New insights into ocular blood flow at very high altitudes

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Ascent to very high altitudes exposes the human body to increasingly hypobaric hypoxic conditions. Survival is only possible because of specific adaptational changes that result in partial restoration of the oxygen uptake capacity of the body, and optimization of oxygen delivery to the tissues. The aim of the Swiss High-Altitude Medical Research Expedition was to examine ophthalmic, neurological, respiratory, and circulatory changes in humans exposed to extreme altitudes. Findings presented here on ocular blood flow changes at high altitudes pertain to the ophthalmology project within the scope of this research expedition.

Blood flow alterations in both the brain and the eye occur under the influence of prolonged hypoxia (13, 14). Cerebral blood flow (CBF) at high altitudes has been shown to increase during the first 24 h and to decrease gradually to normal levels within days (10, 38) and then remain stable after acclimatization (25). Changes in CBF at different altitudes are of interest as a sign of autoregulatory properties. According to one leading hypothesis, an increase in CBF on a capillary level resulting from altered autoregulation at high altitudes constitutes a risk factor for acute mountain sickness (AMS) and high-altitude cerebral edema (HACE) by leading to capillary overperfusion and vasogenic cerebral edema. The retina represents the only part of the central nervous system where capillary blood flow is visible and can be measured by noninvasive means. In this study we aimed to gain insights into retinal and choroidal autoregulatory properties during hypoxia and to correlate circulatory changes to symptoms of AMS and clinical signs of HACE. This observational study was performed within the scope of a high-altitude medical research expedition to Mount Muztagh Ata (7,546 m). Twenty seven participants underwent general and ophthalmic examinations up to a maximal height of 6,800 m. Examinations included fundus photography and measurements of retinal and choroidal blood flow, as well as measurement of arterial oxygen saturation and hematocrit. The initial increase in retinal blood velocity was followed by a decrease despite further ascent, whereas choroidal flow increase occurred later, at even higher altitudes. The sum of all adaptational mechanisms resulted in a stable oxygen delivery to the retina and the choroid. Parameters reflecting the retinal circulation and optic disc swelling correlated well with the occurrence of AMS-related symptoms. We demonstrate that sojourns at high altitudes trigger distinct behavior of retinal and choroidal blood flow. Increase in retinal but not in choroidal blood flow correlated with the occurrence of AMS-related symptoms.

cerebral blood flow; retina; choroid; acute mountain sickness

METHODS

Subjects and Course of Expedition

This prospective, multidisciplinary, observational cohort study was performed within the scope of a high-altitude medical research expedition. Exclusion criteria were any type of ocular, cardiac, or respiratory disease, or a history of high-altitude pulmonary edema or other conditions at high altitudes. There is evidence that an increase in cerebral blood flow resulting from altered autoregulation constitutes a risk factor for acute mountain sickness (AMS) and high-altitude cerebral edema (HACE) by leading to capillary overperfusion and vasogenic cerebral edema (17, 41). However, due to the technical difficulties associated with investigations at very high altitudes, examination of CBF has to date only been possible on the level of larger arteries.

There was a close correlation between the regulation of blood supply to the brain and to the retina, due to similar vascular regulatory processes (9, 28). The direct visualization of the retinal vasculature and the measurement of blood flow in the capillaries of the macular region of the fundus as well as in the subfoveal choriocapillaris are now possible in an outdoor setting. This allows for the assessment of blood flow on a capillary level, downstream from the large cerebral arteries in an observable part of the central nervous system.

In this study, we aimed to determine the effect of long-term hypoxemia on retinal and choroidal blood flow during a slow ascent to very high altitudes. We investigated whether high-altitude changes in retinal/choroidal blood flow correlate with alterations of retinal vessels and optic disc, and how these changes mirror symptoms and signs of high-altitude cerebral illness.

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high-altitude cerebral edema (HACE) after a rapid ascent (<3 nights) at altitudes below 3,500 m. Thirty-four healthy mountaineers were initially enrolled. Seven participants were excluded from the study because of ocular disease before the expedition (n = 2) or because of incomplete data collection during the expedition (n = 5). Data of 27 mountaineers (age 26–62 yr; mean 43 yr; 6 women and 21 men) were processed. The participants were randomly distributed into two groups, with a different ascent profile for each group (Fig. 1). The study was approved by the Ethical Committee of the University Hospital, Zurich, and adheres to the tenets of the Declaration of Helsinki (1983 Revision). Informed, written consent was obtained from all subjects before the examinations.

