Retinal Blood Flow Autoregulation after Dynamic Exercise in Healthy Young Subjects

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Abstract

Purpose: To evaluate the retinal blood flow before and after the increase in systemic blood pressure to assess the autoregulation in healthy young subjects. Methods: Twenty eyes of 20 healthy volunteers were examined. The retinal blood flow was assessed by a Heidelberg retina flowmeter (HRF), while the systemic pressure was assessed by a portable electronic sphygmomanometer. Furthermore intraocular pressure (IOP) was always measured by a Goldmann tonometer immediately after HRF assessments. All measurements of physiological and flow parameters were performed with the subjects seated at rest and then immediately after stair climbing. Results: The IOP decreased significantly after dynamic exercise, while the heart rate and the systemic artery pressure increased significantly. At the baseline, the mean retinal blood flow was 276.8 ± 80.7 arbitrary units (AU) in the superotemporal area, 243.4 ± 63.68 AU in the superonasal area, 258.2 ± 67.37 AU in the inferotemporal area and 243.9 ± 72.24 AU in the inferonasal area. After dynamic exercise the mean retinal blood flow was 249.8 ± 86.78 AU in the superotemporal area, 248.7 ± 63.87 AU in the superonasal area, 245.4 ± 83.85 AU in the inferotemporal area and 228.8 ± 62.53 AU in the inferonasal area. No significant change in retinal blood flow was found. Conclusion: Our data support the hypothesis that in normal subjects autoregulation is sufficient to compensate the increase in blood pressure and maintain a stable retinal blood flow after exercise.

Introduction

Vascular resistance is physiologically regulated by changing the local diameter of the arterioles to keep the local blood flow constant. This physiological process is called autoregulation. Different types of regulatory factors such as metabolic, myogenic and neurogenic factors can act on vascular tone systems. Although many factors such as age, heart, blood pressure, intraocular pressure (IOP) and psychic stress can influence the retinal blood flow, only few studies have examined the effect of physical exercise on orbital blood flow velocities of different ocular tissues [1–6]. Since the Heidelberg retina flowmeter (HRF; Heidelberg Engineering, Heidelberg, Germany) has been intro-
duced, the capillary blood flow has been assessed without injecting any contrast fluid in the body. Earlier studies have shown that HRF reproducibility was acceptable; however, when an additional program – the automatic full-field perfusion image analyzer (AFFPIA) – was used, the intraobserver and interobserver reproducibility improved [7, 8].

The aim of this study was to evaluate the retinal blood flow before and after an increase in systemic blood pressure to assess the autoregulation in healthy young subjects.

 Patients and Methods

Twenty eyes of 20 healthy volunteers were recruited from the residents and medical school subjects. For each subject only the right eyes were considered. They were not excluded on the basis of gender, age or race; however, only Caucasian subjects were included in the study. To be included the refractive error had to range from –7 to +7 dpt. The research followed the tenets of the Declaration of Helsinki, and informed consent was asked from all the considered subjects.

All the subjects’ eyes were examined by slitlamp and opthalmoscopy and only healthy eyes were included in the study. The medical history was negative for migraine, vasospasm and Raynaud’s syndrome. No subject was on medication.

The visual field of each subject was assessed by the Frequency Doubling Technology (FDT, Welch-Allyn, Skaneateles, N.Y., Zeiss-Humphrey, San Leandro, Calif., USA). The FDT screening program was used to analyze the central 20° of the visual field [9–12].

The retinal blood flow was assessed by the HRF, while the systemic pressure was assessed by a portable electronic sphygmomanometer. Furthermore intraocular pressure (IOP) was always measured by a Goldmann tonometer immediately after HRF.

Heidelberg Retina Flowmeter

The HRF combines the principles of a confocal scanning laser and a laser Doppler flowmeter (670 nm; 100 μW). After 128 scans of each examined point, the HRF calculates a bidimensional map of the laser Doppler shift within a 300-μm slice of tissue, over a rectangular area (5 × 20°) of the posterior pole of the eye. The calculation is done using a fast Fourier transformation. The laser Doppler shift values recorded at different locations are displayed on the monitor in a color code image. For each pixel a frequency shift is calculated [13–18].

