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Research article

Effects of Heat Stress on Ocular Blood Flow during Exhaustive Exercise

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Abstract
The hypothesis that heat stress reduces the ocular blood flow response to exhaustive exercise was tested by measuring ocular blood flow, blood pressure, and end-tidal carbon dioxide partial pressure ($P_{ET}CO_2$) in 12 healthy males while they performed cycle ergometer exercise at 75% of the maximal heart rate at ambient temperatures of 20ºC (control condition) and 35ºC (heat condition), until exhaustion. The blood flows in the retinal and choroidal vasculature (RCV), the superior temporal retinal arteriole (STRA) and the superior nasal retinal arteriole (SNRA) were recorded at rest and at 6 and 16 min after the start of exercise period and at exhaustion [after 16 ± 2 min (mean ± SE) and 24 ± 3 min of exercise in the heat and control condition, respectively]. The mean arterial pressure at exhaustion was significantly lower in the heat condition than in the control condition at both 16 min and exhaustion. The degree of $P_{ET}CO_2$ reduction did not differ significantly between the two thermal conditions at either 16 min or exhaustion. The blood flow velocity in the RCV significantly increased from the resting baseline value at 6 min in both thermal conditions (32 ± 6% and 25 ± 5% at 20ºC and 35ºC, respectively). However, at 16 min the increase in RCV blood flow velocity had returned to the resting baseline level only in the heat condition. At exhaustion, the blood flows in the STRA and SNRA had decreased significantly from the resting baseline value in the heat condition (STRA: –19 ± 5% and SNRA: –30 ± 6%), and SNRA blood flow was lower than that in the control condition (–14 ± 6% vs –30 ± 6% at 20ºC and 35ºC, respectively), despite the finding that both thermal conditions induced the same reductions in $P_{ET}CO_2$ and vascular conductance. These findings suggested that the heat condition decreases or suppresses ocular blood flow via attenuation of pressor response during exhaustive exercise.

Key words: Hyperthermia, exercise, healthy subjects, retinal circulation, choroidal circulation, laser-speckle flowgraphy.

Introduction

The ocular circulation consists of the choroidal and retinal vasculature, adequate blood flow to which is essential for the maintenance of visual functions. In a previous study we found that a change in retinal and choroidal blood flows induced by manipulating ventilation is associated with a change in the visual acuity (Hayashi et al., 2011a). Concomitant increases in both retinal blood flow and contrast sensitivity have been noted in healthy subjects after the administration of sildenafil (Sponsel et al., 2000).

It has been demonstrated that submaximal exercise increases the choroidal blood flow velocity relative to the increase in mean arterial pressure (MAP) (Hayashi et al., 2011b; Ikemura et al., 2011). However, the increase in choroidal blood flow velocity was suppressed, and retinal blood flow was decreased by the hyperventilation-induced decrease in the arterial partial pressure of carbon dioxide ($PaCO_2$) during exhaustive exercise (Ikemura and Hayashi, 2012b). This was explained by a high sensitivity of both ocular blood vessels to variations in the $PaCO_2$ (Delaey and Van de Voorde, 2000; Geiser et al., 2000; Harris et al., 1995; Sponsel et al., 1992).

Heat stress could also directly influence the ocular circulation via physiological changes such as to MAP, sympathetic nerve activity, cardiac output and $PaCO_2$ (Cui et al., 2010; Keller et al., 2006; Roddie et al., 1956; Rowell et al., 1969). However, the retinal and choroidal blood flow responses to exhaustive exercise under heat-stress have yet to be determined. Heat stress could decrease the retinal and choroidal blood flow responses to exercise by inducing hyperventilation, and a consequent reduction in $PaCO_2$ (Rowell et al., 1969). A combination of exhaustive exercise and heat stress could result in additional reduction to the $PaCO_2$. This raises the possibility that the greater reduction in $PaCO_2$ could strong vasoconstriction in both retinal and choroidal vasculatures since both ocular blood vessels are sensitive to variations in $PaCO_2$. Thus, we hypothesized that exhaustive exercise under heat condition induces further decreases in both ocular blood flows.

