The Effect of Ocular Warming on Ocular Circulation in Healthy Humans

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Objective: To examine the effect of ocular warming on retinal blood flow (RBF) and subfoveal choroidal blood flow (CBF) in humans.

Methods: Ocular warming was induced in 10 healthy volunteers using an ocular warming lamp for 10 minutes. The ocular surface temperature was measured before and after warming. The RBF in the retinal artery and vein and the CBF in the foveal region were examined with a retinal laser Doppler velocimetry system and a laser Doppler flowmeter, respectively. Ocular blood flow measurements were performed before and 3, 6, and 9 minutes after warming.

Results: The ocular surface temperature significantly increased just after warming and returned to baseline 10 minutes later. Three minutes after warming, the mean±SE RBF significantly increased in the retinal artery (14.2%±3.5%, P=.01) and vein (15.8%±3.6%, P=.006). Six minutes after warming, the RBF returned to baseline in the artery and vein. Three and 6 minutes after warming, the mean±SE CBF significantly decreased 16.6%±4.2% and 24.2%±4.7%, respectively (P=.001 for both). Nine minutes after warming, the measurements returned to baseline.

Conclusions: The RBF increased and the CBF decreased in the foveal region after cessation of ocular warming in healthy young volunteers. The CBF in the foveal region may contribute to maintaining a constant retinal temperature in response to ocular warming.

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Some studies recently have reported that patients with age-related macular degeneration (AMD) have choroidal perfusion anomalies. In addition, a recent study using color Doppler imaging reported that transscleral thermotherapy, which has been used successfully to treat occult subfoveal choroidal neovascular membranes in patients with AMD, could cause alterations in the choroidal circulation. Although those authors speculated that the decrease in choroidal blood flow (CBF) may be caused by occlusion of the choroidal neovascular membrane or the choriocapillaris, leading to increased vascular resistance, the exact mechanism of the alteration of choroidal circulation induced by transscleral thermotherapy is unclear. One possibility is that the increased ocular tissue temperature may be associated with alteration of the choroidal circulation. When the effect of transscleral thermotherapy on ocular blood flow in patients with AMD is considered, it is also necessary to consider how ocular blood flow changes in response to the rise in ocular tissue temperature.

Few studies have examined the relation between ocular temperature and ocular blood flow. In previous investigations of the relation between choroidal circulation and retinal temperature in monkeys and humans, Parver et al suggested that the choroidal circulation maintains a stable temperature in the outer retinal layer. However, they measured the ocular tissue temperature as an index of ocular blood flow. Therefore, it remains to be examined how the ocular blood flow changes in response to ocular warming in humans. We investigated the physiologic response of ocular circulation to ocular warming in healthy humans. For this purpose, we used a laser Doppler velocimetry system and laser Doppler flowmetry to evaluate the retinal blood flow (RBF) and CBF, respectively.

Methods

Subjects

Measurements were obtained from 10 eyes of 10 healthy young male volunteers (mean±SE age, 27.3±1.4 years; range, 21-36 years). The procedure followed the tenets of the Declara-
tion of Helsinki. Written informed consent was obtained from all subjects after the study was fully explained. All subjects had corrected visual acuity better than 20/20, clear media, and no history of ocular or systemic disease or therapy. The temperature in the examination room was maintained within a constant range from 22°C to 24°C. The subjects abstained from drinking coffee and smoking for at least 2 hours before the test. To prepare for the test, each subject rested for 10 to 15 minutes in a quiet room before the test.

MEASUREMENT OF OCULAR SURFACE TEMPERATURE

We measured the temperature changes of the ocular surface using noncontact infrared thermography (LAIRD-S270ME; Nikon, Tokyo, Japan), which is sensitive to temperatures between −40°C and 160°C, with a resolution of 0.1°C. This technique has been described elsewhere using a prototype device.9,10 Briefly, the temperature data were rapidly transformed into a color-coded image that was displayed on the monitor. A region of interest was electronically outlined and the mean temperature computed, as described previously.9 In the present study, we defined the mean value of the bilateral scleral region as the ocular temperature.

