Effect of Aging on Foveolar Choroidal Circulation

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Objective: To determine the effect of aging on choroidal blood flow (ChBFlow) in the foveolar region of the normal ocular fundus.

Method: Choroidal blood flow was determined using laser Doppler flowmetry. Twenty-nine eyes of 29 normal subjects whose ages ranged from 15 to 76 years (mean±SD, 42±18 years) were included in this study. Relative choroidal blood velocity (ChBVel), choroidal blood volume (ChBVol), and ChBFlow were determined in the foveolar region by asking the subjects to fixate on the probing laser beam.

Results: Significant negative correlations were observed between ChBVol and the subject’s age ($R = -0.52, P = .004$) and between ChBFlow and the subject’s age ($R = -0.54, P = .003$). No significant correlation was detected between ChBVol and the subject’s age ($R = 0.07, P = .70$). Significant differences were observed in ChBVol and ChBFlow between the younger subjects aged 15 to 45 years (mean±SD, 0.48±0.20 arbitrary units [AU] and 18.9±5.8 AU, respectively) and the older ones aged 46 to 76 years (mean±SD, 0.34±0.11 AU and 13.3±3.3 AU, respectively; unpaired Student t test, $P = .04$ and $P = .007$, respectively).

Conclusion: In the subjects studied, foveolar ChBFlow decreases with age. This change is probably related to the decrease in density and diameter of the choriocapillaries that occurs with increasing age.


CHOROIDAL circulation provides nutrients and removes waste products from the outer half of the retina. An abnormal choroidal blood supply may disrupt the normal retinal function and lead to visual deterioration.

Abnormalities of the choroidal circulation have been hypothesized as part of the mechanism that leads to the development of age-related macular degeneration,1-3 one of the most common causes of visual impairment in older individuals.4-6 To determine what constitutes an abnormal choroidal blood flow (ChBFlow), it is important to determine the physiologic effect of aging on the choroidal circulation of the normal eye.

We have previously reported evidence suggesting that blood flow in the retinal macular microcirculation decreases with age.7 The purpose of this study was to determine if a similar decrease is also present in the foveolar choroidal circulation.

RESULTS

The ChBVel ranged from 0.29 to 0.82 arbitrary units (AU) and the average (±SD) ChBVel for the entire group was 0.46±0.10 AU. The ChBVol ranged from 0.19 to 0.85 AU and the average ChBVol was 0.43±0.18 AU. The ChBFlow ranged from 7.5 to 32.1 AU and the average ChBFlow was 16.8±5.6 AU.

Statistically significant, negative linear correlations were observed between ChBVol and the subject’s age ($R = -0.52, P = .004, \text{Figure 2}$) and between ChBFlow and the subject’s age ($R = -0.54, P = .01, \text{Figure 3}$). No significant correlation was detected between ChBVel and the subject’s age ($R = 0.07, P = .70, \text{Figure 4}$). No significant correlation was observed between the pulsatile component of ChBFlow and age ($R = 0.26, P = .17$).

The age span of the study subjects was divided arbitrarily into 2 groups with similar age spans of 30 years each. The group of younger subjects included those between 15 and 45 years of age (18 subjects) and the group of older subjects included those between ages 46 and 76 years (11 subjects).

Significant differences were observed in ChBVol and ChBFlow between the younger group, aged 15 to 45 years (0.48±0.20 AU and 18.9±5.8 AU, respectively), and the older group, aged 46
SUBJECTS AND METHODS

Twenty-nine volunteers whose ages ranged from 15 to 45 years (18 subjects) and 46 to 76 years (11 subjects) were included in this study. All subjects had no pathologic findings on external, slitlamp, and fundusoscopic examinations. None of the subjects had large drusen (>63 µm), retinal pigment epithelial abnormalities, or any other abnormality consistent with age-related macular degeneration. The intraocular pressure (IOP) was less than 21 mm Hg, and the best-corrected visual acuity was 20/25 or better in all subjects. Mean brachial artery systolic pressure was 128±20 mm Hg (range, 100-181 mm Hg) and mean brachial artery diastolic pressure was 68±14 mm Hg (range, 51-107 mm Hg). Refractive errors ranged between −5.5 diopters (D) and +4.5 D of spherical equivalent. The average refractive error was −1.2±±2.1 D.

Information about medical history and current systemic and ocular therapy was obtained from each subject. Four subjects had elevated cholesterol levels. Of these 4 subjects, 2 were receiving simvastatin and 2 were receiving lovastatin. Two of the 4 subjects with elevated cholesterol levels also had a history of systemic hypertension. Of these, one was receiving therapy with enalapril and the other with hydrochlorothiazide. The other 25 subjects had no history of chronic systemic disease and were not receiving systemic therapy. No significant difference in any of the circulatory parameters were observed between the subjects who received medication for systemic hypertension or elevated cholesterol levels and those who did not.

Three of the 29 subjects were smokers. No significant difference in any of the circulatory parameters were observed between smokers and nonsmokers.