Raw data were analyzed using a program called AFFPIA. The details of this technique have been published elsewhere [7, 8, 13, 14]. In brief, AFFPIA calculated the Doppler frequency shift, and the hemodynamic factor or flow of each pixel according to the theory of Bonner and Nossal. For valid estimation of retinal blood flow some assumptions must be made: adequate brightness, no ocular movement, Doppler shift considerably lower than 2,000 Hz. To meet these requirements, the resulting perfusion image is processed to account for underexposed and overexposed pixels, saccades and the retinal vessel tree. With AFFPIA the operator marks saccades and the location of the rim area; in a further step the capillaries and large vessels of the retina are identified automatically by a vessel detection algorithm based on the intensity and the perfusion image. Underexposed and overexposed pixels and the saccades are automatically excluded. The local inhomogeneities of the perfusion map are softened by a moving average procedure, performed with a size of 5 × 5 pixels [7]. For capturing each image, the time needed is 2 s. This allows averaging the cardiac circle for areas larger than a pixel. The heart-beat-associated pulsation of capillary blood flow was accounted for by plotting the mean capillary flow of each horizontal line against time.

The subjects had to fix a distant target with the contralateral eye. All the optic nerve heads were theoretically divided into three horizontal sections (superior, central and inferior section). In this study the superior and inferior optic nerve head sections were acquired and analyzed. In each HRF image, the superior or inferior optic rim and the adjacent temporal and nasal peripapillary areas were analyzed by the AFFPIA program. The users had to draw the inner and outer rim contour line and the program was automatically able to calculate the flow in the 3 following areas: rim, temporal and nasal areas.

For each analysis and for each sector, 4 parameters were obtained: the ‘mean flow’, measured in arbitrary units (AU), together with its standard deviation and the ’area’ used to calculate the flow, measured as percentage of the total area and as percentage of the analyzed area [18].

For each analysis, only the temporal and nasal retinal measurements were considered, while the rim analysis was not considered in this study.

Portable Electronic Sphygmomanometer

The method of measure was an oscillometric one; the range of measuring was between 0 and 300 mm Hg of pressure and between 40 and 160 heart beats. The range of blood pressure measuring was between 50 mm Hg (the lowest diastolic value) and 250 mm Hg (the greatest systolic value). The laboratory accuracy was about 3 mm Hg (accuracy of the armlet) and 5% (heart beat). Insufflation was automatic and the subject’s blood pressure adapted, while an electronic controlled valve made desufflation. The subject’s heart beat adapted.

The armlet fitted on wrists between 13.5 and 20 cm of circumference. The clinical accuracy was in accordance with the AAMI-SPI10 auscultatory standard: 5 mm Hg of systematic bias and 8 mm Hg of standard deviation.

To obtain correct results, the wrist sphygmomanometer had to be taken just at the same level of the heart; the bias caused by a bad position of the sphygmomanometer increased proportionally to the difference between the heart level and the wrist level at the moment of measurement.

All measurements of physiological and flow parameters were performed with subjects seated at rest. Comparisons of resting conditions with dynamic exercise were made by obtaining data at rest and then by making measurements immediately after exercise. Each subject had to run and climb 20 stairs for 3 min to increase blood pressure more than 20% from the baseline values.

Statistical Analysis

The data were analyzed by a descriptive analysis. The paired t test was used to compare physiological and flow results between baseline and after dynamic exercise when the distribution of the
The Wilcoxon nonparametric test was used instead, when the distributions of the data were nonnormal. Correlations between retinal blood flow and the other parameters were analyzed by Pearson’s r coefficient when the distribution was normal, otherwise by Spearman correlation. A p value less than 0.05 was considered to be statistically significant.