RBF MEASUREMENT

In the present study, a retinal laser Doppler velocimetry system (Canon Laser Blood Flowmeter, model CLBF 100; Canon, Tokyo) was used to estimate the RBF. This device has recently been described.11,12 Briefly, it allows noninvasive measurement of the absolute values of the red blood cells flowing in the center line of the vessel, based on the bidirectional laser Doppler velocimetry.13 This device also contains a vessel diameter measurement system and a vessel tracking system. Laser Doppler measurements were obtained from a temporal retinal artery and adjacent vein in 1 eye of each subject. The arteries chosen for measurement had relatively straight segments that were sufficiently distant from adjacent vessels. Measurement sites were generally between the disc margin and the first bifurcation in the super temporal retinal vessels. The location of the measurement site was recorded on a color fundus photograph. As previously described, the RBF in the retinal artery was calculated as RBF = V(area/2), where V is the mean of the center line blood speed during the cardiac cycle, and area is the cross-sectional area of the retinal artery at the laser Doppler measurement site.14 The area was calculated from the arterial diameter, assuming a circular cross section. The factor of 2 in the formula for the blood flow arises from the assumption of Poiseuille flow.15

MEASUREMENT OF CBF IN THE FOVEAL REGION

Determinations of relative foveolar choroidal blood velocity, blood volume, and CBF were obtained using a method based on laser Doppler flowmetry technique.16 Detailed descriptions of the method have been published previously.17 Velocity is expressed in hertz, and volume and flux are expressed in arbitrary units. In a previous study,18 the mean coefficients of variability of choroidal blood volume, choroidal blood velocity, and CBF in 5 healthy subjects were 12.7%, 10.0%, and 6.8%, respectively. Subjects fixated on the probing laser beam to determine the foveolar CBF. During blood flow measurements, proper fixation was ascertained by direct observations of the fovea through the fundus camera. All measurements were performed with the subjects seated in a dark room.

The choroidal circulation was measured continuously in each participant for about 30 seconds. Measurements were performed twice in each subject. All flow variables were then averaged over 2 periods of 30 seconds each. Before the data were analyzed, spikes due to micromovements and blinks were removed, as described previously.19 Data analysis was performed by a masked observer using a computer (NeXT Computer, Redwood City, Calif) with software specifically developed to analyze Doppler signals from ocular tissues.20

STUDY PROTOCOL

A traditional ocular warming lamp (Hand Ophlar; Handaya Co, Tokyo) was used to induce ocular warming. This instrument, which is held in front of the eye, heats the eyelid and ocular tissue with an electric bulb. This device has long been used to treat hordeolum, meibomian gland obstruction, and acute conjunctivitis in Asia.10 The participants’ eyes were warmed for 10 minutes through closed eyelids. The study eyes were chosen randomly. Care was taken not to press the eye during warming. The ocular temperature was measured before warming, immediately after, and 10 minutes after cessation of the warming. After ocular warming, the eyes were examined at the slitlamp, and the mean arterial blood pressure and heart rate were estimated by electronic sphygmomanometer (model EP-88Si; Colin, Tokyo) at the same time the ocular temperature was measured.

The procedure was performed in a masked fashion. The ocular circulation was evaluated before ocular warming and 3, 6, and 9 minutes after cessation of ocular warming. Before ocular warming, 5 measurements of each variable were obtained every minute, and the mean value was defined as the baseline value. Measurements of variables were performed for 30 seconds before each time point after cessation of warming. Ocular warming was performed twice for all subjects on 2 separate days, because the RBF and CBF were measured on another day in the same manner and at the same time of day. The measurement of RBF or CBF was performed randomly in each subject.

STATISTICAL ANALYSIS

All values are expressed as mean ± SE. For statistical analysis, we used the repeated measures analysis of variance followed by post hoc comparison with Dunnett procedure. P < .05 was considered statistically significant.