A pressor response, i.e., increase in blood pressure attenuated by heat stress can be another factor decreasing retinal and choroidal blood flows further during exhaustive exercise under the heat condition. Previous studies have reported that heat stress attenuates the pressor response induced by an exercise (Nybo et al., 2002). The pressor response could be attenuated by heat stress during exhaustive exercise. Changes in the MAP affected the choroidal circulation (Hayashi et al., 2011b; Ikemura et al., 2011), and although the retinal circulation is affected less by MAP fluctuations due to the existence of autoregulation, both ocular blood flows may be influenced by attenuation of the pressor response during exhaustive exercise in the presence of heat stress. Ikemura et al. (2012b) demonstrated that hypocapnia decreases the blood flow in both ocular blood flows during exhaustive exercise, in spite of retinal autoregulation. It is therefore possible that attenuation of the pressor response by heat stress induces a further reduction in retinal and choroidal blood flows during exhaustive exercise under the heat condition.

The purpose of the present study was to test the hypothesis that the greater reduction in $PaCO_2$ and/or attenuation of the pressor response, which induced by

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heat stress decrease ocular blood flow during exhaustive exercise. Toward this end, the ocular blood flow response to an exhaustive exercise was assessed under both control and heat conditions.

Methods

Subjects

Twelve healthy males [age, 25 ± 1 years (mean ± SD); height, 1.72 ± 0.02 m; body mass, 67 ± 3 kg] participated in this study. All of the subjects were free of any known autonomic dysfunction and cardiovascular and ocular disease, and were not taking any medications. The Ethics Committee of the Institution of Health Science, Kyushu University, Japan, approved the experimental protocol, and all subjects provided written informed consent to participate prior to the commencement of the study. All of the protocols used conformed to the Declaration of Helsinki. Each subject visited the laboratory before taking part in the experiments for familiarization with the techniques and procedures of the protocol.

Protocol

The subjects arrived at the laboratory after having abstained from caffeinated beverages and strenuous exercise for 6 h, and from eating for at least 2 h. The individual target work rate at 75% of their maximal heart rate (153 ± 7 W) was determined, using an incremental cycle ergometer test in the control condition (20ºC) at least 7 days prior to the experiment. On two separate experimental days, the subjects performed the exercise on a cycle ergometer until exhaustion in control or heat (35ºC) conditions. The order of the thermal condition was randomized. After a 3-min resting period in both conditions, the subjects began cycling at a half of the target work rate. At 1 min after the exercise onset, the exercise intensity was increased to the target work rate. The exercise was continued until the subjects could no longer maintain a pedaling cadence of 60 rpm, or could no longer fix their body trunk to allow acquisition of the ocular blood flow data. During ocular blood flow measurement, the subjects were permitted to some bulr their body trunk, since this did not affect the blood flow analysis. The analyzer software is able to identify the blood vessels to estimate the ocular blood flow at the same target areas each time by identifying bifurcations of retinal arteries as markers. This exercise was followed by a resting recovery period.

The blood pressure and heart rate (HR) were recorded continuously throughout the trial. The ocular blood flow velocity, external ear temperature and respiratory variables were obtained every 3 min during the resting, exercise, and recovery periods. Subjects were asked to open their right eye without blinking for 4 s during the image recording for ocular blood flow measurement. Three laser-speckle images were obtained for the right eye. Subjects were asked to keep their face motionless in front of the apparatus for laser-speckle flowgraphy (LSFG) apparatus while laser-speckle images were obtained. Subjects who normally wore glasses or contact lenses removed them before the experiment. The subjects did not receive any drugs, such as for mydriasis.

Measurements

The beat-by-beat blood pressure was monitored with an automatic sphygmomanometer attached to the left middle finger (Finometer, Finapres Medical Systems, Amsterdam, The Netherlands). The ECG was recorded continuously using a bioelectrical amplifier (MEG2100, Nihon-Kohden, Tokyo, Japan). The external ear temperature was obtained for the right ear every 3 times during the resting, exercise and recovery periods, and the values were averaged for each period (infrared thermometer, Omron, Kyoto, Japan). The minute-by-minute HR and MAP were calculated from the bioelectrical amplifier and blood pressure recordings. The averaged data for the last 1 minute of each period was used for analysis.

