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J. Gonzalez-Alonso, M. K. Dalsgaard, T. Osada, S. Volianitis, E. A. Dawson, C. C. Yoshiga and N. H. Secher
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Effects of hyperthermia on cerebral blood flow and metabolism during prolonged exercise in humans

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Nybo, Lars, Kirsten Møller, Stefanos Volianitis, Bodil Nielsen, and Niels H. Secher. Effects of hyperthermia on cerebral blood flow and metabolism during prolonged exercise in humans. *J Appl Physiol* 93: 58–64, 2002. First published March 1, 2002; 10.1152/jappphysiol.00049.2002.—The development of hyperthermia during prolonged exercise in humans is associated with various changes in the brain, but it is not known whether the cerebral metabolism or the global cerebral blood flow (gCBF) is affected. Eight endurance-trained subjects completed two exercise bouts on a cycle ergometer. The gCBF and cerebral metabolic rates of oxygen, glucose, and lactate were determined with the Kety-Schmidt technique after 15 min of exercise when core temperature was similar across trials, and at the end of exercise, either when subjects remained normothermic (core temperature = 37.9°C; control) or when severe hyperthermia had developed (core temperature = 39.5°C; hyperthermia). The gCBF was similar after 15 min in the two trials, and it remained stable throughout control. In contrast, during hyperthermia gCBF decreased by 18% and was therefore lower in hyperthermia compared with control at the end of exercise (43 ± 4 vs. 51 ± 4 ml·100 g⁻¹·min⁻¹; $P < 0.05$). Concomitant with the reduction in gCBF, there was a proportionally larger increase in the arteriovenous differences for oxygen and glucose, and the cerebral metabolic rate was therefore higher at the end of the hyperthermic trial compared with control. The hyperthermia-induced lowering of gCBF did not alter cerebral lactate release. The hyperthermia-induced reduction in exercise cerebral blood flow seems to relate to a concomitant 18% lowering of arterial carbon dioxide tension, whereas the higher cerebral metabolic rate of oxygen may be ascribed to a Q_{10} (temperature) effect and/or the level of cerebral neuronal activity associated with increased exertion.

brain; cardiac output; heat stress

THE CEREBRAL METABOLISM DURING prolonged exercise with hyperthermia has never been investigated. The middle cerebral artery mean blood velocity (MCA V_{mean}) gradually decreases during prolonged exercise with progressive hyperthermia, whereas it remains stable when moderate-intensity exercise is carried out under a normothermic condition (32). The reduced MCA V_{mean} in response to hyperthermia is associated

with a hyperventilation-induced drop in the arterial carbon dioxide tension (P_{aCO_2}), indicating that also the global cerebral blood flow (CBF; gCBF) may be reduced. However, changes in MCA V_{mean} are not always a reflection of changes in whole brain blood flow (15, 23, 23), and direct measurements of volume flow are essential for an evaluation of the brain's metabolism during prolonged exercise with hyperthermia. A hyperthermia-induced reduction in gCBF could potentially impair the delivery of substrates as well as the removal of cerebrally produced metabolites. The Kety-Schmidt technique (16) is regarded as the standard procedure for determination of gCBF, and it is widely acknowledged as the most accurate method for determination of the global cerebral metabolism (21). Exercise-induced hyperthermia further reduces the central activation ratio during a sustained, maximal voluntary muscle contraction, and it may be speculated that an altered metabolism of the brain could be associated with this “central fatigue” (31). An impaired cerebral perfusion could also provoke the presyncopal symptoms sometimes experienced during exercise in hot environments.

Therefore, the purpose of this study was to determine to what extent hyperthermia would affect the cerebral circulation and metabolism of oxygen, glucose, and lactate during prolonged exercise.

METHODS

The eight endurance-trained men participating in the study had a mean age of 27 ± 2 yr (mean \pm SE), height of 182 ± 2 cm, weight of 73 ± 3 kg, and maximal oxygen uptake of 63 ± 2 ml·kg⁻¹·min⁻¹ or 184 ± 5 ml·kg^{-0.75}·min⁻¹. All participants gave written, informed consent to participate in the study as carried out in accordance with the Declaration of Helsinki and approved by the Ethical Committee of Copenhagen and Frederiksberg (KF 01-135/00).