After a detailed explanation of the procedures, all subjects were asked to sign an appropriate consent form approved by the human experimental committee of our institution. The tenets of the Declaration of Helsinki were followed.

Before the measurements, pupils were dilated with 1% tropicamide (Alcon, Fort Worth, Tex) and 10% phenylephrine hydrochloride (Sanofi Winthrop, New York, NY). Blood flow measurements were obtained in one eye of each subject. The eye to be included in this study was determined by tossing a coin.

Relative choroidal blood velocity (ChBVel), choroidal blood volume (ChBVol), and ChBFlow were obtained using a method based on the laser Doppler flowmetry technique. Choroidal blood velocity corresponded to the speed of moving blood cells, and ChBVol represented the amount of blood present at the measurement site. Choroidal blood flow was calculated by the instrument from these 2 parameters. Detailed descriptions of the method have been previously published.6-11 A diode laser beam (670 nm) with an intensity of 20 µW was delivered through a fundus camera (model TRC, Topcon, Tokyo, Japan). The diameter of the probing laser beam was approximately 200 µm.

During blood flow measurements, an area of the posterior retina (30° in diameter) was illuminated by the fundus camera at a wavelength of 570 µm. This illumination enabled the observation of the position of the probing laser during the measurements. Subjects were asked to fixate on the probing laser beam to determine foveolar ChBFlow. Proper fixation during the measurements was ascertained by direct observation of the foveola through the fundus camera. All measurements were performed with the subjects seated in a darkened room.

In each subject, a single continuous measurement of the choroidal circulation was obtained for about 20 to 30 seconds. An observer masked with regard to the age and all other attributes of each subject performed the analysis of the data using a NeXT computer (NeXT Computer, Inc, Redwood City, Calif) with software (NeXT Software, Inc, Redwood City) specifically developed for the analysis of Doppler signals from ocular tissues.12

The masked observer selected for analysis parts of the recording that showed stable circulatory parameters. This selection was necessary because disturbances such as eye motion, head motion, blinks, and poor fixation produced unstable blood flow readings. Therefore, only stable portions of the measurements were included in the analysis. The average recording time that was included in the analysis of the data was about 3 seconds. Figure 1 shows a typical recording in a 44-year-old subject. The highlighted section (toward the end of the recording) depicts a segment of about 3 seconds selected for analysis.

In 16 subjects, the above-described procedure was repeated and 3 separate determinations were conducted on the same experimental session to assess the reproducibility of the measurements. Coefficient of variability (CV) was defined as $CV = (\text{mean}/\text{SD}) \times 100$.

The average pulsatile component of ChBFlow was determined over the cardiac cycle that was recorded with an infrared pulse monitor. The pulsatile component of ChBFlow was calculated as ($1\text{−ChBFlow}_{\text{pulsatile}}$)$/$ChBFlow$_{\text{diasstatic}}$.

Brachial artery systolic and diastolic blood pressures (BP s, BP d, respectively) and heart rate were determined after blood flow measurements. Intraocular pressure (IOP) was measured by application tonometry. The mean brachial artery pressure (BP m) was calculated according to the following formula: $BP_m = BP_s + ½(BP_d - BP_s)$.

Perfusion pressure (PP) for the study eye was determined according to the following formula: $PP = (BP_m - IOP)$.

Nonpaired Student t tests, linear regressions, and correlations were used in the statistical analysis of the results. The assumption of normality for ChBFlow was assessed with the Shapiro-Wilk test and by the examination of the residuals of the regression analysis. Probability values less than .05 were considered statistically significant.
Significant negative correlations were observed between BPm and ChBVol ($R = -0.49, P = .007$) or ChBFlow ($R = -0.46, P = .012$), and between PP and ChBVol ($R = -0.44, P = .017$) or ChBFlow ($R = -0.43, P = .019$). No other significant correlations were detected between heart rate, BPm, IOP, or PP and our hemodynamic parameters.

Multiple regression models were used to determine if the relationship between age, ChBVol, and ChBFlow could be attributed to refraction, BPm, IOP, or PP and our hemodynamic parameters. None of these covariates had a statistically significant effect on ChBVol or ChBFlow when considered simultaneously with age.

**COMMENT**

Our results show a decrease in foveolar ChBVol and ChBFlow in normal subjects with increasing age. The correlation between age and ChBVol has a regression coefficient of $R = -0.52$ and the correlation between age and ChBFlow has a regression coefficient of $R = -0.54$, suggesting that approximately 27% ($R^2$) of the change in ChBVol and 29% ($R^2$) of the change in ChBFlow can be predicted by age.

We chose to perform our circulatory measurements in the foveola for several reasons: (1) the importance of the foveola in terms of visual function, (2) the fact that at this site there is no retinal circulation, (3) technically, the measurements are easy to obtain because there is no need for a fixation device (subjects are asked to fixate on the measuring laser beam), and (4) it is a site that is affected by pathologic conditions that may have a choroidal vascular origin (ie, age-related macular degeneration and macular dystrophies).

