Effect of Acute Decreases of Perfusion Pressure on Choroidal Blood Flow in Humans

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Purpose. To investigate the relationship between choroidal blood velocity (ChBVel), blood volume (ChBVol) and blood flow (ChBF) in the foveal region of the human ocular fundus and ocular perfusion pressure and to determine whether the choroidal circulation has some autoregulatory capacity.

Methods. Measurements of ChBVel, ChBVol and ChBF were obtained by laser Doppler flowmetry in healthy subjects (age range, 21 to 57 years) with normal eye examination results. Measurements were performed at normal intraocular pressure (IOP) and during successive step increases in IOP induced by scleral suction. In experiment 1, in six eyes (five subjects), the IOP was increased rapidly, in steps of 50 to 100 mm Hg of suction pressure, which each lasted approximately 10 seconds to a level above diastolic ophthalmic artery blood pressure (IOP = »72 mm Hg). In experiment 2, in 14 eyes (seven subjects), the IOP was increased slowly in four successive steps at 2-minute intervals to a level of approximately 42 mm Hg. We also determined the pulsatility of the flow parameters during the heart cycle, pulsatility = 1 — diast value/syst value.

Results. For both rates of suction cup increase, the relationship between ChBFm (mean ChBF over the heart cycle) and mean perfusion pressure was not linear. At high pressure, ChBFm was less affected by decreases in the pressure than expected from a passive vascular system. In some cases, no change in ChBFm was detectable, although significant changes in PCHBK occurred. Further decreases in perfusion pressure resulted in a proportional decrease in ChBFm. On release of suction, a significant increase in ChBFm over baseline value was detectable in experiment 1.

Conclusions. The relationship between ChBFm and ocular mean perfusion pressure appears to be bilinear and reveals some autoregulation for moderate step decreases in perfusion pressure. The temporal characteristics of the ChBFm-response suggest a neural or passive hemodynamic process rather than a myogenic or metabolic compensatory mechanism. Invest Ophthal mol Vis Sci. 1997;38:1752—1760.

Despite the low extraction rate of oxygen from choroidal blood, 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. To match the local metabolic needs, this supply requires an adequate rate of choroidal blood flow (ChBF). In addition, meeting metabolic demands may not be the only function of the choroidal circulation, which leads to competing physiologic responses.

Blood flow through an organ such as the eye depends on the arterial and venous pressure difference and the vascular resistance between the arterial input and the venous output. In the eye, the venous pressure is usually assumed to be equal to the intraocular pressure (IOP), except at low IOP. The ChBFm, the mean ChBF during the heart cycle, is therefore approximated by the relation:

$$\text{ChBF}_{\text{m}} = \frac{(\text{MOAP} - \text{IOP})}{\text{R}_{\text{m}}} = \frac{\text{PP}_{\text{m}}}{\text{R}_{\text{m}}} \quad (1)$$

where MOAP is the mean ophthalmic artery blood pressure.
When the decrease in R exactly compensates the effect of the decrease in pressure, the flow remains constant and the vascular system is said to autoregulate in the strict sense. This property applies to various vascular systems, such as those of the heart, brain, retina and optic nerve.

Numerous studies of the effect of increased IOP on ChBF in animal eyes have failed to show evidence of autoregulation in the choroidal vascular system. Recently, however, investigations in rabbits by Kiel and van Heuven strongly suggest that the choroid has some capability to autoregulate, which is particularly pronounced when the perfusion pressure is decreased by increasing the IOP at constant mean ophthalmic artery pressure. Whether this is the case for the human eye is not known because of the lack of an appropriate noninvasive technique for ChBF measurements.

The purpose of this work was to determine the relationship between ChBF and perfusion pressure using a newly developed method for the measurement of ChBF in the foveal region of the fundus in human subjects and to determine whether the choroidal circulation in this region has some capability to autoregulate.