Experimental design. All subjects completed two exercise bouts on a cycle ergometer (Monark 829E) at a power of 170 ± 4 W at 80–90 revolutions/min, which corresponded to ~50% of maximal oxygen uptake. In one trial, exercise was carried out in a thermoneutral environment (20°C, control), whereas a hyperthermic condition was achieved in the other

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trial (hyperthermia) by dressing the subjects in waterproof clothing, plastic hood, and rubber gloves. This exercise condition led to an uncompensable heat stress with the core temperature steadily increasing throughout the exercise period. The two 65-min exercise trials were separated by 1 h of recovery, and the treatment order was randomly assigned and counterbalanced across subjects.

Subjects arrived at the laboratory ~1 h before the start of the first exercise bout. On arrival, an esophageal thermocouple was inserted and a heart rate (HR) monitor was attached to the subject. Subjects then rested on a couch while catheters were inserted into the radial artery of the nondominant arm and into the bulb of the right internal jugular vein by use of the Seldinger technique. An antecubital venous catheter for infusion of ^{133}Xe was placed contralaterally to the arterial catheter to avoid contamination of arterial blood samples by diffusion of ^{133}Xe directly from the infusion site. Thereafter, the subject rested for an additional half hour before baseline measurements of HR, core temperature, and blood samples were obtained. During the two exercise bouts, blood pressure, cardiac output, HR, and core temperature were measured every 10 min, and a rating of perceived exertion (RPE; Ref. 1) was expressed on the Borg scale from 6 to 20. The gCBF was determined at the beginning (from 10 to 20 min) and at the end of the trials (55–65 min of exercise).

CBF. The gCBF was measured by the Kety-Schmidt technique in the desaturation mode with ^{133}Xe infusion as the radioactive tracer. ^{133}Xe dissolved in 0.9% saline was administered intravenously over a 30-min period at a rate of 1.5–2.5 mCi/min (depending on the size of the subject and his ventilation) via the catheter placed in the antecubital vein. Arterial blood samples were obtained from the radial artery, and cerebral venous blood was sampled from the internal jugular vein. To empty the catheter dead space, 3 ml of blood were drawn simultaneously from the catheters immediately before 1 ml of blood was drawn into syringes of known weights at exact times ($t = -2, -1, 0, \frac{1}{2}, 1, 2, 3, 4, 6, 8,$ and 10 min ($t = 0$ denoting the stop of infusion). To obtain the weight of the blood sample, the syringes were immediately reweighed; they were subsequently sealed in gas-tight cylinders to avoid the escape of ^{133}Xe and then counted for 10 min on a scintillation counter (Cobra II, Packard Instruments, Meriden, CT) for determination of decay- and background-corrected ^{133}Xe activity in counts per minute per gram.

During each CBF measurement, for determination of blood gas variables, hemoglobin (Hb), glucose, and lactate concentrations, paired arterial and jugular venous blood samples were drawn in triplicate at $t = -1, 4,$ and 8 min. Blood samples were stored on ice and analyzed within 30 min of sampling on an ABL 615 apparatus (Radiometer, Copenhagen, Denmark). All values were corrected for temperature. The gCBF was calculated by use of the Kety-Schmidt equation (16) with the brain-blood partition coefficients for ^{133}Xe calculated on the basis of the individual [Hb] at the time of sampling (12). The partition coefficients were also corrected for the influence of temperature on the tissue to blood partition coefficients for xenon (5). Cerebral arteriovenous differences for oxygen ($a\text{-vD}_{\text{O}_2}$), glucose ($a\text{-vD}_{\text{glucose}}$), and lactate ($a\text{-vD}_{\text{lactate}}$) were determined on basis of the paired blood samples, and cerebral metabolic rates of oxygen (CMR_{O_2}), glucose ($\text{CMR}_{\text{glucose}}$), and lactate release were calculated by multiplying CBF by the arteriovenous differences.