The subjects breathed through a mouthpiece for 1 min during each measurement period. This mouthpiece was connected to a hot-wire flowmeter (RM-300, Minato Medical Sciences, Fukuoka, Japan) for the measurement of tidal volume (V_T), end-tidal partial pressure of O_2 ($P_{E\text{-}T}O_2$), and end-tidal partial pressure of CO_2 ($P_{ET}CO_2$). The flowmeter was calibrated using a 2-l syringe. Samples of respired gas (1 $ml \cdot s^{-1}$) were regularly withdrawn from the mouthpiece and analyzed for O_2 and CO_2 with a mass spectrometer (WSMR-1400, Westron, Chiba, Japan). The mass spectrometer was calibrated with fresh air and precision gases. $PaCO_2$ was estimated from V_T and $P_{ET}CO_2$ (Jones et al., 1979). The data obtained during the 1-min collection period were averaged.

Laser-speckle images were obtained using an LSFG system (SoftCare, Fukuoka, Japan) as described for our previous studies (e.g., Ikemura et al., 2011). The LSFG measurements were repeated three times in each measurement period (i.e., resting, exercise and recovery), and averaged values for each period were used for analysis. The LSFG can noninvasively assess ocular blood flow (Sugiyama et al., 2010). This methodology provides similar results to other methodologies such as laser Doppler flowmetry (Riva et al., 2010) and retinal vessel analysis (Garhöfer et al., 2010). The LSFG measurements are highly reproducible in both normal and glaucoma subjects (Aizawa et al., 2011). Ocular blood velocity data were obtained from retinal and choroidal vasculature (RCV), superior temporal retinal arteriole (STRA), and superior nasal retinal arteriole (SNRA). The RCV covered a field of observation between the optic nerve head and the macula. This field was fixed in each subject. The RCV blood flow velocity data reflect not only the choroidal circulation but also the retinal circulation, since the LSFG apparatus cannot distinguish these two signals. Nevertheless, the blood flow velocity determined in the RCV reflects mainly the choroidal circulation, since choroidal blood flow occupies 85% of the total ocular blood flow to the retina (Alm and Bill, 1973). The blood flows in the STRA and SNRA were calculated from the integral of a cross-sectional map of blood velocity within the selected arteriole. The STRA and SNRA blood flow data reflect the retinal circulation, since these arterioles supply blood to the retina (Netter, 2006). The RCV blood flow data were not calculated from the RCV blood velocity data, since particular blood vessels cannot be found by LSFG in this area. However, the velocity data can reflect blood flow, as

pointed out by Ikemura et al. (2011). The RCV data were obtained from identical areas within each subject. If it is assumed that there is no vasomotion in the area, the summed velocity data will be equal to the blood flow. In addition, choroidal blood flow was found to be proportional to choroidal blood flow velocity in both in vivo and in vitro studies (Sugiyama et al., 2010; Tamaki et al., 1994). The retinal artery and vein are easily identified. In the present study, the artery was identified based on the following features: (1) the vessel diameter is smaller for the retinal artery than the vein, and (2) the cross-sectional profile of the blood flow velocity in artery is steeper in the artery than that in the vein. The mean blood flow velocities or blood flows were obtained for the RCV, STRA, and SNRA. The conductance index (CI) of each ocular vessel was calculated by dividing the ocular blood flow by the MAP.

Data analysis

Data were expressed as mean ± SE values. Ocular blood-flow measurements were used for analysis only when clear laser-speckle imaging data were obtained over at least two consecutive heart beats. The interindividual coefficient of variation of the LSFG data in our laboratory was 3–5 %. The data were obtained at rest, at 6 min, 16 min (i.e., exhaustion in the heat condition) and 24 min after the start of the exercise period (i.e., exhaustion in the control condition) and after 6–9 min of recovery. The effects of time and trial were examined by repeated-measures ANOVA. When a significant F value was detected, this was analyzed further against the baseline value using Dunnett's post-hoc test. The effect of thermal conditions on the variables was compared using paired t tests. The degree of autoregulation in vessels was assessed by calculating the ratio of the relative change in ocular blood flow to the change in MAP, in accordance with previous studies (Lucas et al., 2010; Panerai, 2008). The level of statistical significance was set at $p < 0.05$. All of the statistical analyses were performed using SAS (version 8.2, SAS Institute, Cary, NC, USA) at the Computing and Communications Center, Kyushu University, Japan.

