than +3 D), an astigmatism above 2.5 D, an anaplytional IOP (Goldmann applanation tonometry) of 20 mm Hg or greater, a pupil diameter less than 3 mm, or any pathological findings on ophthalmologic examination, including slitlamp biomicroscopy and indirect funduscopy with a 90-D Volk lens.

Choroidal blood flow was determined using a method based on the laser Doppler flowmetry (LDF) technique. The principle of choroidal blood flow measurement by means of LDF has been validated by Riva et al.18 With this technique, a continuous laser light is projected into the fovea and the back-scattered light is then analyzed. It has been demonstrated that when the laser beam is focused on the fovea, the Doppler signal arises predominantly from the choriocapillaris.18 The back-scattered laser light contains 2 components: light scattered by relatively stationary structures, such as vessel walls and tissue, and light scattered by moving blood cells. Most of the light is back scattered without a shift of the frequency. Moving particles, however, cause a Doppler shift on scattered light in proportion to the velocity of the moving particles. 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. Based on the theory of Bonner and Nossal, hemodynamic parameters such as volume (proportional to the number of moving particles in the sampled volume), velocity (proportional to the mean velocity of the moving particles in the sampled volume), and flux (volume × velocity) are calculated from this spectrum.19,20 Each parameter is given in arbitrary units and behaves linearly with respect to changes in blood flow.

In the present study, a new device with specific characteristics, the compact choroidal laser Doppler flowmeter (IRO, Sion, Switzerland) was used. The technical details of this instrument have been described elsewhere.21 Briefly, the optical system is based on a confocal arrangement. The point laser-light source, the illumination point at the foveola, and the photodetector system are conjugated. A polarized laser source (810 nm) is focused with a microscope objective to a point source, which is relayed by a lens on the image plane of an ocular lens. When the subject is looking at this image, the latter is projected on the fovea. The light of the laser beam is focused on a small spot of about 10 to 20 µm in diameter on the retina. The size of the incoming beam is 400 µm at the pupil. The scattered light is collected by the optical system through a confocal pinhole, and is detected by either a single fiber-photodetector system (direct mode) or a fiber bundle-

Table 1. Descriptive Statistics for Choroidal Hemodynamic Parameters

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Minimum</th>
<th>2.5th</th>
<th>50th</th>
<th>97.5th</th>
<th>Maximum</th>
<th>Mean (SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Velocity</td>
<td>1.11</td>
<td>1.19</td>
<td>1.71</td>
<td>2.33</td>
<td>2.37</td>
<td>1.72 (0.32)</td>
</tr>
<tr>
<td>Volume</td>
<td>0.30</td>
<td>0.31</td>
<td>0.61</td>
<td>1.13</td>
<td>1.44</td>
<td>0.65 (0.21)</td>
</tr>
<tr>
<td>Flux</td>
<td>10.64</td>
<td>11.46</td>
<td>24.71</td>
<td>46.16</td>
<td>52.96</td>
<td>25.23 (8.08)</td>
</tr>
</tbody>
</table>

CORRELATIONS BETWEEN CHOROIDAL HEMODYNAMICS WITH AGE, BLOOD PRESSURE, AND IOP

The correlations between choroidal hemodynamic parameters and age, mean systemic blood pressure, and IOP are shown in Table 2. There was a significant correlation between velocity and age as well as between volume and IOP. There were no statistically significant differences between female and male subjects in a t test ($P = .53$, $P = .63$, and $P = .71$ for velocity, volume, and flux, respectively). Ten subjects were smokers, but no statistically significant differences between smokers and nonsmokers were observed in a t test ($P = .72$, $P = .65$, and $P = .58$ for velocity, volume, and flux, respectively).

However, the power for the last 3 comparisons to be significant at the level of $P = .05$ was 5.8%, 7.2%, and 13.6%, respectively.

REGRESSION ANALYSIS

The influence of age, mean systemic blood pressure, IOP, smoking, and sex on velocity, volume, and flux was analyzed in a regression model (Table 3). Velocity decreased significantly ($P < .03$) with advancing age of the subjects and volume increased significantly ($P < .02$) with increasing IOP of the subjects. The variables mean blood pressure, smoking, and sex had no influence on the choroidal hemodynamic parameters. Interocular difference in IOP correlated significantly with interocular differ-
photodetector system (indirect mode). The detection sites of the latter fibers are organized with 6 fibers arranged circularly around a central fiber pointing at the fixation point, all within the avascular area of the fovea so that they do not touch any retinal blood vessels. This disposition favors measurement of choroidal blood flow, because the lack of retinal vessels in the avascular area of the fovea allows to eliminate any contribution of retinal blood flow. During the direct mode of detection, the signal is recorded with the central fiber, while detection with the 6 outer fibers corresponds to an indirect measure. Based on Bonner and Nossal’s model, it is hypothesized that the indirect mode of detection will sense scattering alteration occurring as deep within the tissue as 100 to 300 µm, corresponding to the choriocapillaris. Consequently, the indirect mode of detection was used in the present study.