Temperature and systemic cardiovascular measurements. Core temperature was measured in the esophagus with a thermocouple (model MOV-A, Ellab) inserted through the nasal passage at a distance equal to one-fourth of the subject's standing height. HR was recorded with a Polar Vantage

NV (Polar), and mean arterial pressure (MAP) was calculated as $[(2 \times \text{diastolic pressure}) + \text{systolic pressure}]/3$ from a continuous recording via the arterial catheter (Danica, Copenhagen, Denmark). In six of the eight subjects, cardiac output was estimated from the arterial pressure wave by a nonlinear, three-element model flow analysis (41).

Statistical analysis. One- and two-way (time-by-trial) repeated-measures ANOVAs were performed to evaluate differences between and within trials. After a significant F -test, pair-wise differences were identified by using Tukey's honestly significance post hoc procedure. The significance level was set at $P < 0.05$. Data are presented as means \pm SE unless otherwise indicated.

RESULTS

Core temperature, [Hb], and arterial blood glucose concentration showed no difference before the two exercise conditions (mean range between trials, 36.9–37.0°C, 135–137 g/l, and 5.3–5.4 mM, respectively). During exercise, core temperature was similar at 10 min (37.8 ± 0.1 vs. $37.7 \pm 0.1^\circ\text{C}$) and 20 min (37.9 ± 0.1 vs. $38.0 \pm 0.1^\circ\text{C}$) in the two trials. In the control trial, core temperature then stabilized at $37.9 \pm 0.1^\circ\text{C}$ for the remainder of the exercise period. In contrast, during the hyperthermic trial, core temperature kept increasing throughout exercise. It was significantly higher than control after 30 min and reached a peak value of $39.5 \pm 0.2^\circ\text{C}$ at the end of the trial.

CBF and metabolic rate. In the control trial, gCBF and PaCO_2 were unchanged from 15 to 60 min of exercise (Fig. 1A and Table 1). By contrast, during the hyperthermic trial gCBF decreased from 49.6 ± 4.0 ml \cdot 100 g $^{-1}\cdot$ min $^{-1}$ at 15 min to 42.9 ± 4.3 ml \cdot 100 g $^{-1}\cdot$ min $^{-1}$ at 60 min of exercise with a corresponding reduction in the PaCO_2 from 41.4 ± 1.1 to 35.1 ± 1.5 Torr ($P < 0.001$). Therefore, gCBF became lower in hyperthermia compared with control by the end of exercise (Fig. 1A). Concomitantly with the reduction in gCBF during the hyperthermic trial, there was an increase in $a\text{-vD}_{\text{O}_2}$ and $a\text{-vD}_{\text{glucose}}$ (Figs. 1 and 2). However, the relative increases in $a\text{-vD}_{\text{O}_2}$ ($33 \pm 5\%$) and $a\text{-vD}_{\text{glucose}}$ ($32 \pm 5\%$) were both larger than the relative decrease in CBF ($18 \pm 3\%$). Thus the resulting CMR_{O_2} and $\text{CMR}_{\text{glucose}}$ were significantly higher at the end of the hyperthermic trial compared with control ($P < 0.05$). The percent increases in CMR_{O_2} ($7 \pm 2\%$) and $\text{CMR}_{\text{glucose}}$ ($10 \pm 4\%$) during the hyperthermic trial were not significantly different, and the ratios between oxygen and glucose uptake were similar in the two trials. There was a small release of lactate from the brain in both exercise conditions, but neither $a\text{-vD}_{\text{lactate}}$ nor the cerebral lactate release differed during hyperthermia compared with control. When CMR_{O_2} was plotted against core temperature and the RPE, it appeared that the CMR_{O_2} correlates to both variables (Fig. 3).

Systemic cardiovascular responses. Cardiac output was similar under the two exercise conditions, and it remained stable over time in both trials (Table 1). In the control trial, HR, MAP, [Hb], and arterial and jugular venous pH also remained unchanged from 15 to 60 min of exercise. During the hyperthermic trial, HR