Results

Exercise significantly increased the MAP, external ear temperature, and HR in both the control and heat conditions (Table 1).

Systemic changes

The duration to exhaustion was significantly shorter under the heat condition than the control condition (16 ± 2 vs 24 ± 3 min, respectively), and the MAP was significantly lower and external ear temperature was significantly higher in the heat condition than in the control condition at 16 min of exercise and at exhaustion. $PaCO_2$ was unchanged at 6 min after the onset of exercise, but significantly decreased from the resting baseline level at 16 and 24 min of exercise, and during the recovery period in both conditions. The degree of $PaCO_2$ reduction did not differ between the two thermal conditions at exhaustion (33 ± 1 vs 34 ± 1 mmHg). $P_{ET}O_2$ was significantly increased at exhaustion and during the recovery period in both conditions.

Changes in the ocular circulation

The RCV blood flow velocity has increased significantly from the resting baseline at 6 min of exercise in both thermal conditions, whereas the STRA and SNRA blood flows had not changed significantly in either condition at this time point (Figure 1 and 2).

At 16 min of exercise (i.e., the mean time to exhaustion in the heat condition), the RCV blood flow velocity was higher than the baseline in the control condition, but had returned to the baseline level in the heat condition. The STRA and SNRA blood flows decreased significantly from the resting baseline value only in the heat condition. The decreases in RCV blood flow velocity and in the STRA and SNRA blood flows were greater in the heat condition than in the control condition at 16 min after exercise onset. However, the CI values for the RCV, STRA and SNRA did not differ significantly between the two thermal conditions.

The initial increase in RCV blood flow velocity disappeared after 24 min of exercise in the control

Table 1. HR, MAP, $P_{ET}CO_2$, $P_{ET}O_2$, $PaCO_2$, and external ear temperature during rest, exercise and recovery periods. Values are means (±SE).

		Exercise period				
		Rest	6 min	16±2 min	24±3 min	recovery
Control condition	HR (bpm)	66 (3)	140 (5)*	165 (5)*	168 (5)*	106 (6)*
	MAP (mmHg)	96 (6)	128 (4)*	125 (5)*	118 (5)* ‡	89 (4)
	$P_{ET}CO_2$ (mmHg)	38 (1)	45 (2)*	38 (1)	36 (1)*	33 (1)*
	$P_{ET}O_2$ (mmHg)	108 (2)	109 (2)	113 (2)*	14 (2)*	117 (1)*
	$PaCO_2$(mmHg)	39 (1)	42 (2)	36 (1)*	33 (1)*	31 (1)*
	External ear temperature (°C)	35.9 (.2)	36.2 (.0)	36.7 (.2)*	36.8 (.3)*	36.6 (.2)*
Heat condition	HR (bpm)	75 (3)†	152 (4)*	170 (4)*	-	123 (7)*†
	MAP (mmHg)	89 (3)	118 (5)*	107 (6)*†	-	82 (3)
	$P_{ET}CO_2$ (mmHg)	37 (1)	43 (1)*	36 (1)	-	32 (1)*
	$P_{ET}O_2$ (mmHg)	108 (2)	110 (2)	115 (2)*	-	116 (2)*
	$PaCO_2$(mmHg)	37 (1)	40 (1)	34 (1)*	-	32 (1)*
	External ear temperature (°C)	36.5 (.2)†	36.8 (.1)	37.5 (.1)*†	-	37.7 (.1) *†

HR, heart rate; MAP, mean arterial pressure; $P_{ET}CO_2$, end-tidal partial pressure of CO_2; $P_{ET}O_2$, end-tidal partial pressure of O_2; $PaCO_2$, arterial partial pressure of CO_2. * $p < 0.05$ vs. resting baseline. † $p < 0.05$ control condition vs heat condition in the same period. ‡ $p < 0.05$ control condition vs heat condition at exhaustion (16 min in heat condition vs 24 min in control condition).