The photocurrent from the photodetector is Fourier transformed and the hemodynamic parameters, flux, volume, and velocity are computed. Spikes within the continuous signal due to micromovements of the eye are removed and the hemodynamic parameters are averaged over 3 to 10 seconds of continuous measurements. The subjects had to confirm that the central spot and the peripheral speckle pattern remained visible throughout the examination, ensuring a proper alignment. One measurement of 10 to 15 seconds was obtained for each eye, always beginning with the right eye. For processing, data points are averaged in phase with the heart pulse, which is continuously recorded. All data points with the same phase delay after the start of the pulse are averaged together, and this procedure is repeated for all phase delays, producing an average waveform representative of each flow parameter. The LDF signal was stored and analyzed later with a NeXT computer (no longer trading), using an algorithm implemented in the computer connected to the flowmeter (BPM403A, Vasamedics, Minneapolis, Minn; PeriFlux PF3, Perimed, Stockholm, Sweden) and based on Bonner and Nossal’s photon diffusion theory. During the measurements, care was taken to keep the direct current component, which is a measure of the total amount of light reaching the detector, as constant as possible throughout the recording.

The mean values; minima; maxima; 2.5th, 50th, and 97.5th percentiles; and the SDs were calculated for the mean values of the hemodynamic parameters (velocity, volume, and flux) recorded during an average heart beat. Data from one randomly selected eye per subject were included in this analysis. The differences from normality of the frequency distribution of the hemodynamic parameters were assessed by means of the Shapiro-Wilk W test. The latter test was preferred to the Kolmogorov-Smirnov test for normality because the mean and SD of the normal distribution are not known for choroidal LDF parameters.

The correlations between choroidal hemodynamic parameters and age, actual mean systemic blood pressure, and IOP were computed by means of the Pearson linear correlation factor. In addition, the influence of age, mean systemic blood pressure, IOP, smoking, and sex was assessed in a multiple linear regression model. Finally, the mean values; minima; maxima; 2.5th, 50th, and 97.5th percentiles; and the SDs were calculated for the absolute values of interocular differences in the mean values of the hemodynamic parameters recorded during an average heart beat.

### Table 4

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Min</th>
<th>Max</th>
<th>Mean</th>
<th>SD</th>
<th>2.5th</th>
<th>50th</th>
<th>97.5th</th>
</tr>
</thead>
<tbody>
<tr>
<td>Velocity</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Volume</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Flux</td>
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<td></td>
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</tr>
</tbody>
</table>

**COMMENT**

Choroidal blood flow parameters, as assessed by means of LDF, were evaluated in 70 healthy subjects. None of the choroidal hemodynamic parameters—velocity, volume, and flux—was normally distributed, and all 3 distribution curves showed a skew toward higher values (Figure). Choroidal blood flow velocity decreased with increasing age of the subjects, while the volume of moving erythrocytes increased with higher genuine IOP. Interocular difference in IOP correlated positively with interocular difference in the hemodynamic parameter volume. Mean blood pressure did not influence choroidal hemodynamics. There were no differences in choroidal hemodynamic parameters between female and male subjects or between smokers and nonsmokers. However, because only 10 smokers were included in this analysis, definite conclusions with regard to smoking are precluded due to a lack of statistical power.

Numerous techniques have been used for measurement of choroidal blood flow, including calorimetry, direct measurement from choroidal veins, radioactive krypton desaturation, radioactively labeled microspheres, hydrogen clearance, and, more recently, LDF. Laser Doppler flowmetry has been applied invasively in cats and rabbits in the investigation of the effect of various physiological and pharmacologic conditions on choroidal blood flow. In these studies, surgery was performed to apply the fiberoptic probe of a commercial flowmeter against the exposed sclera of cats, or to introduce the probe into rabbit eyes and to place it near the retinal surface, facing the choroid. Studies in minipigs, as well as in humans and cats, have demonstrated that LDF could also provide noninvasive measurements of choroidal blood flow. For choroidal blood flow evaluation by means of LDF, the foveal region of the fundus is chosen as the measuring site because it is free of retinal vessels, and, because the subject fixates directly at the laser beam, its localization is straightforward. In fact, measurements...
of blood flow variation during systemic blood gas manipulations could demonstrate that, when the laser beam is focused on the fovea, the Doppler signal arises predominantly from the choriocapillaris.18

The present investigation of choroidal LDF in healthy subjects evaluated the largest published sample of individuals and used a new device which, in contrast to previously used devices, does not require dilatation of the pupil.21 Previous evaluations of choroidal blood flow by means of LDF had found no significant differences between female and male subjects,1,18 which was confirmed in the present study. However, while one study described a significant decrease in the choroidal hemodynamic parameters volume and flux with increasing age,1 arguing that such a finding is compatible with a decrease in the density of the choriocapillaris, such a relationship could not be confirmed in another study19 or in the present investigation. However, a negative correlation between velocity (instead of volume) and age was found in the present study, an observation which might be due, for example, to an increased sclerosis of the vasculature with advancing age. Potentially, the differences observed with regard to age in the different studies might be due to differences in populations and/or differences in statistical power. The subjects described by Grunwald et al1 were older than those included in the investigation by Riva et al18 or in the present study, and the total number of subjects included was larger in the present study compared with the 2 previous investigations. Similar arguments might explain differences observed with regard to correlations between choroidal blood flow parameters and systemic blood pressure or perfusion pressure. Indeed, the range of admitted normal systemic blood pressure was much larger in the

![Image](https://example.com/image1)

Histograms representing the statistical distribution of the choroidal hemodynamic factors velocity, volume, and flux. The continuous line describes the expected aspect of a normal distribution.