**MATERIALS AND METHODS**

**Subjects**

Measurements were obtained from 17 eyes of nine healthy male volunteers, ranging in age from 21 to 57 years (mean, 36 years; ±11 SD years). All participants had excellent target fixation, no history of systemic or ocular diseases, and the results of ocular examinations were normal. Spherical refractive errors ranged from −3 to +3 diopters. Mean IOP was 12 ± 2.5 SD mm Hg. Participants were asked to abstain from coffee and cigarette smoking for 24 hours before the study. They were seated. The pupils were dilated with one or two drops of 1% tropicamide. Brachial artery blood pressure was measured using an electronic sphygmomanometer. The procedures were approved by the University of Lausanne Medical Faculty Ethical Committee and followed the tenets of the Declaration of Helsinki. Informed consent was obtained from all subjects after the nature and possible consequences of the study were explained fully.

**Measurement of ChBF**

The laser Doppler flowmetry (LDF) method for measuring ChBF in the foveal region was published recently. Briefly, subjects were asked to fixate a diode laser beam (wavelength = 811 nm, 95 μW at the cornea), which was delivered to the eye through a fundus camera (Topcon TRC, Tokyo, Japan). Light scattered by moving erythrocytes in the tissue volume sampled by the incident laser beam was detected at the fundus image plane of the camera by an optical fiber. The diameter of the beam at the fundus of an emmetropic eye was approximately 300 μm. Relative ChBF was determined by analyzing the LDF signal with a NeXT (Redwood City, CA) computer, using an algorithm based on Bonner and Nossal’s photon diffusion theory. This algorithm is similar to the one implemented in commercial laser Doppler flowmetry systems (BPM403A, Vasamedics, MN, USA; PeriFlux PF3, Perimed, Stockholm). In addition to ChBF, it provides a relative continuous measurement of the mean velocity (ChBVel) and volume (ChBVol) of blood within the sampled tissue volume and the dc-component, which is a measure of the total amount of light reaching the detector. Care was taken to keep the dc as constant as possible during the whole recording. The LDF software also automatically excludes the Doppler signal during blinks, thereby minimizing potential artifacts. The flow parameters are related to each other through the relationship ChBF = const × ChBVel × ChBVol. Each parameter, although given in arbitrary units, is linear with respect to changes.

In this work, ChBVelm, ChBVolm and ChBFm, the mean of ChBVel, ChBVol, and ChBF during the heart cycle, were obtained from approximately 10 seconds to 20 seconds of recording time. Pulsatility of ChBF, PChBF, is defined as (1 − ChBF dias/ChBF sys), where ChBF dias and ChBF sys are the values of ChBF at end-diastole and peak-systole, respectively. Values for PChBVel and PChBVol are defined in a similar way. For determining P, each flow parameter is continuously measured at intervals of 60 msec. Data points are then 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 (Fig. 1). To calculate pulsatility for a given flow parameter, the systolic and diastolic values of this parameter were taken as the maximum and minimum of the average waveform, respectively.

**Step Increases in Intraocular Pressure**

After application of Novesine 0.4% (oxybuprocain hydrochloridum, Ciba Vision AG, Niederwangen, Switzerland) for local conjunctival and corneal anesthesia,
FIGURE 1. Recordings of ChBVel, ChBVol, and ChBF using the laser Doppler flowmetry technique in response to a rapid increase in intraocular pressure (IOP). Analysis of the photocurrent was performed with a NeXT computer. Time constant of the recordings was 0.06 second. For the display, a running average window of 1.0 second was chosen. On the right, the average time courses of the flow parameters with the standard deviations (n = 19 heart cycles) have been plotted over two heart cycles for the segments of the recordings designated as a and b (shaded areas, each approximately 20-second duration). They were obtained by averaging all data points within the corresponding segment, taking into account the phase within the heart cycle (see text for more details). From these time courses, the pulsatility of each flow parameters was calculated as described in Materials and Methods.