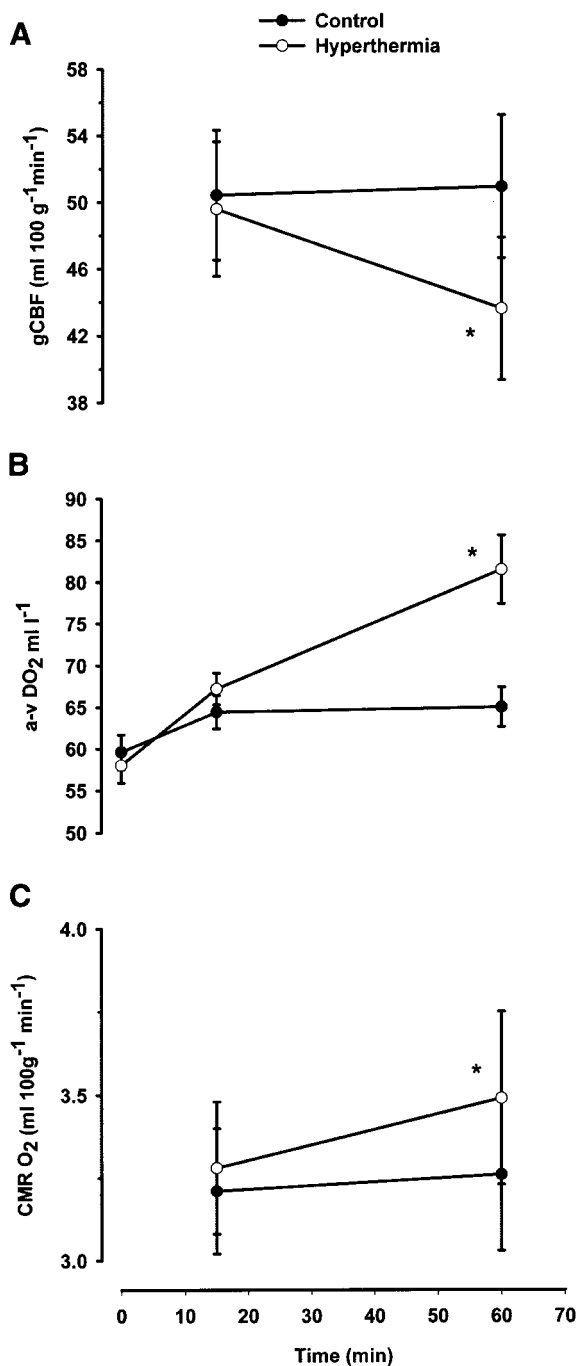


Fig. 1. A: global cerebral blood flow (gCBF). B: arteriovenous difference of oxygen (a-vDO₂). C: cerebral metabolic rate of oxygen (CMRO₂), measured during prolonged exercise with and without hyperthermia. Values at time (*t*) = 0 min represent resting measurements. All values are means ± SE for 8 subjects. *Significantly different from control (*P* < 0.05).

increased from 131 ± 2 beats/min at 15 min to 160 ± 4 beats/min at 60 min, and MAP decreased from 109 ± 5 to 97 ± 4 mmHg (both *P* < 0.05). [Hb] increased by $2.3 \pm 0.3\%$ during the hyperthermic trial, whereas arterial and jugular venous pH increased from 7.40 ± 0.01 and 7.34 ± 0.00 to 7.46 ± 0.02 and 7.38 ± 0.01 , respectively. The arterial concentrations of glucose,

K⁺, Na⁺, and epinephrine showed no significant differences between the two trials. In both the arterial and the jugular venous blood, the concentration of norepinephrine increased by ~250% during the hyperthermic trial and was higher compared with control at the end of the exercise period (*P* < 0.05; Table 1).

DISCUSSION

During the prolonged exercise bouts, hyperthermia resulted in an increased cerebral metabolic rate of oxygen and a higher cerebral glucose utilization. The increased CMRO₂ and CMR_{glucose} in response to hyperthermia were established through higher a-vDO₂ and a-vD_{glucose} and emerged despite a reduction in the global CBF. The reduced gCBF during the hyperthermic trial may be ascribed to the concomitant lowering of PaCO₂, whereas the increased CMRO₂ seems to be related to the rise in core temperature (Q₁₀ effect) and the increased RPE.