The climb for both groups started at 3,750 m, then continued to base camp (BC = 4,497 m), camp 1 (C1 = 5,533 m), camp 2 (C2 = 6,265 m), camp 3 (C3 = 6,865 m), and to the summit (7,546 m), within 20 and 19 days. The average ascent rate was 190 and 200 m/day, respectively (Fig. 1). Examinations were performed at BC and on each subsequent day on arrival at each new high camp and at return to base camp (BC2), having reached at least C2 (Fig. 1).

**Measurements**

The participants underwent general and ophthalmic baseline examinations 1 mo before the expedition (ZH1) and 4.5 mo after returning from the expedition (ZH2) at the University Hospital of Zurich (490 m). Baseline eye examinations included testing of best-corrected visual acuity (BCVA) with log MAR charts [ETDRS letters (12)], fundus photography, and fluorescein angiography (Zeiss FF 450 plus camera, Carl Zeiss AG, Oberkochen, Germany), measurement of retinal blood flow by blue-field simulation (BFS-1000, Oculix, Berwyn, PA), choroidal blood flow by laser-Doppler flowmetry (LDF) (Institut de Recherche en Ophtalmologie, Sion, Switzerland), and measurements of intraocular pressure (IOP; Tono-Pen XL; Medtronic-Solair, Jacksonville, FL). At high altitude, all examinations except fluorescein angiography were performed; fundus photographs were acquired using a hand-held digital fundus camera (Genesis-D, Kowa, Tokyo, Japan). At every examination, 12 digital fundus photographs were taken of each eye with a 30-s interval between each photograph.

**Retinal vessel diameters.** Vessel diameters of the temporal superior branch retinal artery and vein were measured by projecting identical branch retinal artery and vein were measured by projecting identical

**Choroidal blood flow measurements.** At high altitude, all examinations except fluorescein angiography was allowed by protocol, whereas other medication was taken only on recommendation by the independent expedition physician.

**Systemic parameters.** Diastolic (P_{A, diast}) and systolic (P_{A, syst}) brachial artery blood pressure were measured with a sphygmomanometry device. Mean systemic blood pressure was defined as P_{A, diast} + 1/3 (P_{A, syst} − P_{A, diast}). Hct was measured in capillary blood samples using a template to determine the values after centrifugation (Haemotokrit 2010, Hettich, Switzerland). Daily pulse oximetry was performed in the evening during quiet rest in a standing position with a finger pulse oximeter (Onyx 9500 SportStat, Nonin Medical, Plymouth, MN). Stable values after at least 3 min were recorded. Cerebral AMS (AMS-c) scores were assessed daily during the expedition utilizing the Environmental Symptom Questionnaire (ESQ III) (24, 37). The AMS-c score reflects symptoms of altered cerebral function in conjunction with the feeling of being ill. A score of ≥0.7 reliably identifies a person with AMS (24, 37). Drug intake was assessed by analyzing daily personal diaries. Intake of nonsteroidal anti-inflammatory agents was allowed by protocol, whereas other medication was taken only on recommendation by the independent expedition physician.

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Fig. 1. Ascent profile and test altitudes for both groups of climbers on Mount Muztagh Ata. BC, base camp; C1, C2, and C3 are camps 1, 2, and 3.
Acclimatization occurred over the course of the expedition as evidenced by a SaO2 at return to base camp that exceeded values first measured.

Eye-Related Changes

Retinal vessel diameter and blood flow. Both arterial and venous calibers increased significantly at high altitudes \([F(6,84) = 69.4, P < 0.0001]\) for arterial vessels; \([F(6,84) = 91.78, P < 0.0001]\) for venous vessels] (Fig. 2), the increase of arteries being greater than that of veins \((P = 0.004)\). The most marked changes were noted at BC1 (arterial and venous change compared with ZH1: \(P < 0.0001\)) and at C1 (alteration compared with BC1: \(P = 0.03\) for arterial vessels and \(P < 0.0001\) for venous vessels). Above C1, arterial and venous diameters stabilized and enlarged only insignificantly up to C3. On descent arterial and venous diameters returned to their initial values, and no significant differences were observed between BC1 and BC2, and ZH1 and ZH2.