(a) Suction cup values, (b) The expanded time scale of the segment between 121 and 128 seconds shows that a step increase in suction (here from 200 to 250 mm Hg; start of the increase in IOP is indicated by dotted line at t = 123 seconds) occurs in approximately 1 second, as illustrated by the rapid change in ChBF.

The IOP was recorded using a Digilab, model 30R pneumatonometer. A transparent plastic scleral suction cup (diameter 10 mm) was then placed 2 mm away from the limbus and a suction level of 50 mm Hg was applied. This level of suction was just enough to hold the cup on the sclera and was therefore considered as the baseline condition. LDF measurements were obtained for this level of suction before the suction was further increased. Two types of experiments were performed.

Rapid Rate. In six eyes of five subjects, the suction was increased in several steps of 50 mm Hg to 100 mm Hg, each time leaving the suction level steady for about 10 seconds duration to give adequate time for a reliable sample of the flow parameters. The step increase in IOP was continued until an IOP above diastolic ophthalmic artery blood pressure was reached, as revealed by the subjective appearance of a darkening and shrinking of the visual field (pulsating tree), which consisted of speckles from the probing beam. The cup was then removed quickly, and the LDF recordings continued. The same procedure was repeated within 2 days in the identical manner without LDF measurements, but instead the IOP was measured at every suction value used in the first session. Before the LDF measurements, the fundus was illuminated in green light for alignment of the fundus camera. This light was then turned off, and the subject was asked to steadily fixate the laser beam, which appeared as a dim but sharp red spot.

In two eyes, the IOP was quickly raised to diastolic value as documented by the appearance of the “pulsating tree” for short durations (2 sec to 15 sec). The flow parameters were measured at baseline and immediately after the release of the pressure.

Slow Rate. In 14 eyes of seven volunteers, after the cup was placed using a suction of 50 mm Hg, the suction was increased in three consecutive steps to 100, 150, and 200 mm Hg. Each suction level was maintained for 2 minutes during which the flow parameters were intermittently measured. The cup was then removed, and the LDF measurements continued for another 5-minute interval. This procedure was repeated within 2 days in an identical manner without LDF measurements, but instead the IOP was measured at each step, just before and after the increment or removal of suction.

Normalization of the Mean Ocular Perfusion Pressure

The minimum pressure driving ChBF is $PP_{min} = MOAP - IOP_{syst} = MOAP - 2/3 BP_{syst}$, where $IOP_{syst}$
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is the pressure at which \( \text{ChBF} = 0 \). Note that with \( \text{PP}_m \) as defined in equation 1, \( \text{PP}_{m,\text{min}} \) is a negative number. To compare the results of all eyes, and because different eyes have different systolic ophthalmic artery pressures, we define a normalized perfusion pressure, \( \text{PP}_{\text{norm}} \), corresponding to the range of IOPs from baseline to IOP syst to 100% in each eyes as:

\[
\text{PP}_{\text{norm}} = \frac{2/3\text{BP}_{\text{sys}} - \text{IOP}}{2/3\text{BP}_{\text{sys}} - \text{IOP}_{\text{bl}}} \times 100\% \quad (2)
\]

\( \text{IOP}_{\text{bl}} \) is the baseline IOP. One observes that \( \text{PP}_{\text{norm}} \) is a linear function of IOP, which is 100% when IOP = \( \text{IOP}_{\text{bl}} \) and 0% when IOP = 2/3 \( \text{BP}_{\text{sys}} \).