Cerebral metabolic rates of oxygen and glucose. The hyperthermic exercise bout resulted in a 1.6°C higher core temperature and a 7% increase in cerebral oxygen uptake compared with control. The effect of fever was investigated by Heyman et al. (10) in patients with asymptomatic neurosyphilis, and they found no effect on the CMRO₂ of a 2° increase in body temperature. However, it seems likely that the Q₁₀ effect demonstrated during hypothermia in humans (22, 40) and in animal species (19, 24) also affects CMRO₂ in humans when the body temperature is increased. Assuming that the increased CMRO₂ was due to a Q₁₀ effect, we can calculate that a Q₁₀ of ~1.5 will explain the 7% higher cerebral oxygen uptake at the end of the hyperthermic trial (42), and this is consistent with the Q₁₀ values of ~1.5 to ~3 observed in anesthetized humans during hypothermia (6, 22, 40). Theoretically the Q₁₀ effect is expected to be exponential (9, 39), but the shape of the CMRO₂-temperature relationship is not sufficiently determined (6), and the present data do not allow the use of statistical models to illustrate the relationship. During the hyperthermic trial, the rise in CMRO₂ was followed by a proportional increase in the cerebral glucose uptake. Corroborating this finding, Mickley et al. (25) demonstrated that a 2° increase in midbrain temperature of the rat was accompanied by a general rise in the cerebral glucose utilization. Several studies using different animal models have further observed a rise in CMRO₂ when whole body and/or local cerebral hyperthermia are applied (3, 4, 26, 27, 30), thereby supporting the idea that hyperthermia per se leads to a rise in whole brain energy turnover.

Hyperthermia results in an increased degree of "central fatigue" during prolonged maximal muscle contractions (31), and the increases in core temperature and perceived exertion during cycling in the heat are further associated with an altered electrical activity pattern of the brain (33). Thus it should be considered that, toward the end of the hyperthermic trial, CMRO₂ could be augmented as a consequence of an increased mental effort and an altered neuronal activity. Yet it is

Table 1. Cardiovascular responses and core temperature at rest and during prolonged exercise with and without hyperthermia

	Rest	Control		Hyperthermia	
		15 min	60 min	15 min	60 min
PaCO ₂ , Torr	41.0 ± 1.0	42.3 ± 1.1	41.6 ± 1.1	41.4 ± 1.1	35.1 ± 1.5*†
Core temperature, °C	37.0 ± 0.1	37.8 ± 0.1	37.9 ± 0.1	37.9 ± 0.1	39.5 ± 0.1*†
pH, arterial	7.40 ± 0.01	7.40 ± 0.01	7.40 ± 0.01	7.40 ± 0.00	7.46 ± 0.02*†
pH, jugular vein	7.35 ± 0.00	7.34 ± 0.00	7.34 ± 0.00	7.35 ± 0.00	7.38 ± 0.01*†
Hb, g/l	135.0 ± 1.8	141.7 ± 1.7	142.5 ± 1.6	142.3 ± 1.3	146.0 ± 1.3*†
Arterial [glucose], mM	5.4 ± 0.2	4.2 ± 0.2	4.8 ± 0.2†	4.3 ± 0.3	5.1 ± 0.2†
Arterial [lactate], mM	1.3 ± 0.3	1.1 ± 0.1	1.0 ± 0.1	1.3 ± 0.3	1.9 ± 0.2*
Arterial [K ⁺], mM	3.7 ± 0.1	4.7 ± 0.1	4.7 ± 0.1	4.6 ± 0.1	4.7 ± 0.1
Arterial [Na ⁺], mM	139 ± 1	141 ± 1	142 ± 1	140 ± 0	142 ± 0
SaO ₂ , %	97.0 ± 0.1	96.7 ± 0.2	96.6 ± 0.3	97.1 ± 0.1	97.3 ± 0.2
SvO ₂ , %	64.4 ± 1.0	63.8 ± 0.9	63.6 ± 0.9	63.0 ± 0.9	55.9 ± 2.5*†
Arterial [epinephrine], nM	0.83 ± 0.12	1.38 ± 0.16	2.04 ± 0.31†	1.39 ± 0.13	2.99 ± 1.11†
Venous [epinephrine], nM	0.83 ± 0.11	1.43 ± 0.15	2.42 ± 0.45†	1.49 ± 0.17	3.17 ± 1.19†
Arterial [norepinephrine], nM	0.62 ± 0.04	5.49 ± 1.03	6.19 ± 1.04	5.77 ± 1.19	16.16 ± 3.96*†
Venous [norepinephrine], nM	0.96 ± 0.19	5.38 ± 0.74	6.96 ± 1.36	6.78 ± 1.62	17.17 ± 3.43*†
Cardiac output, l/min		15.0 ± 0.5	15.2 ± 0.4	14.9 ± 0.5	14.8 ± 0.4
MAP, mmHg		108 ± 5	107 ± 4	109 ± 5	97 ± 5*†
HR, beats/min	48 ± 2	129 ± 1	131 ± 2	133 ± 2	160 ± 4*†