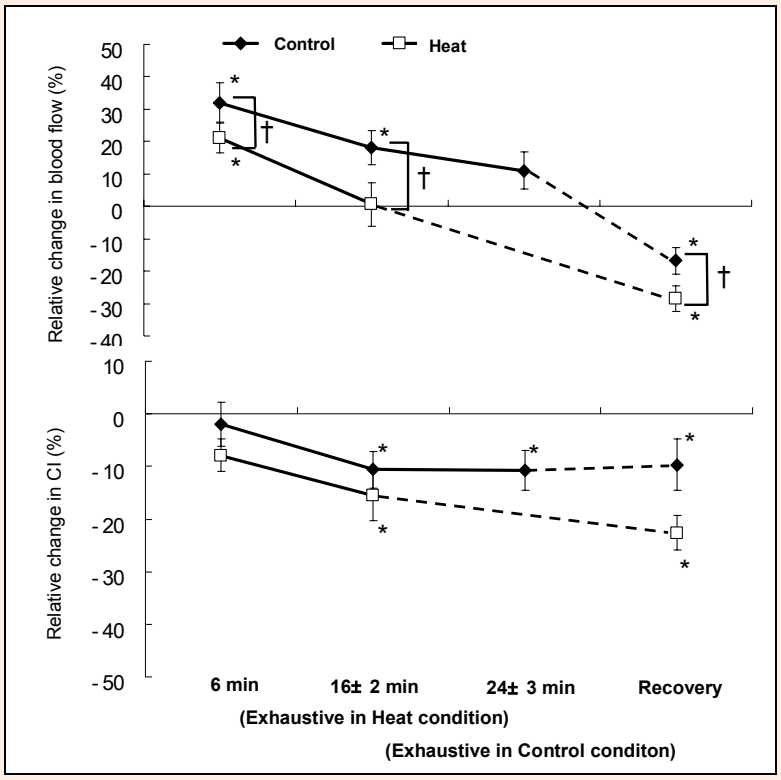

Figure 1. Relative changes in blood flow (upper panel) and CI (lower panel) in the RCV. CI, conductance index; RCV, retinal and choroidal vessels (index of choroidal circulation). Values are means±SE. * $p < 0.05$ vs resting baseline; † $p < 0.05$ between control condition and heat conditions.

condition, and the STRA blood flow had decreased significantly from the baseline.

Comparison of data at exhaustion (i.e., 16 min in the heat condition vs 24 min in the control condition), revealed that the SNRA blood flow differed significantly between the two conditions, whereas the CI in the SNRA did not.

At recovery, the blood flow velocity in the RCV and blood flows in the STRA and SNRA were significantly lower than at baseline in both thermal conditions. Decreases in all ocular blood flows were greater in the heat condition than in the control condition. The CI values for in all ocular vessels did not differ significantly between the two thermal conditions.

Relationship between ocular blood flow and MAP

The ratio of the relative change in blood flow to that in MAP during exercise and recovery are shown in Figure 3. In the heat condition, the ratio of change in RCV blood flow velocity to that in MAP was greater than that for SNRA during exercise ($p < 0.05$). The change in RCV blood flow velocity was greater than for the other vessels during exercise in the control condition. There was no significant difference between the two thermal conditions during exercise and recovery.

Discussion

The main finding of the present study was that decreases in retinal blood flow (in the STRA and SNRA) were greater and the choroidal blood flow velocity (RCV) was lower during exercise under the heat conditions than in the control condition. This further reduction in retinal blood flow and suppression of choroidal blood flow in the heat condition can be explained by attenuation of the pressor response. The decrease was not due to vasoconstriction of the ocular vessels, since the CI did not differ between the two conditions. Moreover it was not due to the influence of $PaCO_2$, since this parameter did no differ between the two thermal conditions.