### Results

Eleven males and 9 females were recruited in this study. One subject was excluded because of a nonadequate flow map. HRF flow maps were considered adequate for analysis when the focus was at the superficial vessels, capillaries in the flow image had to be visible, and saccades had to be less than 2 and HRF DC values ranged from 40 to 250. In this case, the abnormal flow values were probably due to some slow saccades that could increase retinal flow. The mean age of the sample was 27.9 ± 3.4 years (mean ± standard deviation; ranging from 23 to 36 years) and the mean refraction error was –1.85 ± 1.98 dpt (ranging from –7 to 0 dpt). The FDT showed a normal visual field for each considered subject.

While the IOP decreased significantly between before and after dynamic exercise, the heart rate and the systemic artery pressure increased significantly (tables 1–3).

At the baseline the mean retinal blood flow was 276.8 ± 80.7 AU in the superotemporal area, 243.4 ± 63.68 AU in the superonasal area, 258.2 ± 67.37 AU in the inferotemporal area and 243.9 ± 63.68 AU in the inferonasal area (table 1). After dynamic exercise the mean retinal blood flow was 249.8 ± 86.78 AU in the superotemporal area, 248.7 ± 63.87 AU in the superonasal area, 245.4 ± 83.85 AU in the inferotemporal area and 228.8 ± 62.53 AU in the inferonasal area (table 2). When the data before and after exercise were compared, the mean retinal blood flow difference was 27 (9.75%) in the superotemporal area.
area, –5.3 (–2.18%) in the superonasal area, 12.8 (4.96%) in the inferotemporal area and 15.1 AU (6.19%) in the inferonasal area (table 3). Only in the superotemporal area had the retinal blood flow difference a tendency to be significant (table 3).

No significant difference between values before and after dynamic exercise was found for the standard deviation of the flow measurements and for the total area. The percentage of the analyzed area values was found to be significantly different at rest and after dynamic exercise in the inferotemporal area (tables 1–3).

When the retinal flow data were compared among the 4 different considered areas, no significant difference was found both at rest and after dynamic exercise.

The retinal blood flow data were also compared to the physiological parameters we considered in this study. No correlation was found between retinal flow and age while refractive error was found to be correlated with pre-superonasal (r = –0.48, p = 0.039) and pre-inferotemporal flow (r = –0.49, p = 0.035) and to post-superotemporal flow (r = –0.46, p = 0.048). A correlation was found between postexercise retinal flow and postexercise heart rate in the superonasal area (r = 0.48, p = 0.039). Furthermore in the inferotemporal area, postexercise retinal flow and systemic blood pressure – both systolic (r = 0.55, p = 0.015) and diastolic (r = 0.50, p = 0.013) – were significantly correlated as well as postexercise retinal flow and the pre-diastolic pressure (r = 0.59, p = 0.007).

**Discussion**

The retinal capillaries have a substantially small caliber (5–7 μm) compared to the choroids; the capillaries leave large vessel-free spaces, and in particular the macula is vessel free [19]. To compensate this, the 2-layered retinal capillary systems become 3 or 4 layers in the central part of the retina.

In the literature it has been found that the dynamic exercise could influence the flow velocity in the ophthalmic artery and the central retinal artery for the lack of automatic innervations in the retinal blood vessels [20–22].

Many studies have shown that choroid flow did not change during exercise because of autoregulation [1–6]. In particular the dynamic exercise should increase the flow velocity due to the increase in heart rate and systemic pressure, but theoretically local regulation could keep ocular flow at the same level or decrease the choroid and retinal capillary flow during exercise. Heart rate and arterial blood pressure were found to be dependent on the general systemic changes in the automatic nervous system that occurred after dynamic exercise. The changes in the sympathetic tone significantly influenced the physiological parameters. Using different techniques, other authors showed autoregulation in the retinal blood flow. Robinson et al. [23] found that there was no detectable change in retinal blood flow until the mean brachial artery pressure rose 40% above the baseline values while Movaffagh et al. [2] showed that IOP was significantly increased above baseline at the end of squatting and decreased during recovery to keep the perfusion constant during the increase in the mean brachial artery pressure.