Oxygen saturation was a significant predictor of vessel diameters \((R^2 = 0.548, \beta = 0.740, P < 0.0001\) for arterial vessels; \(R^2 = 0.712, \beta = 0.844, P < 0.0001\) for venous vessels). Decrease of oxygen saturation by 1% was associated with increase of 1.4 \(\pm\) 0.1%, and of 1.3 \(\pm\) 0.06% in arterial and venous vessel diameter, respectively.

Arterial and venous vessel diameters were found to correlate weakly with retinal blood flow velocity as measured by BFS (arterial vessel diameter \(R^2 = 0.142, \beta = 0.377, P < 0.0001\); venous vessel diameter \(R^2 = 0.052, \beta = 0.220, P = 0.008\)). No significant correlation with systemic mean arterial blood pressure was found.

Changes in retinal blood flow parameters are shown in Fig. 3 and summarized in Table 2. BFS-Vel differed significantly at different altitudes \([F(5,120) = 20.37, P < 0.0001]\). On initial ascent, central macular blood flow velocity increased and peaked at medium altitudes (6,265 m) and then decreased on continuing ascent. Significant changes were observed between baseline levels and BC1 \((P < 0.0001)\), whereas a trend for decrease in BFS-Vel was measured between C1 and C2. The values for rcO2 varied significantly at different altitudes \([F(2.39,62.16) = 15.86, P < 0.0001, \epsilon = 0.59]\). The statistically insignificant decrease in BFS-Vel between C1 and C2 was obliterated after correction for Hct to calculate rcO2. Calculated oxygen delivery rDO2 did not show a significant change at different altitudes \([F(2.68,69.84) = 1.15, P > 0.05, \epsilon = 0.67]\) but remained stable throughout the expedition. Arterial oxygen saturation was a significant predictor for BFS-Vel \((R^2 = 0.243, \beta = -0.439, P < 0.0001)\) and rcO2 \((R^2 = 0.142, \beta = 0.377, P < 0.0001)\).

Table 1. Number of examined subjects and mean SaO2, AMS-c scores, MAP, and Hct at different altitudes

<table>
<thead>
<tr>
<th></th>
<th>ZH1 (490 m)</th>
<th>BC (4,497 m)</th>
<th>C1 (5,533 m)</th>
<th>C2 (6,265 m)</th>
<th>C3 3 (6,656 m)</th>
<th>BC2 (4,497 m)</th>
<th>ZH2 (490 m)</th>
<th>Significance (ANOVA)</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>27</td>
<td>27</td>
<td>27</td>
<td>27</td>
<td>15</td>
<td>27</td>
<td>27</td>
<td></td>
</tr>
<tr>
<td>SaO2, %</td>
<td>84±3</td>
<td>75±6</td>
<td>73±6</td>
<td>66±3</td>
<td>87±5</td>
<td>87±5</td>
<td>87±5</td>
<td>(P &lt; 0.0001)</td>
</tr>
<tr>
<td>AMS-c</td>
<td>0.15±0.25</td>
<td>0.20±0.29</td>
<td>0.23±0.47</td>
<td>0.41±0.46</td>
<td>0.01±0.05</td>
<td>0</td>
<td>ns</td>
<td>(P = 0.0013)</td>
</tr>
<tr>
<td>MAP, mmHg</td>
<td>87±11</td>
<td>89±7</td>
<td>94±8</td>
<td>90±7</td>
<td>90±7</td>
<td>93±6</td>
<td>93±6</td>
<td>ns</td>
</tr>
<tr>
<td>Hct, %</td>
<td>44±3</td>
<td>45±4</td>
<td>50±4</td>
<td>50±4</td>
<td>43±2</td>
<td>43±2</td>
<td>ns</td>
<td>(P &lt; 0.0001)</td>
</tr>
</tbody>
</table>

Values are means ± SD; \(n = \) no. of examined subjects. ZH1, baseline examinations at University Hospital of Zurich 1 mo before expedition; BC, initial base camp; C1, C2, and C3, camps 1, 2, and 3; BC2, return to base camp; ZH2, examinations at University Hospital of Zurich 4.5 mo after returning from expedition; SaO2, arterial oxygen saturation; AMS-c score, cerebral acute mountain sickness score [Environmental Symptom Questionnaire (ESQ III)]; MAP, mean systemic blood pressure; Hct, hematocrit; ns, not significant.
95% confidence interval (CI) 1.006–1.066, revealed arterial retinal vessel diameter [odds ratio (OR) 1.03, and occurrence of AMS. Systemic blood pressure did not correlate with choroidal blood flow parameters. Interestingly, de-