The blood flow velocity in the RCV increased from the resting baseline at 6 min of exercise in both conditions, whereas blood flows in the STRA and SNRA did not change. These results are consistent with our previous studies finding that the choroidal blood flow increases during submaximal exercise whereas the retinal blood flow remains relatively constant (Hayashi et al., 2011b; Ikemura et al., 2011; Ikemura and Hayashi, 2012b). The different responses in the choroidal and retinal circulations could have functional relevance, as we have suggested previously (Ikemura and Hayashi, 2012b). Overperfusion could obstruct the light, and is thus not preferable in the retina vessels, since retinal vessels are located superficial to the photoreceptors (Bill, 1975; Delaey and van de Voorde, 2000; Netter, 2006). In contrast, the choroidal vessels are located under the photoreceptors, and so increases in flow could be considered advantageous (Lovasik and Kergoat, 2004).

The difference between the retinal and choroidal circulatory responses can be explained by autoregulation, as we have already suggested. It has been reported that autoregulation occurs in the retinal vessels but not in the

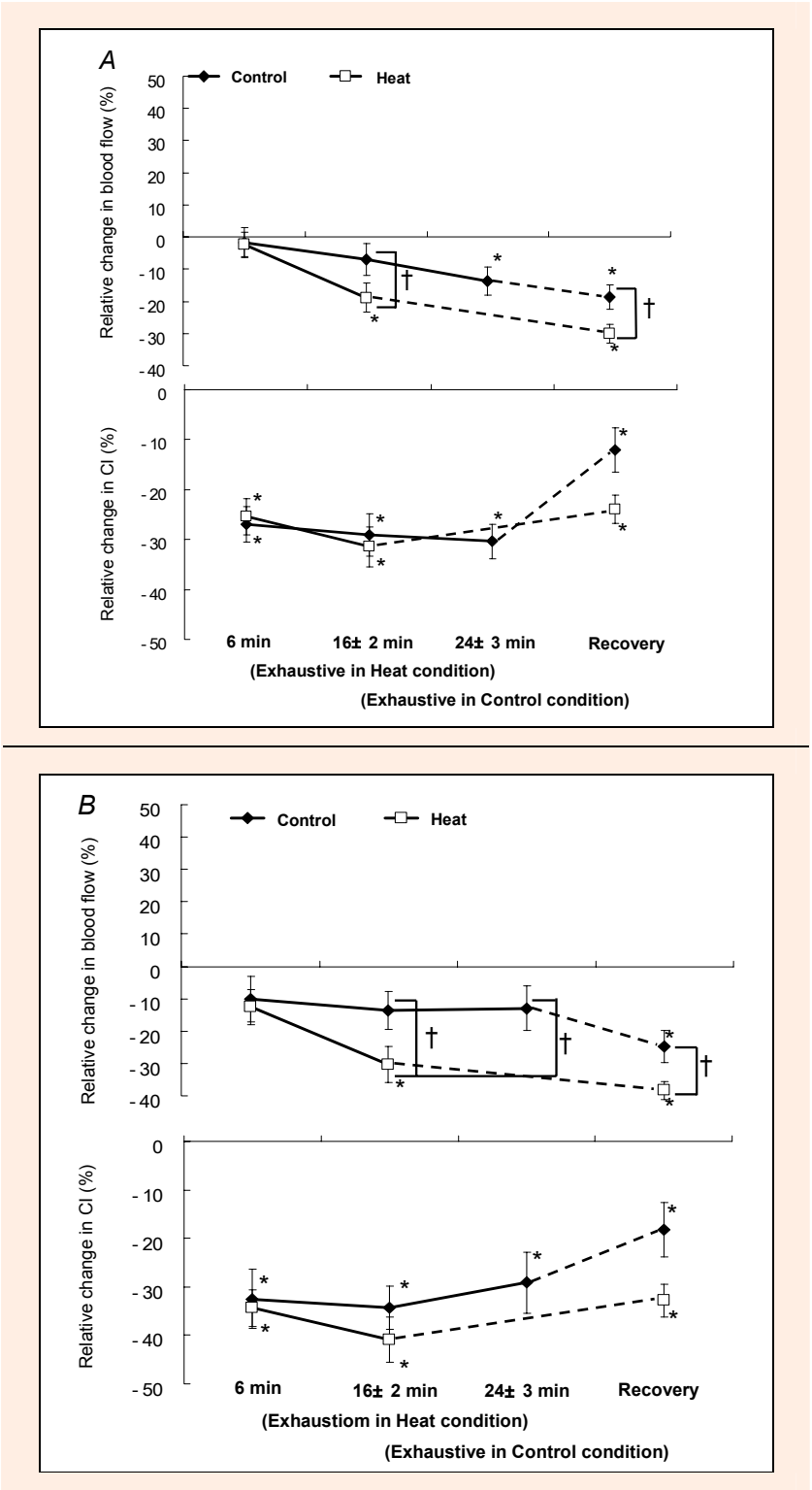

Figure 2. Relative changes in blood flow and CI in the STRA (A) and SNRA (B). Values are means±SE. STRA, superior temporal retinal artery; SNRA, superior nasal retinal artery. *$p < 0.05$ vs resting baseline; † $p < 0.05$ between control condition and heat conditions.