The ocular flow has been shown to be correlated with the systemic artery pressure and the IOP. After dynamic exercise, blood pressure and heart rate were significantly increased. IOP could significantly decrease by 6 mm Hg, as Marcus et al. [24] have shown, after 4 min of dynamic

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Table 3. Comparison between baseline and after exercise values for physiological and flow parameters

<table>
<thead>
<tr>
<th></th>
<th>Difference</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>IOP, mm Hg</td>
<td>2.00 (14.62)</td>
<td>0.003</td>
</tr>
<tr>
<td>Heart frequency, beats/min</td>
<td>–58.97 (–78.07)</td>
<td>0.000</td>
</tr>
<tr>
<td>Systolic blood pressure, mm Hg</td>
<td>–36.30 (–31.08)</td>
<td>0.000</td>
</tr>
<tr>
<td>Diastolic blood pressure, mm Hg</td>
<td>–18.74 (–24.34)</td>
<td>0.000</td>
</tr>
<tr>
<td>Blood flow, AU</td>
<td></td>
<td></td>
</tr>
<tr>
<td>TS</td>
<td>27.00 (9.75)</td>
<td>0.055</td>
</tr>
<tr>
<td>NS</td>
<td>–5.30 (–2.18)</td>
<td>0.696</td>
</tr>
<tr>
<td>TI</td>
<td>12.80 (4.96)</td>
<td>0.419</td>
</tr>
<tr>
<td>NI</td>
<td>15.10 (6.19)</td>
<td>0.168</td>
</tr>
<tr>
<td>Blood flow SD, AU</td>
<td></td>
<td></td>
</tr>
<tr>
<td>TS</td>
<td>5.80 (3.50)</td>
<td>0.467</td>
</tr>
<tr>
<td>NS</td>
<td>–11.80 (–7.52)</td>
<td>0.206</td>
</tr>
<tr>
<td>TI</td>
<td>–4.60 (–2.76)</td>
<td>0.599</td>
</tr>
<tr>
<td>NI</td>
<td>6.00 (3.38)</td>
<td>0.375</td>
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<tr>
<td>Total area, %</td>
<td></td>
<td></td>
</tr>
<tr>
<td>TS</td>
<td>0.13 (0.30)</td>
<td>0.953</td>
</tr>
<tr>
<td>NS</td>
<td>1.00 (2.11)</td>
<td>0.563</td>
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<tr>
<td>TI</td>
<td>–0.45 (–1.03)</td>
<td>0.682</td>
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<tr>
<td>NI</td>
<td>0.55 (1.19)</td>
<td>0.567</td>
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<tr>
<td>Percent area, %</td>
<td></td>
<td></td>
</tr>
<tr>
<td>TS</td>
<td>6.75 (11.45)</td>
<td>0.321</td>
</tr>
<tr>
<td>NS</td>
<td>–7.80 (–20.35)</td>
<td>0.206</td>
</tr>
<tr>
<td>TI</td>
<td>10.15 (15.94)</td>
<td>0.044</td>
</tr>
<tr>
<td>NI</td>
<td>–5.15 (–11.98)</td>
<td>0.180</td>
</tr>
</tbody>
</table>

Figures in parentheses are percentages. Difference = Difference between pre-exercise and post-exercise values; SD = standard deviation; TS = temporal-superior sector; NS = nasal-superior sector; TI = temporal-inferior sector; NI = nasal-inferior sector.
exercise, while Riva et al. [1] found a decrease of 4 mm Hg in IOP during squatting. Other studies did not find large changes in IOP after exercise [1, 25, 26]. In our study, a decrease of 2 mm Hg in IOP was found after the dynamic exercise and the IOP decreases were statistically but not clinically significant.