Sensitivity of the ChBF m Measurements

Sensitivity, \( S \), of ChBF m, [e.g., the minimum change that can be detected by the technique for the group of seven subjects (average of both eyes)] was calculated at \( \text{IOP}_{\text{bl}} \) and at 200 mm Hg suction. In the first case, two ChBF m values were obtained in each eye of the seven subjects based on 2 recording segments of 10 seconds. For each subject (i), we determined ChBF m,bl1 and ChBF m,bl2 in both eyes and calculated the means, i.e., ChBF m,bl1(OU) and ChBF m,bl2(OU). We then calculated the difference \( \Delta^i = \text{ChBF m,bl1(OU)} - \text{ChBF m,bl2(OU)} \). After determining the standard deviation \( S_{bl} \) of the \( \Delta^i \)'s from the seven subjects, \( S_{bl} \) was obtained using the formula

\[
S_{bl} = \frac{2 \times t \times S_{bl}}{(\text{ChBF m,bl1} + \text{ChBF m,bl2}) \times \sqrt{n}} \times 100\% \quad (3)
\]

In this equation, \( n = 7 \), \( t = 2.447 \) is the two-tailed critical value of the t-distribution for 6 degrees of freedom, at the 0.05 level of significance. \( \text{ChBF m,bl1} = \Sigma \text{ChBF m,bl1(OU)} \) and \( \text{ChBF m,bl2} = \Sigma \text{ChBF m,bl2(OU)} \). The same procedure was used to calculate \( S_{200} \) based on two 10-second recordings obtained immediately after the increase in suction from 150 to 200 mm Hg.

Statistics

Average changes in blood flow parameters and pulsatility were assessed for significance by the \( \pm 95\% \) confidence interval of the mean.

RESULTS

Experiment 1 (Rapid Increase in Intraocular Pressure)

Average baseline PP m for all subjects was 48 ± 3 mm Hg. A sample recording of the changes in the choroidal flow parameters in response to rapid increases in IOP is shown in Figure 1. Responses demonstrating similar features were obtained from the other five eyes tested in this way. Although the suction cup pressure was raised, ChBVelm, ChBVolm, and ChBF m changed little at first and then decreased continuously. For the six eyes, the average change in ChBF m between an average IOP of 22 mm Hg and 32 mm Hg (≈18% decrease in \( \text{PP}_{\text{m}} \)) was \(-2.6 ± 3\% \) because of a \( 5 ± 4\% \) decrease in ChBVelm and a \( 5 ± 4\% \) increase in ChBVolm. A clear break in the ChBF m recording appeared on raising the suction pressure above 100 mm Hg (five eyes) and 150 mm Hg (one eye). At an average IOP of 72 mm Hg (\( \text{PP}_{\text{m}} = -12 \) mm Hg), average ChBVelm, ChBVolm and ChBF m were lower than at baseline IOP by \( 35 ± 34\%, 69 ± 26\% \) and \( 84 ± 14\% \), respectively.

After the cup was off, the average IOP was 6 mm Hg and average \( \text{PP}_{\text{m}} \) was 54 mm Hg. For the six eyes, average ChBF m was \( 45 ± 35\% \) larger than at baseline, as illustrated by the sample recording of Figure 1. This increase was mainly caused by an increase in ChBVelm. The ChBF m returned to a constant value corresponding to a \( \text{PP}_{\text{m}} = 54 \) mm Hg within 15 ± 7 seconds.

Figure 2 shows ChBF measured before application and after release of the suction pressure that raised the IOP to diastolic ophthalmic artery pressure for approximately 8 seconds. Compared with baseline value, the average increase in ChBF m during the first 3 seconds after the release was 58%. ChBF m was not significantly different from baseline approximately 50 seconds later.

Experiment 2 (Slow Increase in Intraocular Pressure)