### Table 2. Correlations Between Intraocular Pressure, Systemic Blood Pressure, Age, and Choroidal Hemodynamic Parameters

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Correlation R (P)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td></td>
</tr>
<tr>
<td>Mean Blood Pressure</td>
<td></td>
</tr>
<tr>
<td>Intraocular Pressure</td>
<td></td>
</tr>
<tr>
<td>Velocity</td>
<td>−0.26 (.04)</td>
</tr>
<tr>
<td>Volume</td>
<td>0.05 (.72)</td>
</tr>
<tr>
<td>Flux</td>
<td>−0.09 (.48)</td>
</tr>
</tbody>
</table>

### Table 3. Correlations of Factors Influencing Choroidal Hemodynamic Parameters

<table>
<thead>
<tr>
<th>Factor</th>
<th>Partial Correlation R (P)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>−0.29 (.03)</td>
</tr>
<tr>
<td>Mean blood pressure</td>
<td>0.09 (.48)</td>
</tr>
<tr>
<td>Intraocular pressure</td>
<td>−0.14 (.27)</td>
</tr>
<tr>
<td>Smoking</td>
<td>0.09 (.49)</td>
</tr>
<tr>
<td>Sex</td>
<td>−0.09 (.32)</td>
</tr>
</tbody>
</table>

*By a multiple linear regression model.

### Table 4. Descriptive Statistics for the Interocular Difference in the Choroidal Hemodynamic Parameters

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Minimum</th>
<th>2.5th</th>
<th>50th</th>
<th>97.5th</th>
<th>Maximum</th>
<th>Mean (SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Velocity</td>
<td>0.008</td>
<td>0.014</td>
<td>0.210</td>
<td>0.714</td>
<td>0.913</td>
<td>0.280 (0.219)</td>
</tr>
<tr>
<td>Volume</td>
<td>0.004</td>
<td>0.004</td>
<td>0.144</td>
<td>0.622</td>
<td>1.004</td>
<td>0.181 (0.165)</td>
</tr>
<tr>
<td>Flux</td>
<td>0.098</td>
<td>0.352</td>
<td>5.147</td>
<td>23.824</td>
<td>28.587</td>
<td>7.532 (6.159)</td>
</tr>
</tbody>
</table>
subjects described by Grunwald et al compared with the investigation conducted by Riva et al or the present study. While subjects with a systolic blood pressure above 140 mm Hg or a diastolic blood pressure above 90 mm Hg were excluded in the present study, Grunwald et al included subjects with systolic blood pressure readings up to 181 mm Hg or diastolic blood pressure readings up to 107 mm Hg. Furthermore, in the latter study, after correcting for age in a multiple regression analysis, the relationship between choroidal blood flow and systemic blood pressure could not be observed. With regard to age, it must be stressed that no reduction in choroidal blood flow was found in older healthy individuals. Only velocity of blood flow increased. Velocity and flow should not be confused, since an increased velocity does not necessarily mean a change in blood flow. In a constricted vascular bed, the erythrocytes in the blood may simply rush faster through the vessels without any decrease in the total number of erythrocytes passing through the system. The consequences of a faster blood flow through a capillary system such as the choriocapillaris is not clear. The data suggest that no reduction in overall flow occurs in the choriocapillaris underneath the fovea of older individuals. The question whether the increased velocity impinges on the exchange between the capillary blood and the tissue is, however, not clear and will need further investigations.

Interestingly, volume increased with increasing IOP, and the interocular difference in volume correlated positively with the interocular difference in IOP. This is in contrast to the findings described in the 2 previous studies on choroidal LDF in healthy humans. A marked decrease in velocity and flux were observed with artificially increased IOP. These observations and the present study suggest that the relationship between genuine IOP and choroidal blood flow is not identical to that during experimental manipulation of IOP. The present data do not allow a sound explanation for this difference. Could it be simply an artifact? Could it be related to the device used? Could it be that, within the normal range of IOP, the venous outflow from the choroidal circulation is altered with increasing IOP, while the arterial inflow remains unperturbed? These questions need to be addressed in further studies.

Choroidal blood flow alterations might play an important pathogenetic role in various diseases. Consequently, detailed knowledge of physiologic parameters in choroidal blood flow regulation could be of marked importance in the management of patients. The noninvasive technique and the ease of use of the choroidal LDF might allow the analysis of larger samples, potentially enabling the elucidation of some intriguing blood flow regulatory pathways in the choroid. It must be emphasized, however, that our present findings pertain only to blood flow within the choriocapillaris and only in the area of the choroid underneath the fovea. Because the density of photoreceptors is so much greater in this area, it is likely that blood flow in this area is different from blood flow elsewhere in the choroid.

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REFERENCES


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