Values are means ± SE for 8 subjects. For cardiac output, $n = 6$ subjects. PaCO₂, arterial P_{CO₂}; Hb, hemoglobin; SaO₂ and SvO₂, arterial and jugular venous oxygen saturation; MAP, mean arterial blood pressure; HR, heart rate. Brackets denote concentration. *Significantly different from control ($P < 0.05$). †Significantly different from 15-min value ($P < 0.05$).

controversial whether dynamic exercise is associated with increased cognitive mental activation (14, 23). The discrepancies between the findings of CMRO₂ alterations during the transition from rest to exercise may be ascribed to different exercise intensities. During exercise at mild to moderate intensity, CMRO₂ is unchanged compared with rest (18, 23, 37, 43), whereas more vigorous exercise results in an increased oxygen uptake of the brain (36). The workload in the present study was identical in the two trials, and it was not altered during the exercise period. However, an increased difficulty in retaining power during the hyperthermic cycle trial was reflected in the RPE, and the mental effort of the subjects might have increased during the hyperthermic trial. Some forms of stress seem to be accompanied by a general stimulation of overall cerebral synaptic activity, as reflected in an increased CMRO₂ (for references see Ref. 2). However, the present study cannot differentiate between effects of increased RPE, increased sensory feedback, and temperature, and further investigations are needed to clarify whether increased RPE or other forms of mental stress during prolonged exercise are associated with an augmented CMRO₂.

CBF. The 18% reduction in gCBF during the hyperthermic trial seems to be linked to the concomitant 18% lowering of PaCO₂. Reduced CBF in response to hyperthermia is in accordance with our previous study in which hyperthermia-induced hyperventilation resulted in a similar drop in PaCO₂ and a 26% reduction in MCA V_{mean} (32). In that study, the observed decrease in MCA V_{mean} was compared with the decrease that would be expected from the drop in PaCO₂, as calculated by the individually determined CO₂ reactivity. Apparently, only 56% of the decline in MCA V_{mean} could be accounted for by the drop in PaCO₂, prompting

us to propose that a decline in cardiac output and arterial blood pressure accounted for the remaining part of the hyperthermia-induced reduction (see Ref. 32 for further discussion). Individual CO₂ reactivity was not measured in the present study, but on the basis of whole brain blood flow CO₂ reactivity (34) it could be expected that that flow would be reduced by ~19% as a consequence of the 6.3-Torr decline in PaCO₂ during the hyperthermic trial. Thus it seems as if hyperventilation accounted for the hyperthermia-induced reduction in gCBF in the present study. The discrepancy could be due to methodological differences (Kety-Schmidt vs. Doppler-determined evaluation of the cerebral circulation). However, it is likely that CBF was reduced to a larger extent in the previous study, because in that study cardiac output was reduced during the hyperthermic trial whereas it was preserved in the present study. A reduction in cardiac output is expected to lower the cerebral perfusion during exercise with a large muscle mass (13), and reduced cardiac output during combined exercise and heat stress is only observed if both heat stress and exercise intensity are quite high (8, 29, 35). Core temperature at the end of the hyperthermic trial was not as high as in the former study (39.5 vs. 40.0°C), and the subjects exercised at a lower work intensity because the duration of the exercise period had to be longer than 1 h to allow enough time to make two Kety-Schmidt determinations of CBF.