Compared with baseline levels in examinations at University Hospital of Zurich (490 m) 1 mo before the expedition (ZH1). Arterial vessel diameter increased compared with baseline levels in examinations at University Hospital of Zurich (55.83, 2.14) F (15.41, 2.20) P 0.0001 for LDF-Vel; P 0.004 for LDF-Vol) and SaO2 and vessel diameters on the other hand, thus explaining this finding.

Best-corrected visual acuity and fluorescein angiography. No significant decrease in BCVA was noted during the course of the expedition. No changes in fluorescein angiography were found after the expedition compared with initial examinations.

DISCUSSION

The present study demonstrates significant changes in the circulation parameters of the eye with increasing altitude. Both retinal and choroidal blood flow velocity increased during prolonged hypoxic conditions. The initial increase in macular retinal blood velocity was followed by a decrease at higher altitudes despite further ascent, whereas choroidal flow increase occurred later, at even higher altitudes. Moreover, parameters reflecting the retinal circulation, that is, macular retinal blood velocity and increase in vessel caliber, correlated with the development of AMS symptoms, suggesting a pathophysiological link, whereas such associations were not detected for choroidal circulation parameters. Interestingly, despite these marked and significant temporary changes, the eye’s visual acuity was not affected, and no temporary or persistent damage could be detected.
The retina is one of the most metabolically active tissues (4) in the human body; it features a distinctly regulated dual circulation by retinal and choroidal vessels. The outer retina, comprised of photoreceptors with a very high oxygen consumption rate, mainly relies on choroidal perfusion, whereas the inner retina, encompassing bipolar, amacrine, horizontal, and ganglion cells, mainly depends on retinal perfusion (7). The retinal blood flow is tightly regulated by tissue oxygen tension (PO2) (2, 11, 27); thus a drop in arterial oxygen partial pressure (PaO2) induces an immediate increase in retinal blood flow. In contrary, the choroidal blood flow shows less apparent oxygen regulation (7); choroidal oxygen delivery is characterized by high blood flow rate and low oxygen extraction and is less sensitive to lower PaO2 (3, 22).

Short-term hypoxia has been shown to induce dilation of retinal vessels (20). Long-term hypobaric hypoxia studies by Frayser et al. (13), who examined mountaineers at a maximum altitude of 5,300 m, showed a marked increase in retinal blood flow. They reported an increase of 89% in retinal blood flow within 2 h of arrival at altitude, a 128% increase over control flow after 5 days, and an increase of 174% after 7 wk (14).

Our study subjects were exposed to chronic and severe hypobaric hypoxia, and their retinal arterial and venous vessel caliber increased during ascent to higher altitudes and quickly decreased on descent. This finding supports the results of the animal study by Ahmed et al. (1), in which the maximum vascular dilation was found to occur at PaO2 values < 40 mmHg. The vessel calibers stabilized above 5,500 m and enlarged only insignificantly at 6,800 m. We suggest the causes to be mechanical and anatomic restrictions of these retinal vessels.

Retinal blood flow velocity showed a steady decline during the climb above 5,500 m after an initial increase (Fig. 3). As blood flow velocity is dependent on vessel diameter, perfusion pressure, and blood viscosity, the significant increase in hematocrit with time spent at high altitudes may have contributed to this deceleration. The sum of all adaptational mechanisms was shown to result in a stable retinal oxygen delivery (rdO2) throughout the high-altitude expedition. The quick adaptation of the retinal circulation to hypoxemia with increasing altitude may be due to the preexisting maximum oxygen extraction (40) and due to the known sensitivity of the retinal circulation to altered blood oxygen concentration (16).