Average baseline PP m for all subjects was 50 ± 3 mm Hg. For each eye and each suction pressure (50, 100, 150, and 200 mm Hg), we determined \( \text{PP}_{\text{norm}} \) and ChBF m during 10 seconds just before changing the suction pressure to the next level. There was no significant correlation between the ChBF m values in the right eye (OD) and the left eye (OS) at baseline (\( P = 0.4 \)), as well as a suction cup pressure of \( 200 \) mm Hg (\( P = 0.09 \)). Plots of the changes in \( \text{PP}_{\text{norm}} \) in OS versus those in \( \text{PP}_{\text{norm}} \) in OD (Fig. 3a) and changes in ChBF m in OS versus those in ChBF m in OD (Fig. 3b) showed significant correlations (\( P < 0.001 \)) in these quantities between both eyes. Because of the correlation between
the ChBF<sub>m</sub> values in OS and OD, we averaged the ChBF<sub>m</sub> data in both eyes of each subject obtained at a similar PP<sub>norm</sub> (the difference in PP<sub>norm</sub> was less than 6% between the two eyes over the whole range of PP<sub>norm</sub>) and the resulting 35 values of ChBF<sub>m</sub>(OU) were normalized so that ChBF<sub>m</sub>(OU) at baseline IOP was equal to 100%.

In Figure 4, there is a plot of normalized ChBF<sub>m</sub>(OU) versus PP<sub>norm</sub>. A linear fit of the data below a PP<sub>norm</sub> of 64 mm Hg provided a \( r = 0.76 \) \((P < 0.01)\), a better correlation coefficient than a linear fit of all data \( r = 0.68 \). Extrapolation of the latter fit provided a value of PP<sub>norm</sub> at which flow is zero of \(-22.5\%\), compared with 27.5 units with the former. A linear regression of the data at a PP<sub>norm</sub> > 65% units provided a regression coefficient \( r = 0.34 \) (not significant).

When the ChBF<sub>m</sub>(OU)-PP<sub>norm</sub>-data were averaged in groups of seven consecutively, ChBF<sub>m</sub>(OU) was significantly below resting value (one-way Anova, Tukey-Kramer HSD test, \( P < 0.05 \)) at a PP<sub>norm</sub> of approximately 57%, corresponding to an average IOP = 41 mm Hg. The maximum decrease in PP<sub>norm</sub> (55% from baseline), which represented an increase in IOP from baseline to 42 mm Hg induced significant reductions of 35 ± 14% \((P < 0.001)\) in ChBV<sub>el</sub><sub>m</sub>(OU), 42 ± 13% \((P < 0.001)\) in ChBF<sub>m</sub>(OU) and a nonsignificant decrease of 9% in ChBV<sub>ol</sub><sub>m</sub>(OU). Immediately after removal of the cup, there was a significant transient increase in ChBV<sub>el</sub><sub>m</sub>(OU) by 10 ± 10% \((P < 0.05)\) but no significant changes in the other two flow parameters. For the group of seven subjects, the values of \( S_{10} \) and \( S_{200} \) for ChBF<sub>m</sub>(OU) were 3% and 6%, respectively.

**Time Course of the ChBF Changes in Response to Step Increases at Moderate Intraocular Pressure**

In Figure 5, segments of the time course of the flow parameters in two eyes are displayed on an extended...
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FIGURE 5. (top) Expanded time scale of the segment 107–113 seconds of the recordings of Figure 1. The flow parameters have been displayed using a time constant of 0.06 second. The interruptions in the recordings were caused by blinks. The start of the intraocular pressure (IOP) increase was at 109 seconds. On the right, the average time courses of the flow parameters during approximately three to five heart beats, corresponding to the shaded parts a and b, are shown. (bottom) Recordings obtained from another eye. The increase in suction cup pressure from 100 to 150 mm Hg (IOP from 30 to 38 mm Hg) started at 112 seconds.

Time constant of the recordings was 0.06 seconds. At the top, no significant change in ChBF was detectable between IOPs of 23 mm Hg and 36 mm Hg (23% increase in PP). On the other hand, PCpBeVo increased from 0.08 to 0.22, PCpBeVo from 0.12 to 0.26, and PcHBf from 0.11 to 0.36. A similar behavior was observed for the eye with the recordings shown at the bottom of Figure 5. In this eye, a 16% decrease in PP resulted in a 4% decrease in ChBF and an approximately 2-fold increase in PcHBf.