Riva et al,8 have previously demonstrated the validity of the laser Doppler flowmetry technique for the non-
invasive assessment of relative ChBFov in the human foveola. These ChBFov measurements derive mainly from erythrocytes moving in the choriocapillaries rather than the large vessels behind them. As discussed by Riva et al, this is supported by the relatively low Doppler frequency shifts obtained, which represent slower blood velocities, and the exponential shape of the Doppler spectrum, which typically corresponds to a signal deriving from the microcirculation. The relatively small pulsatile component observed in our ChBFov measurements provides further evidence that the method measures blood flow in the choriocapillaries.

Because measurements are performed in the center of the foveola, most of the signal obtained is derived from the choroidal and not the retinal circulation. This is supported by experiments showing that hyperoxia does not cause any significant change in foveolar ChBFov measurements.

The choroidal circulation is insensitive to hyperoxia, whereas the retinal circulation is known to decrease by 30% to 60% under conditions of 100% oxygen breathing. The lack of response of ChBFov to hyperoxia suggests that the measurements are derived from the choroidal circulation and not the retinal circulation.

Significantly higher BPm and PP are present in our study in older individuals (Table), and significant negative correlations are observed between these parameters and ChBFov. This is somewhat surprising since increased PP would theoretically be associated with an increase in ChBFov and not a decrease. An autoregulatory response, if present, would probably modulate such an increase in ChBFov but would not result in decreased ChBFov, unless the metabolic needs of the choroid would considerably change.

Our results suggest that the effect of aging on ChBFov is probably more important than the effects of increases in BPm or PP. This is indeed supported by the multiple regression analyses showing that age is the only significant variable associated with ChBFov changes. The relationship between age and ChBFov cannot be explained by any of the other variables previously mentioned.

A recent report by Ravalico et al has shown that pulse amplitude, measured with the Langham OBF System (Langham Ophthalmic Technologies, Timonium, Md.), decreases with age. Although there is a controversy as to what exactly these measurements represent hemodynamically, these results suggest that the pulsatile component of ocular blood flow may decrease with age because a decreased pulsatility probably results in a lower pulse volume and perhaps a lower pulsatile blood flow.

These measurements, however, represent the effect of an overall intraocular blood flow since they are inferred from the change in IOP produced by the heart beat. Our measurements, in contrast, are obtained directly from the choroidal circulation at the foveola.

Our results are somewhat different from those of Ravalico et al since we do not find a decrease in the pulsatile component of ChBFov with age. The discrepancy between the 2 studies may be due to the marked differences in the techniques used and the parameters measured.

The decrease in ChBFov with age observed in our study is mainly due to a decrease in ChBFv since there is no statistically significant correlation between ChBFv and age. This decrease in ChBFv can be explained by the findings of Ramrattan et al showing that between the first and the 10th decades, there is a 45% decrease in the density and a 34% decrease in the diameter of the lumen of the choriocapillaries, in the normal human macula.

In addition, there are a number of age-related structural changes that occur in the retina that could lead to a decrease in ChBFov. Such age-related changes include decreases in photoreceptor density and retinal pigment epithelial cell cytoplasm volume. A decrease in the number of viable cells in the retina and choroid could result in a decreased metabolic demand and, consequently, a decrease in both choroidal and retinal blood flows.

**Figure 5. Relative choroidal blood flow in younger (between 15 and 45 years) and older (between 46 and 76 years) subjects. Average choroidal blood flow was 29% lower in older subjects (2-tailed, unpaired Student t test, P = .007).**

**Average Pressures in Younger and Older Subjects**

<table>
<thead>
<tr>
<th>Age of Subjects, y</th>
<th>&lt;46 (n=18)</th>
<th>&gt;46 (n=11)</th>
<th>P†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood pressure</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systolic</td>
<td>118±10</td>
<td>145±21</td>
<td>.001</td>
</tr>
<tr>
<td>Diastolic</td>
<td>63±10</td>
<td>78±14</td>
<td>.003</td>
</tr>
<tr>
<td>Mean</td>
<td>81±10</td>
<td>100±15</td>
<td>.001</td>
</tr>
<tr>
<td>Intraocular pressure</td>
<td>14.2±2.4</td>
<td>16.1±2.4</td>
<td>.05</td>
</tr>
<tr>
<td>Perfusion pressure</td>
<td>39±7</td>
<td>50±9</td>
<td>.001</td>
</tr>
</tbody>
</table>

*Values expressed as mean±SD.
†Calculated using 2-tailed, nonpaired Student t test.
Age-related changes in the retinal circulation have been previously reported. Groh et al.\(^2\) using pulsed Doppler sonography, reported a decrease in blood flow in the retinal macular capillaries of older individuals. Groh et al.\(^2\)\(^6\) using pulsed Doppler sonography, reported a decrease in blood velocity in the central retinal artery.

Although speculative at this stage, it is possible that a concurrent decrease of both the choroidal and the retinal blood flow in older individuals may have a role in the development of age-related macular degeneration. Further assessment of the circulation of these vascular beds in patients with this disease are needed to support or refute this speculation.

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REFERENCES