In contrast to the retinal perfusion, choroidal blood flow velocity and oxygen-carrying capacity did not increase after ascent to medium heights of 4,497 m (BC1) and 5,533 m (C1) but did increase after ascent to 6,265 m (C2) and was sustained after descent to 4,497 m (BC2). Calculated oxygen delivery showed a similar trend to increase, which was not, however, statistically significant. As changes in choroidal oxygen requirements are improbable, we assume that other factors may have been responsible for the delay of increase in oxygen-carrying capacity and oxygen delivery. Oxygen extraction is very low in the choroid, resulting in a high reserve of oxygen transport capacity (2, 43). Given this low oxygen extraction rate in nonhypoxic conditions, we hypothesize that the initial drop in oxygen delivery can be compensated by an increase in oxygen extraction. Choroidal blood flow increases only after a substantial drop in venous saturation, which results in reduced oxygen diffusion from the vessels into the tissue to avoid a further increase of the arteriovenous oxygen difference. Additionally, retinal and choroidal blood flow is influenced by the arterial carbon dioxide tension (PaCO2) (19, 32, 39). This effect is mediated by pH changes in the extracellular tissue surrounding the blood vessels, which leads to arterial vasconstriction in the retina as well as the choroidal circulation. Pronounced hypocapnia occurs at high altitude due to a hypoxia-induced increase in alveolar ventilation. In the course of the acclimatization process, renal compensation of respiratory alkalosis takes place, thus reducing pH and hypocapnic vasconstriction. The vasconstrictory effect of hypocapnia at the beginning of the acclimatization period is likely to be more pronounced in the choroidal circulation. The oxygen transport capacity is not flow limited in the choroidal circulation, compared with the retinal circulation, which depends on an increased flow to provide sufficient oxygen for the surrounding tissue. Therefore, while the vasconstrictory effect of hypocapnia per se might be the same on retinal and choroidal blood flow, the more severe hypoxia in the retinal circulation might induce a more pronounced vasodilatory response in the retinal circulation and thus offset the PaCO2 response. We did not measure arterial blood gases and choroidal venous blood Po2 on site, but we hypothesize that hypocapnia may have contributed to the observed differences between choroidal and retinal blood flow in our subjects.

### Table 2. Mean retinal blood flow velocity, oxygen capacity, and oxygen delivery at different altitudes

<table>
<thead>
<tr>
<th>Altitude</th>
<th>BFS-Vel, mm/s</th>
<th>rcO2, mm/s × %Hct</th>
<th>rdO2, mm/s × %Hct × SaO2</th>
</tr>
</thead>
<tbody>
<tr>
<td>ZH1 (490 m)</td>
<td>0.82±0.16</td>
<td>35.2±7.1</td>
<td>34.9±7.0</td>
</tr>
<tr>
<td>BC (4,497 m)</td>
<td>1.13±0.27</td>
<td>49.9±12.7</td>
<td>35.2±17.2</td>
</tr>
<tr>
<td>C1 (5,533 m)</td>
<td>1.24±0.32</td>
<td>53.5±17.4</td>
<td>49.9±17.7</td>
</tr>
<tr>
<td>C2 (6,265 m)</td>
<td>1.08±0.30</td>
<td>52.2±17.7</td>
<td>40.2±12.7</td>
</tr>
<tr>
<td>BC2 (4,497 m)</td>
<td>1.02±0.26</td>
<td>37.7±10.0</td>
<td>38.2±12.7</td>
</tr>
<tr>
<td>ZH2 (490 m)</td>
<td>0.88±0.24</td>
<td>36.9±9.8</td>
<td>ns</td>
</tr>
</tbody>
</table>

Values are means ± SD. BFS-Vel, retinal blood flow velocity (blue-field simulation); rcO2, retinal blood flow oxygen capacity; rdO2, retinal blood flow oxygen delivery. Hct was not available at BC2.
Available data on the influence of hypoxia and hypoxic hypocapnia on human choroidal blood flow are very scarce, and we are not aware of studies assessing the impact of prolonged and marked hypoxic conditions as experienced by our subjects. Kergoat et al. (22) reported the effects of transient mild systemic hypoxia (breathing of 12% oxygen) on choroidal blood flow in healthy volunteers. The described experimental condition is comparable to the severity of hypoxia our climbers were subjected to while ascending to altitudes up to 5,500 m during the initial acclimatization period. The above authors did not find a change in choroidal blood flow in their subjects, which is consistent with the results in our climbers who showed stable choroidal blood flow measurements up to C1 with an increase at even higher altitudes.