choroidal vessels in response to relatively long MAP fluctuations (Iester et al., 2007; Okuno et al., 2006). In accordance with previous studies (Lucas et al., 2010; Panerai, 2008), the ratio of the relative change in blood flow to the change in MAP was calculated in this study. This ratio was greater for the RCV than for either the STRA or SNRA after 6 min of exercise in both thermal conditions (see Fig. 3), implying that autoregulation maintained a more stable flow in the retinal circulation than in the choroidal circulation. Thus, the RCV blood flow velocity was increased mainly by the pressor response, as indicated by the lack of change in CI at 6 min.

At 16 min of exercise (i.e., the mean exhaustion time in the heat condition), the blood flows in the STRA

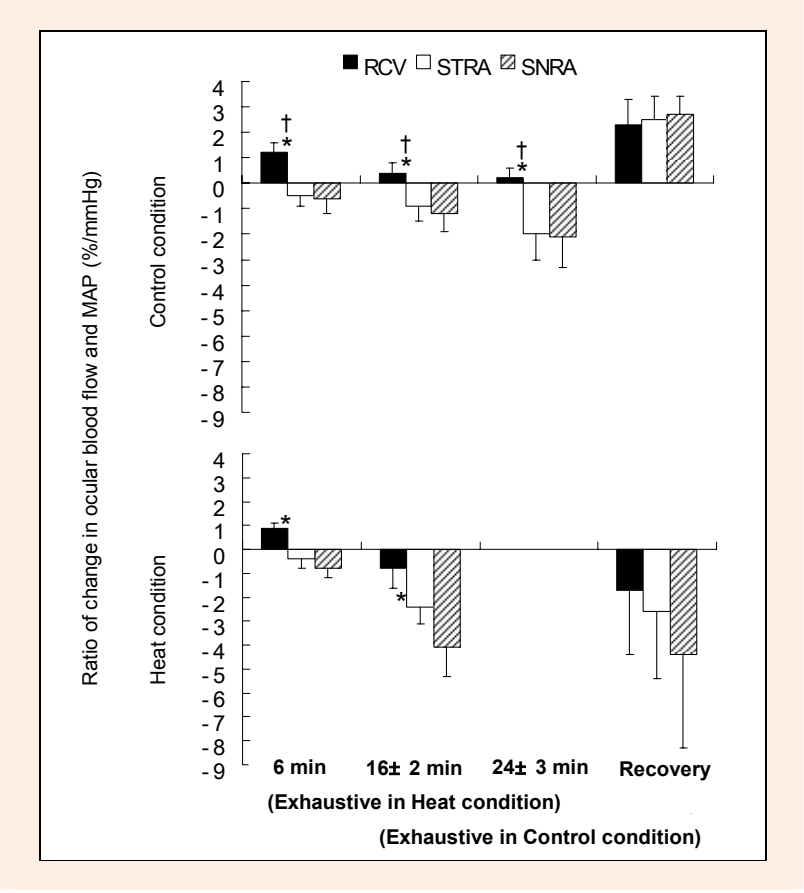

Figure 3. Ratio of relative changes in ocular blood flow to that in mean arterial pressure (MAP) during exercise and at recovery. Values are means±SE. *p < 0.05 vs SNRA; † p < 0.05 vs STRA.

and SNRA decreased, and the initial increase in RCV blood flow velocity was suppressed, but only in the heat condition. All ocular blood flow variables were lower in the heat condition than in the control condition. Heat stress may have been responsible for this differential response, since comparison of both thermal conditions at exhaustion (16 min in the heat condition vs 24 min in the control condition) revealed that the SNRA blood flow was still lower in the heat condition than in the control condition.