The parallel changes of vascular resistance and blood pressure during exercise might be the reason for a constant blood flow in the ophthalmic artery [6]. Some studies have analyzed ocular blood flow after dynamic exercise to understand ocular autoregulation.

Lovasik et al. [5] have found a dissociation between the ocular perfusion pressure and the choroidal flow during biking and the recovery suggesting that in the eye there was some mechanism to keep the choroidal blood flow close to its basal values. Furthermore it has been shown that in spite of increased perfusion pressure the maintenance of a constant choroidal blood flow was achieved through an increase in choroidal vascular resistance [1].

The HRF was able to assess only the retinal blood flow without being influenced by choroidal flow. This was possible for the intrinsic characteristics of the system whose laser light should not pass the pigmented epithelium and the analysis was around (±150 μm) the retinal surface, which was focused by the user (M.I.) [13, 14]. The peripapillary retinal nerve fiber layer height ranged from 400 to 350 μm at the superior and inferior poles in healthy subjects [27], the HRF light reached neither the pigment epithelium nor the choroidal vessels; thus, it was possible to assess the retinal blood flow.

In our study when we analyzed the retinal blood flow, no significant decrease was found; however, in 3 areas a decrease in retinal blood flow was found and in one of them, the superotemporal area, the flow reduction showed a tendency to be significant. However, the coefficient of variation of HRF measurements ranged from 1 to 10% [8]; thus, the flow results could be just noise of measurements.

Although a mild but not significant reduction of retinal blood flow has been found in this study, we believed that the autoregulation mechanism of the ophthalmic artery and central retinal artery could be involved in the autoregulation of the retinal flow in healthy young subjects. This autoregulation could also be present in some stress condition, in which the systemic artery pressure was high, but always between some limits, out of which the retinal flow could not be regulated anymore with a secondary retinal flow reduction.

The standard deviation of the retinal blood flow measurements did not change between baseline and after dynamic exercise suggesting that the intrindividual variation or the noise of the technique did not interfere with the results. This result was mainly due to the AFFPIA program we used, which measures the retinal flow globally. Using AFFPIA we did not analyze the flow in a particular point but in an area: this methodology decreases the importance to find the exact position of the box as we have already shown [8]. Furthermore no significant difference was found for ‘the area considered for the measurements’ before and after the measurements. When these results were analyzed using ‘the area percentage’, only in the inferotemporal area was found a significant difference between the baseline and the follow-up measurements.

Furthermore in our study no significant difference in flow was found among the 4 considered areas both at rest and after dynamic exercise. The different results we found could be due to the different techniques used to analyze the HRF results [28].

These autoregulation mechanisms could change the blood flow in few instants; thus, it was impossible to tell what was occurring in the retinal vasculature at that time, mean retinal flow might initially increase but adapt rapidly before measurements were taken. There was the possibility that the time needed to sit in front of the instrument and to focus in the superior part of the optic nerve head could be too long to really assess the change in the retinal blood flow.

From the data of this study we could conclude that we did not find any significant change in retinal blood flow before and after dynamic exercise ranging from –2.18 to 9.75% from the baseline values; thus, the autoregulatory response of healthy retinas appeared to be present during dynamic exercise. This response could be due to a kind of valve system able to regulate retinal blood flow under some stressed condition. The autoregulation might be accounted for by a sympathetic mechanism for protecting the eye from overperfusion [6] together with the IOP reduction.

Flow spatial variations could also be correlated with the results obtained in other studies in which it has been shown that in cats some subretinal spaces had different pH values [1, 29, 30].

No retinal blood flow change was found after dynamic exercise, in spite of the HRF method used to assess the retinal blood flow and the relatively small number of subjects recruited in this study. The lack of any changes could be due to a mechanism of autoregulation of ocular vessels that as last features carried a decrease in retinal blood supply. More sophisticated techniques should be used to better quantify retinal blood flow during dynamic exercise.
References