RESULTS

SYSTEMIC AND OCULAR VARIABLES AT BASELINE

Systemic circulatory variables and intraocular pressure (IOP) on the first and second trial days at baseline are shown in Table 1 and Table 2. There were no differences between the 2 trial days in any variables.
Changes in Ocular Surface Temperature

Just after ocular warming, the ocular temperature significantly increased from 34.5°C ± 0.2°C to 37.8°C ± 0.3°C in the first trial and from 34.6°C ± 0.3°C to 37.9°C ± 0.2°C in the second trial (P < .001) (Table 3). The ocular temperature then returned to the prewarming level 10 minutes after cessation of warming. In addition, no significant changes in systolic blood pressure, diastolic blood pressure, mean arterial blood pressure, and heart rate were induced by ocular warming.

Changes in RBF

Three minutes after cessation of ocular warming, the RBF in the retinal artery and vein significantly increased by 14.2% ± 3.5% (P = .01) and 15.8% ± 3.6% (P = .006), respectively, compared with baseline (Figure 1). The transient increase in RBF then returned to the prewarming level 6 and 9 minutes, respectively, after warming in the artery and vein. In the retinal artery, although the vessel diameter did not significantly change in response to ocular warming, 3 minutes after cessation of ocular warming the blood velocity significantly increased by 9.3% ± 1.9% by repeated-measures analysis of variance (P = .03). In the retinal vein, the vessel diameter significantly increased by 4.8% ± 1.7% (P = .004) and 4.1% ± 1.7% (P = .01) over baseline 3 and 6 minutes, respectively, after cessation of ocular warming, whereas the change in blood velocity was not significant.

Changes in CBF in the Foveal Region

In contrast to the change in retinal circulation, the mean CBF for the group significantly decreased by 16.6% ± 4.2% and 24.2% ± 4.7% (P = .001 for both), 3 and 6 minutes, respectively, after warming (Figure 2) by repeated-measures analysis of variance followed by post hoc comparison with Dunnett procedure. Nine minutes after warming, the CBF returned to the baseline value. Although the mean choroidal velocity for the group did not significantly change after ocular warming, 6 minutes after warming the choroidal volume significantly decreased by 23.7% ± 4.8% (P = .002), suggesting that the decrease in CBF was mainly caused by the decrease in choroidal volume.

In the present study, we report for the first time (to our knowledge) increases in RBF and decreases in CBF in the foveal region after cessation of ocular warming in healthy young volunteers.

The choroidal circulation is regulated to prevent retinal damage in response to ocular hyperthermia, which can affect the transport of substances within the eye, produce coagulation of intracellular proteins, cause retinal edema, and break down the blood retinal barrier. This function of the choroidal circulation is especially true for the macular region. Parver et al suggested that the CBF acts as a heat source when the temperature of the choroid is higher than the systemic temperature. In the present study, the CBF acted as a heat source, as the temperature of the choroid was higher than the systemic temperature as a result of ocular warming (Table 1). In addition, those authors reported that a decrease in CBF produced by increasing IOP reduced the ocular tissue temperature. Therefore, our results that the CBF decreased in response to ocular warming suggest that the CBF in the foveal region may contribute to maintaining the temperature of the retinal tissue in response to ocular warming. Our finding that the decrease in CBF was mainly caused by the decrease in choroidal blood volume (Figure 1) suggests that the choroidal vasculature, mainly choriocapillaris, may constrict in response to the increase in ocular temperature. These changes in choroidal circulation observed in the present study might be considered thermal autoregulation of the CBF.

In normal conditions, the retinal-choroidal tissue temperature is regulated to the lower level by the cooler anterior segment. In our experiment, the temperature of the anterior segment significantly increased by ocular warming (Table 3). In such a situation, although we could not measure the tissue temperature of the posterior segment, it is reasonable to believe that the ocular warming increased the retinal-choroidal temperature.