There is a close anatomic correlation between the vascular blood supply to the brain and the retina, due to similar vascular regulatory processes (9, 28). Direct visualization of the retina, which is a contiguous part of the central nervous system, and its capillary circulation allows for potential new insights into the pathophysiology of AMS and HACE. A leading hypothesis relates AMS to early stages of brain edema, which might progress to overt HACE in susceptible mountaineers (17). Whether an increase in CBF plays a pathogenic role in AMS, which may result in cerebral edema, leading to the potentially lethal HACE in persons with severe AMS or HACE.

In our study subjects, the development of AMS symptoms correlated with a higher increase in retinal capillary blood flow and with optic disc swelling, as reported earlier (8), but not with changes in choroidal blood flow. It is possible that an increased retinal blood flow may contribute to the development of optic disc swelling (8). Similarly, an increased blood flow in the cerebral capillary bed may lead to vasogenic brain edema in persons with severe AMS or HACE.

Whereas transcranial Doppler measures global CBF in large arteries, Doppler flowmetry allows for the measurement of blood flow in the capillaries of the central nervous system, exactly where an overperfusion and consecutive cerebral edema would be expected to take place. Thus results reported in studies using duplex sonography lacking correlation between an increase in CBF and AMS-related symptoms do not necessarily conflict with our findings, which show a correlation between capillary blood flow and AMS scores.

Despite the logistical and technical difficulties associated with medical research in such a challenging environment, we were able to collect novel data in a large group of subjects in very high altitudes (6,865 m). We could demonstrate that sojourns at high altitudes trigger distinct behavior of retinal and choroidal blood flow. These data support the hypothesis that an increase in cerebral blood flow is an important contributing factor in the development of AMS, which may result in cerebral edema, leading to the potentially lethal HACE in susceptible individuals.

![Fig. 5](image1.png)  
**Fig. 5.** Changes in choroidal blood flow oxygen transport capacity (ccO₂) and oxygen delivery (cdO₂) at different altitudes expressed as percent of baseline values at ZH1. Error bars denote mean ± 95% confidence interval. *P denotes the significance value in multiple-measures ANOVA.

![Fig. 6](image2.png)  
**Fig. 6.** Correlation of retinal blood flow velocity (BFS-Vel) and cerebral acute mountain sickness (AMS-c) scores; $R^2$ denotes the correlation coefficient. *P denotes significance value of correlation analysis.

### Table 3. Mean choroidal blood flow parameters LDF- Vel, LDF- Vol, ccO₂, and cdO₂ at different altitudes expressed as percent changes compared with ZH1

<table>
<thead>
<tr>
<th></th>
<th>BC (4,497 m)</th>
<th>C1 (5,533 m)</th>
<th>C2 (6,265 m)</th>
<th>BC2 (4,497 m)</th>
<th>ZH2 (490 m)</th>
<th>Significance (ANOVA)</th>
</tr>
</thead>
<tbody>
<tr>
<td>LDF-Vel</td>
<td>8.4±15.5</td>
<td>10.4±18.3</td>
<td>38.0±25.2</td>
<td>41.6±19.9</td>
<td>13.2±14.9</td>
<td>*P &lt; 0.0001</td>
</tr>
<tr>
<td>LDF-Vol</td>
<td>42.1±61.8</td>
<td>29.4±61.9</td>
<td>99.2±145.4</td>
<td>174.5±112.7</td>
<td>2.9±83.0</td>
<td>*P = 0.001</td>
</tr>
<tr>
<td>ccO₂</td>
<td>58.3±77.3</td>
<td>39.2±67.3</td>
<td>159.3±174.7</td>
<td>208.5±212.6</td>
<td>76.6±39.0</td>
<td>*P &lt; 0.0001</td>
</tr>
<tr>
<td>cdO₂</td>
<td>8.1±32.2</td>
<td>-4.1±41.3</td>
<td>78.6±81.6</td>
<td>116.0±129.4</td>
<td>70.8±73.0</td>
<td>ns</td>
</tr>
</tbody>
</table>

Values are means ± SD. LDF-Vel, choroidal blood flow velocity; LDF-Vol, volume of red blood cells in choroidal blood flow; ccO₂, choroidal blood flow oxygen capacity; cdO₂, choroidal blood flow oxygen delivery; LDF, laser-Doppler flowmetry.
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