Decreasing the perfusion pressure by 14% (IOP from 23 mm Hg to 31 mm Hg) in 12 eyes (in two eyes, the recordings were not reliable immediately after the increase in suction pressure) produced smaller but significant decreases in ChBF and ChBeVo of 7% and 10%, respectively, and a significant 5% increase in ChBeVo (Table 1). Furthermore, there was a significant average increase in PCpBeVo by a factor of 1.5 because of increases in both PCpBeVo and PCpBeVo. Analysis of the time course of ChBF during the 2-minute recordings after each step increase in suction more than 100 mm Hg (experiment 2) demonstrated a return in ChBF toward the prestep value that, however, can be fully attributed to the increase in perfusion pressure during this time because of the slow decrease in IOP from aqueous outflow. Therefore, no significant change in the mean vascular resistance, Rm = PP/ChBF, could be observed at any step above 100 mm Hg.

DISCUSSION

The data obtained in both experiments suggest that the relationship between ChBF and perfusion pressure is not linear over the whole range of pressures.

<table>
<thead>
<tr>
<th>ChBFel</th>
<th>ChBVol</th>
<th>ChBF</th>
<th>PCpBeVo,100/PCpBeVo,50</th>
<th>PCpBeVo,100/PCpBeVo,50</th>
<th>PCpBeVo,100/PCpBeVo,50</th>
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<tr>
<td>ChBFel</td>
<td>10±4</td>
<td>&lt;0.001</td>
<td></td>
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<tr>
<td>ChBVol</td>
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<td>&lt;0.05</td>
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<tr>
<td>ChBF</td>
<td>7±4</td>
<td>&lt;0.01</td>
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<tr>
<td>PCpBeVo,100/PCpBeVo,50</td>
<td>1.4±0.5</td>
<td>&lt;0.02</td>
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<tr>
<td>PCpBeVo,100/PCpBeVo,50</td>
<td>1.5±1</td>
<td>NS</td>
<td></td>
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<tr>
<td>PCpBeVo,100/PCpBeVo,50</td>
<td>1.5±0.5</td>
<td>&lt;0.02</td>
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IOP = intraocular pressure; P = diastolic value/systolic value; NS = not significant.

*Paired t-tests were performed to determine significant differences.

Average percentage changes are based on mean ± CIM. IOP range, 23 to 31 mm Hg.
In Figure 4, a decrease in PP\textsubscript{norm} pressure by approximately 35% from baseline corresponding to an increase in IOP from 12 to 29 mm Hg does not significantly affect ChBF\textsubscript{m}. This behavior cannot be explained by a lack of sensitivity of the method as the latter was found to be 3% for this group of subjects at baseline IOP. Rather, it suggests some autoregulatory capacity of the choroidal circulation. The results of Figure 5 and those in Table 1 also demonstrate that the change in ChBF\textsubscript{m} when the perfusion pressure is decreased is much less than expected from a nonautoregulating vascular system. Furthermore, a linear fit using all data points in Figure 4 provided a smaller correlation coefficient than the fit based only on the data below a PP\textsubscript{norm} of 65 mm Hg.

Previous work with 16 subjects showed a correlation between the ChBF\textsubscript{m} values in OS and OD. In this study, no correlation was found. The most probable explanation for the difference between the two studies is the range of ChBF\textsubscript{m} values together with the number of subjects. In the former study, where the range of age, pigmentation, and refractive error was bigger than in the current study, the highest ChBF\textsubscript{m} value was approximately 10 times higher than the lowest one; whereas in the current study, maximum and minimum values differed by less than a factor of 3. On the other hand, the changes in ChBF\textsubscript{m} in OS were correlated to those in OD (Fig. 3b). For this reason, we plotted the means of the ChBF\textsubscript{m} values in both eyes in Figure 4.