The unchanged cerebral lactate release and increased oxygen uptake during the hyperthermic trial indicate that the diminished gCBF did not impede the cerebral metabolism. However, the functional importance or consequence of the hyperthermia-induced reduction in CBF is at present not fully understood, and future studies should investigate whether the cerebral

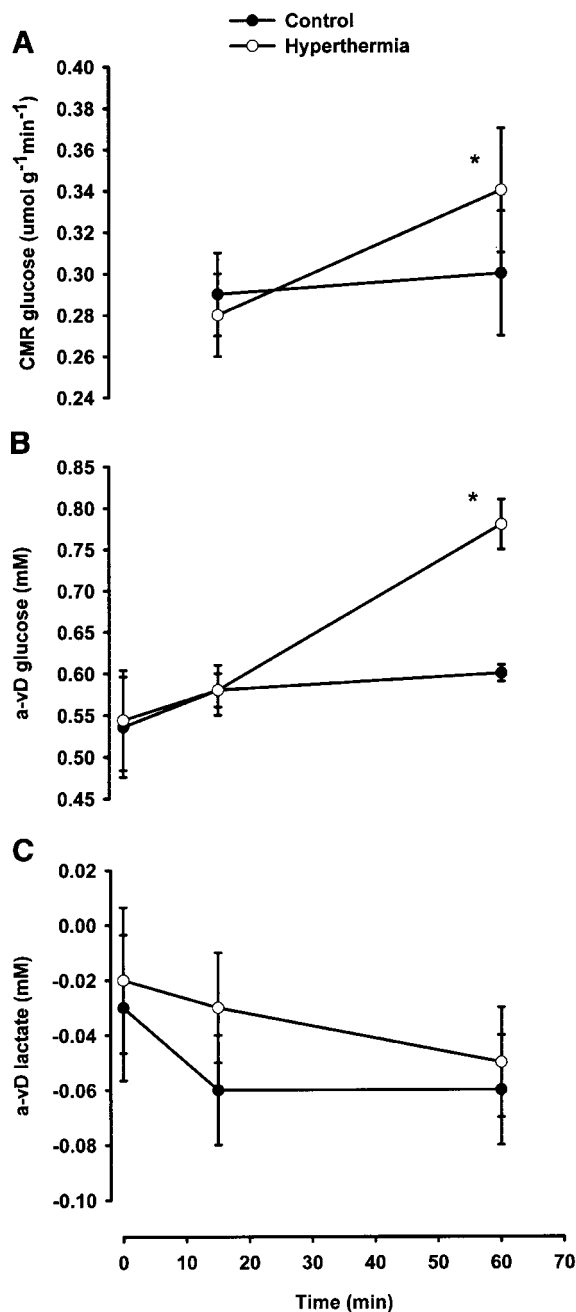


Fig. 2. A: cerebral metabolic rate of glucose (CMR_{glucose}). B: arterio-venous difference of glucose ($a-vD_{\text{glucose}}$). C: $a-vD_{\text{lactate}}$, arterio-venous difference of lactate measured during prolonged exercise with and without hyperthermia. Values at $t = 0$ min represent resting measurements. All values are means \pm SE for 8 subjects. *Significantly different from control ($P < 0.05$).

uptake or release of substances not assayed for in the present study is affected by the diminished blood flow. Nevertheless, the reduction in gCBF in response to hyperthermia during exercise provides some new information about the regulation of whole brain blood flow in situations in which CO_2 reactivity and metabolism affect gCBF in opposite directions. It seems that a lowering of $PaCO_2$ is a stronger regulator of gCBF than an increased metabolic rate, at least in conditions

in which oxygen delivery to the brain is relatively high (i.e., venous oxygen saturation above 50%). Norepinephrine has the potential to increase the basal CMR_{O_2} as well as the ability to reduce CBF (17, 28), and the hyperthermia-induced increase in circulating norepinephrine could contribute to the changes in flow and metabolism during the hyperthermic trial.