It can be assumed that the effect of $PaCO_2$ cannot explain for this difference, since the two conditions used in the present study induced comparable changes in $PaCO_2$ (–9 ± 3% vs –7 ± 3% from the baseline). This assumption is based the findings of our previous study, which suggested hypocapnia as the main factor underlying the decrease in both ocular blood flows during exhaustive exercise (Ikemura and Hayashi, 2012b). In a previous study of hypocapnia during exercise, the exercise duration was 50 min (Rasmusen et al., 2006), while it was 16 min in the heat condition in the present study. The time to exhaustion was much shorter in the present study; the heat stress may have induced an earlier exhaustive state than would have been caused by an additional reduction in $PaCO_2$. The effect of $PaCO_2$ was not tested in the present study.

Further decreasing or suppressing the ocular flood flows in the heat condition in this study can be explained by attenuation of pressor response. In the present study, the MAP was lower in the heat condition than in the control condition at exhaustion, in accordance with previous studies (Cui et al., 2010; Davis and Crandall, 2010; Nybo et al., 2002). If the vascular tone did not differ between the two thermal conditions, it is possible that attenuated ocular perfusion pressure (OPP) induced further reduction in ocular blood flow. The CI of all ocular blood vessels in this study did not differ between the two thermal conditions, indicating no difference in ocular vasomotor tone. Thus, the lower OPP in heat condition should explain the lower blood flow response.

Heat stress did not induce additional vasoconstriction during the heat condition with exhaustive exercise, although in a preliminary study we found that retinal and choroidal blood flows decreased concomitantly with decreases in CI during passive heat stress at rest (Ikemura and Hayashi, 2012a). This is probably due to a ceiling effect. In our previous study, a substantial lowering of the $P_{ET}CO_2$ (i.e., 50% from baseline) decreased the CI in the ocular blood vessels by 10–20% (Hayashi et al., 2011a). In the present study, the CI had already decreased by 10–35% during exhaustive exercise even in the control condition. Exhaustive exercise may have induced a similar or greater degree of vasoconstriction compared with the severe hypocapnia condition, also compared to other stimuli (Delaey and Van de Voorde, 2000; Geiser et al., 2000). Therefore, it is reasonable to suggest that the exhaustive exercise itself induced a nearly maximal vasoconstriction. Consequently, it can be concluded that the

heat condition used in the present study did not impose further vasoconstriction during exhaustive exercise with heat stress.

The change in ocular blood flow observed in the present study cannot be explained by a change in intraocular pressure (IOP). A change in IOP affects the OPP since this is calculated by subtracting IOP from MAP. In previous studies, the IOP decreased by approximately 2–5 mmHg after dynamic exercise (Iester et al., 2007; Risner et al., 2009). Such decreases in IOP could have increased the OPP. The IOP was not recorded in the present study; however, any change in IOP is likely to have been substantially smaller than the change in MAP. Therefore, even if the IOP had decreased, the consequent increase in OPP would have been minor.

Conclusion

In conclusion, the results of this study suggest that the decreases or suppresses in retinal and choroidal blood flows during exhaustive exercise are greater in the heat condition than in the control condition. This can be explained by attenuation of pressor response, since these differences were observed in association with comparable changes in $PaCO_2$ and CI in the two thermal conditions.

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Key points

- The ocular (retinal and choroidal) blood flow response to exhaustive exercise with heat stress is unknown.
- We hypothesized that the heat stress decreases ocular blood flow response to exhaustive exercise, since cerebral flow, which is regulated similarly to ocular flow, was reported to decrease during heat stress.
- To test this hypothesis, ocular blood flow was measured during exhaustive exercise at 20ºC (control condition) and 35ºC (heat condition).
- At exhaustion in the heat condition, the ocular flow response was suppressed or decreased with an attenuated pressor response.
- It is suggested that the heat condition decreases or suppresses the ocular blood flow to exhaustive exercise via attenuation of pressor response.

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