Alm et al\textsuperscript{12} fitted their choroidal blood flow versus perfusion pressure data obtained in cats\textsuperscript{8} and monkeys\textsuperscript{8} with a straight line over the whole range of pressures. This approach was justifiable, considering the large variability of these animal data and the fact that the decrease in perfusion pressure consisted of one single step of more than 50 cmH\textsubscript{2}O (36 mm Hg) per animal.

Kiel and Shepherd\textsuperscript{17} reported a nonlinear relationship between ChBF\textsubscript{m} and perfusion pressure in rabbits, when this pressure was decreased at constant systemic blood pressure (Fig. 3 of reference 17, MAP \( \approx 80 \) mm Hg). We also found as they did in rabbits that ChBVol\textsubscript{m}, an index of choriocapillaris blood volume, was less affected than ChBVel\textsubscript{m} when the IOP was slowly raised because ChBVol\textsubscript{m} was significantly below resting value only at a mean PP\textsubscript{m} of \( \approx 20 \) mm Hg (IOP \( \approx 42 \) mm Hg). The maintenance of constant ChBVol\textsubscript{m} may be attributed to an increased choriocapillaris pressure during increased IOP,\textsuperscript{18} and its drop at high IOP reflects the partial collapse of these vessels as the IOP begins to overcome the intravascular pressure.\textsuperscript{19}

Previous investigators have considered potential problems in the application of LDF that could account for the nonlinear response of the choroidal circulation at high perfusion pressure.\textsuperscript{17}

However, these problems are not likely to arise with our LDF method. The following potential artefacts must be considered: (1) Contribution of retinal blood flow known to autoregulate to\textsuperscript{57} the Doppler signal; because the beam was focused at the fovea, which is free of retinal vessels, this contribution is negligible, as previously demonstrated.\textsuperscript{14} (2) Saturation of the Doppler signal at high ChBF because of the use of a flowmeter (Perimed, Stockholm, Sweden) designed for skin blood flow measurements that may not have had a high enough frequency response for choroidal blood flow.\textsuperscript{17} This is clearly not the case with the NeXT system, which has a bandwidth of 40 kHz, a frequency markedly above the frequency needed to record the signal from the foveal region of the choroid.\textsuperscript{15} (3) The technique is not sensitive enough to demonstrate flow changes. Although changes in ChBF\textsubscript{m} were not observed at low IOP (Fig. 1 & 5), we clearly detected changes in PChBF\textsubscript{m} and PChBF\textsubscript{vei}. (4) Nonlinear response of the Doppler measurements. Laser Doppler flow linearity has been demonstrated in all tissues tested so far and also for ChBF\textsubscript{m} in cats.\textsuperscript{19}

When measurements are obtained in humans, however, absence of the tapetum may allow the probing light to penetrate deeper and reach larger choroidal vessels depending on the thickness of blood in the choriocapillaris. Changes in this thickness caused by the increase in IOP could lead to increased contribution of erythrocytes that move at high velocities in these deep vessels and produce an artificial increase in ChBVel. It is unlikely that this process corrupted our results because collapse of the choroidal vasculature occurs first in veins and not in the choriocapillaris, as indicated by our findings that average ChBVolv\textsubscript{m} did not change significantly despite a \( \approx 50\% \) decrease in perfusion pressure. In addition, compression of the choriocapillaris layer and penetration into large vessels should be more marked at high IOP, which would lead to a less than expected reduction of ChBF\textsubscript{vei} with decreasing perfusion pressure. The fact that the linear fit in Figure 4 reaches zero at a PP\textsubscript{norm} \( > 0 \) does not support this possibility.

The 45% increase in ChBF\textsubscript{m} after cup was taken off and the decrease thereafter in experiment 1 can be explained as representing the refill of the choroidal vasculature after blood had been forced out of it when the IOP was raised to an average of 72 mm Hg. This interpretation is supported by the recording of Figure 2, which shows that increasing the IOP above diastolic ophthalmic artery pressure for only a few seconds evoked a similar response. This response is lacking in experiment 2 because the IOP was probably not raised high enough (average of only 42 mm Hg) to force
blood out of the vasculature, as confirmed by the non-
significant decrease in ChBF\textsubscript{m} below baseline value.