Methodological considerations. The Kety-Schmidt technique (16) is regarded as the standard method for determination of gCBF and CMR, and the values obtained during the control trial are in accordance with the normal values for young adults measured both at rest and during cycling (16, 21, 23). A crucial assumption for the determination of gCBF and CMR is that the blood sampled from the catheter in the internal jugular vein represents cerebral venous blood. Although the catheter was placed with the tip positioned in the bulb of the internal jugular vein, a slight admixture of extracranial origin can be expected. The amount of extracranial contamination is usually small (<2.6%) (20, 38), but a hyperthermia-induced increase in extracranial contamination might influence our results. However, because extracranial contamination is de-

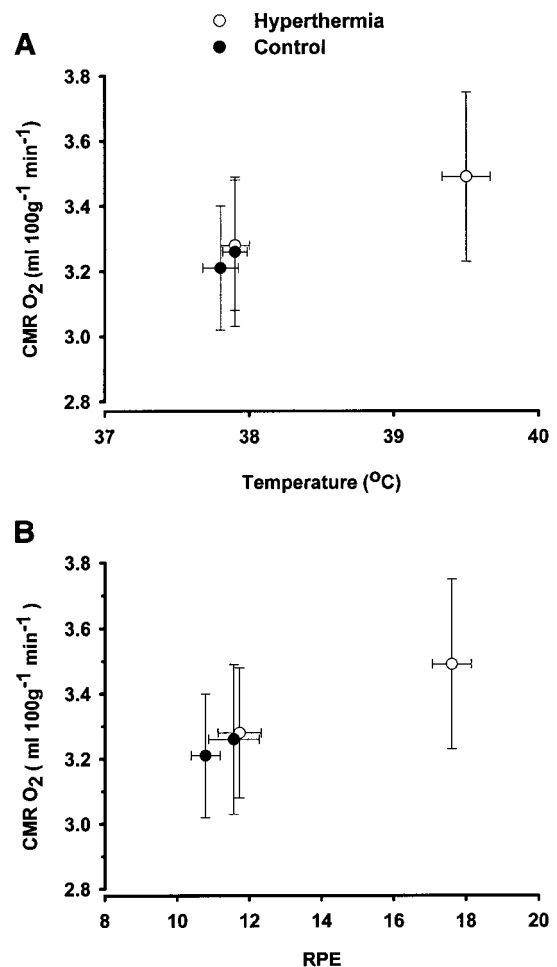


Fig. 3. Cerebral metabolic rate of oxygen (CMR_{O_2}), plotted against core temperature (A) and rating of perceived exertion (RPE; B) during prolonged exercise with and without hyperthermia.

rived from tissues with a low perfusion and metabolic rate (16), CBF may have been overestimated and the arteriovenous differences may have been underestimated as a consequence of a hyperthermia-induced increase in extracranial contamination. Thus the error resulting from extracranial contamination on the relative changes in CMR from control to the hyperthermic trial would be negligible. More than 50 years ago, Himwich et al. (11) pointed out that the two jugular veins do not drain symmetrical portions of the brain. The larger internal jugular vein is normally representative of cortical drainage whereas the other, usually smaller, vein drains blood largely from subcortical areas (7), and the present results could be affected if hyperthermia induces a redistribution of blood flow between cortical and subcortical areas. Finally, a critical assumption when using the Kety-Schmidt technique is that the inert gas tracer tension in all brain tissues is the same as that of the mixed cerebral venous blood at the termination of blood sampling. Using the 10-min (or any finite) measuring period does not totally fulfill this assumption, leading to an overestimation of gCBF (20). The magnitude of overestimation is influenced by the shape of the arterial curve reflecting clearance of ^{133}Xe from all body tissues. Hyperventilation will increase ^{133}Xe clearance through the lungs, which consequently will reduce the overestimation of gCBF. Thus the hyperthermia-induced hyperventilation results in a relative underestimation of gCBF at the end of the hyperthermic trial. However, the arterial input curves were quite similar in the two exercise conditions, and as calculated by Madsen et al. (23) the implication of faster disappearance of ^{133}Xe from the arterial blood as a consequence of a 700% increase in pulmonary ventilation results in a relative underestimation of gCBF of maximally 2%.

The present study demonstrates that the development of hyperthermia during prolonged exercise is associated with a reduction in gCBF, and this reduction seems to be accounted for by the hyperventilation-induced lowering of PaCO_2 . The results also reveal that hyperthermia is associated with an increased cerebral metabolic rate of oxygen and an increased cerebral glucose utilization. The Q_{10} effect is the most likely explanation for the rise in the CMR_{O_2} , but a higher stress level and an increased degree of mental exertion toward the end of the hyperthermic exercise bout may influence the increase in CMR_{O_2} .

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