Parver et al reported that light-induced ocular warming caused the increased CBF in monkeys, indicating the ability of the choroidal circulation to control the retinal thermal environment. Our finding that the CBF in the foveal region decreased in response to ocular warming seems inconsistent with their results. One explanation may be the difference between the methods used to increase the ocular temperature. Light-induced warming, used in their investigation, would mainly increase the temperature at the photoreceptor level, whereas the method we used in the

**Table 2. Retinal and Choroidal Circulation at Baseline**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Retinal artery</th>
<th>Retinal vein</th>
<th>Choroid</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diameter, µm</td>
<td>112.6 ± 5.0</td>
<td>139.0 ± 4.1</td>
<td>140.2 ± 4.2</td>
</tr>
<tr>
<td>Velocity, mm/s</td>
<td>31.5 ± 1.7</td>
<td>21.6 ± 1.6</td>
<td>405.2 ± 24.2</td>
</tr>
<tr>
<td>Blood flow, µL/min</td>
<td>9.5 ± 0.8</td>
<td>9.7 ± 0.7</td>
<td>0.61 ± 0.06</td>
</tr>
<tr>
<td>Blood flow, AU</td>
<td>18.2 ± 1.0</td>
<td>18.2 ± 1.0</td>
<td>18.2 ± 1.0</td>
</tr>
</tbody>
</table>

**Table 3. Changes in Ocular Temperature**

<table>
<thead>
<tr>
<th>Trial</th>
<th>Temperature, °C</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Baseline 0 min 10 min</td>
</tr>
<tr>
<td>First</td>
<td>34.5 ± 0.2 37.8 ± 0.3† 34.8 ± 0.2</td>
</tr>
<tr>
<td>Second</td>
<td>34.6 ± 0.3 37.9 ± 0.2† 34.8 ± 0.2</td>
</tr>
</tbody>
</table>

Abbreviation: AU, arbitrary unit.
*Data are expressed as mean ± SE.
†P < .001 compared with baseline.
The present study warmed the entire eye, probably including the choroid and sclera (Table 3). It is likely that the CBF acts as a heat source in the former but as a heat sink in the latter. Therefore, we speculate that the CBF in the foveal region, which acted as a heat source in the present study, decreased to maintain the retinal temperature. Another possible explanation is that the CBF may increase during the warming phase and then decrease after cessation of warming. We could not examine this because it is not possible to measure the CBF during the warming phase.

In contrast to the choroidal circulation, the RBF increased in response to ocular warming in the artery and vein (Figure 2). To our knowledge, no study has examined how retinal vessels react to an increase in ocular temperature. The underlying mechanisms causing increased RBF in response to ocular warming are incompletely understood. However, based on the present data that velocity significantly increased in the artery but that the vessel diameter increased in the vein, dilation of the retinal vessel produced by ocular warming might occur downstream of the measured retinal artery, especially in the mural cells. Because the downstream arterioles possess the metabolic mechanism of microvascular regulation, we speculate that the change in RBF may be associated with the metabolic change induced by ocular warming. Moreover, a possible explanation of the differences between the retinal and choroidal circulation in response to ocular warming may be the differences in neurologic control, which affects choroidal circulation but not retinal circulation.

Recently, it has been reported that patients with AMD have impaired CBF. Grunwald et al reported that the CBF in the foveal region in patients with AMD was 37% lower than in control subjects, using a laser Doppler flowmeter, which is the same technique used in the present study. In addition, with color Doppler imaging, it was recently reported that transpupillary thermotherapy could lead to alterations in choroidal circulation. These findings indicate that the change in ocular blood flow and the response to increased temperature may play some role in the development and progression of AMD. Although it may be difficult to measure ocular blood flow using laser Doppler velocimetry or laser Doppler flowmetry in older subjects, because these methods require good fixation, we believe that the examination of ocular blood flow in response to ocular warming may be a useful test of ocular vascular responsiveness in older patients with macular disease, especially early-stage AMD.
of the macula should prompt further study of the role of temperature in macular disease. Additional studies in older subjects are needed to elucidate the possibility that the response of the CBF to ocular warming may be an effective marker of macular disease, especially AMD.

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REFERENCES