Figure 1 (bottom) shows that it takes about 1 sec-
tond to produce a step increase in IOP. Because even
when using a time constant as small as \(0.06\) seconds,
the average change in ChBF\textsubscript{m} was less than half of the
15% decrease in mean perfusion pressure and in some
cases there was even no detectable change in ChBF\textsubscript{m}
(Fig. 5), a rapid compensatory change in perfu-
sion pressure occurs after a step change in flow followed
by a recovery to the prestep value with a time constant
of 30 seconds to 10 minutes. We did not observe such
a process with long time constant.

Autoregulatory responses with a time constant of
approximately 2 seconds for the flow recovery after a
step decrease in flow occur in the brain and have been
attributed to a metabolic mechanism.\textsuperscript{23-25} Although
the results in this Figure 4 are similar to those shown in
Figure 3 of Kiel and Shepherd’s study in rabbits\textsuperscript{17} and
in accordance with the predictions of their model,
those of Figure 5 do not support a myogenic mecha-
nism for humans. Studies of autoregulation on iso-
lated posterior cerebral arteries of rats,\textsuperscript{20} pial arteries
of monkeys\textsuperscript{21} and coronary arteries,\textsuperscript{22} all demonstrate
that the myogenic response to a step change in perfu-
sion pressure consists of a step change in flow followed
by a recovery to the prestep value with a time constant
of 30 seconds to 10 minutes. We did not observe such
a process with long time constant.

Recent findings by Flügel et al\textsuperscript{16} of a dense vasodil-
itative innervation of the choroid in human, which was
specifically localized in the temporal-central portion
of the choroid adjacent to the fovea, strongly suggest
a role of a neural control mechanism for the mainte-
nance of ChBF at low IOP. As mentioned by these
investigators, this innervation might be important to
increase choroidal blood flow under certain condi-
tions. Additional work is needed to verify its putative
role in the maintenance of ChBF\textsubscript{m} at high perfusion
pressure. Another process that could play a role, albeit
small, in the maintenance of constant ChBF\textsubscript{m} is a pas-
vive increase in volume of the choriocapillaris. This
could be because of a slight engorgement of this blood
layer in response to the first step increase in IOP above
baseline as evidenced by the small but significant 5%
increase in ChBVOL\textsubscript{m}.

Our measurements provide only information on
ChBF in the foveal region of the fundus. However,
ChBF in other regions of the fundus could react differ-
ently to increases in IOP. For example, regional differ-
ences in the changes in choroidal pO\textsubscript{2} and pH in the
subretinal space have been found in cats in response to
step increases in IOP.\textsuperscript{27,28} These could be caused
by regional differences in the relationship between
ChBF\textsubscript{m} and perfusion pressure. In addition, if a neural
mechanism of autoregulation prevails, a particular be-
havior of the foveal region in human eyes could be
explained by the findings of Flügel et al\textsuperscript{16}

The foveal avascular zone and most of the outer
retina in humans receive nutrition exclusively from
the choroidal circulation. They may therefore be more
susceptible to ischemia than other retinal regions. The
nonlinear response of ChBF\textsubscript{m} versus perfusion pres-
sure may represent a protective mechanism against
moderate increases in IOP above normal. Loss of this
capability, for instance in glaucoma or diabetic reti-
nopathy, caused by decreased vasodilative innervation
or lack of distensible vessels could make the foveal
region more vulnerable to increased IOP, particularly
because the perifoveal retinal circulation appears to
lose its autoregulatory capacity in these diseases.\textsuperscript{29,30}

**Key Words**

autoregulation, blood flow, choroid, laser Doppler flowme-
try, perfusion pressure

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