Special Edition

Changes in Blood Flow and Metabolism in Skin and Muscle During Induced Hyperthermia in Dogs

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Title: Blood flow in skin and muscle during hyperthermia

Abstract : The Present study investigated the changes in blood flow and oxygen kinetics of the hindlimb skin and muscles in eighteen mongrel dogs during induced hyperthermia (38°C to 43°C). Cardiac output increased and systemic vascular resistance decreased during hyperthermia. Muscle, subdermal and dermal blood flow did not change significantly during hyperthermia. The femoral oxygen extraction rate increased significantly as the temperature was increased. The difference in lactic acid concentration between the femoral arterial and venous blood did not increase with hyperthermia. Plasma cAMP levels increased as the temperature rose, whereas cGMP levels did not increase significantly.

Results of the present study suggest that the cause of hyperdynamics during hyperthermia is due to increased cAMP concentration induced by heating. Although blood flow in the muscle and skin did not increase, the oxygen supply was sufficient to maintain normal muscle metabolism during induced hyperthermia.

Key words : hyperthermia, blood flow, cAMP

Introduction

Numerous studies have investigated organ blood flow during hyperthermia. However, none of these studies has been able to demonstrate a clear relationship between hyperthermia and blood flow to the heart, liver, intestines, kidneys and extremities¹⁻⁶⁾. The radioactive microsphere technique has been used to study this relationship, particularly in skin and muscle⁷⁻⁹⁾. However, the results have been still inconsistent.

In order to resolve this controversy, the present study investigated the physiological effects of induced hyperthermia on skin and muscle, including blood flow and oxygen kinetics in the hindlimb of mongrel dogs. Hydrogen clearance and a laser-Doppler blood flowmeters

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were used to measure these parameters. Oxygen content and plasma lactate, cAMP, cGMP, myoglobin and amino acid levels were measured in order to determine the oxygen kinetics and muscle metabolism during induced hyperthermia.

Materials and Methods

Materials

Eighteen mongrel dogs (mean weight: 13.7 ± 2.8 kg) were investigated. The experimental protocol was approved by the animal care committee of Oita Medical University. Furthermore, experiments were carried out according to the guidelines for animal experiments of Oita Medical University.

Surgical procedures

The animals were anesthetized intravenously with $25 \text{ mg} \cdot \text{kg}^{-1}$ of pentobarbital and $0.2 \text{ mg} \cdot \text{kg}^{-1}$ of pancuronium, followed by $2 \text{ mg} \cdot \text{kg}^{-1}$ of morphine and continuous infusion of $5 \text{ mg} \cdot \text{kg}^{-1} \cdot \text{hr}^{-1}$ of pentobarbital. The animals were then intubated with endotracheal tubes and mechanically ventilated (Aika model R-60, Aika, Tokyo, Japan) with an air/oxygen mixture providing $F_{\text{I}}\text{O}_2=0.21$. The respiratory rate was adjusted in order to maintain endtidal CO_2 at 30-40 mmHg, monitored using a capnometer (Normocap, Datex, Helsinki, Finland).

A venous catheter for fluid transfusion was inserted into the right femoral vein. The left femoral artery and vein were cannulated with 24-G Teflon cannulas for blood pressure measurement and blood sampling. An electromagnetic blood flow meter probe was attached to the main trunk of the left femoral artery. Trachotomy was performed through the 4-5th intercostal space; the pericardium was opened, and the electromagnetic blood flow meter probe was attached to the ascending aorta. The probe was connected to the electromagnetic blood flow meter (Model Mot 1200, Nihon Kohden, Tokyo, Japan) in order to measure the left femoral artery blood flow and cardiac output (CO). A 7-Fr. pulmonary artery catheter was inserted into the left external jugular vein in order to monitor central venous pressure (CVP) and sample the mixed venous blood. A thermometer (AW601H, Nihon Kohden Tokyo, Japan) was inserted into the pericardial space in order to measure core body temperature.

Needle-type platinum electrodes were inserted into the subdermal tissue and adductor muscle of the left thigh. Those electrodes were connected to the hydrogen clearance tissue blood flowmeter (Model UPS 400, Unique Medical, Tokyo, Japan). A laser-Doppler blood flowmeter probe was sutured to the shaved skin of the thigh and connected to the laser-Doppler blood flowmeter (ALF21, Advance, Tokyo, Japan).

After completing the surgical procedures and confirming that the hemodynamics had stabilized, each animal was wrapped in a vinyl sheet and then immersed in a warm-water bath in the supine position. The water was heated by a thermal unit (Model 302, Taiyo Co., Tokyo, Japan). The body temperature of each animal rose at a constant rate of $1^\circ\text{C}/\text{hour}$ to 43°C .

During induced hyperthermia, 6% glucose lactate Ringer's solution was infused at a rate

of 10-20 ml · kg⁻¹ · hr⁻¹ in order to maintain normal CVP (5-10 cmH₂O) and normal blood glucose levels (100-200 mg · dl⁻¹).

Physiological and biochemical measurements

Hemodynamic parameters, including heart rate (HR), mean arterial pressure (MAP), CVP, CO and left femoral artery blood flow were measured. Systemic vascular resistance (SVR) was calculated using the following formula.

$$\text{SVR (dynes} \cdot \text{sec} \cdot \text{cm}^{-5}) = (\text{MAP} - \text{CVP}) \cdot 80 \cdot \text{CO}^{-1}$$

Arterial, mixed venous and femoral venous blood oxygen content (CaO₂, CvO₂ and CfvO₂, respectively) was measured using a hemoxymeter (OSM 3, Radiometer, Copenhagen, Denmark). Oxygen uptake (VO₂) was calculated using the following formula.

$$\text{VO}_2 (\text{ml} \cdot \text{min}^{-1}) = (\text{CaO}_2 - \text{CvO}_2) \cdot \text{CO} \cdot 10$$

Lactic acid levels were measured using an commercially available oxydase kit (Kyowa Medix No. 1, No. 2 kit, Kyowa Medex Co. Ltd., Tokyo, Japan). Aminograms were analyzed by high performance liquid chromatography (JLC300, Nihon-denshi, Tokyo, Japan). Plasma cAMP and cGMP levels were measured by radioimmunoassay (RIA) as described by Honma¹⁰⁾. Plasma myoglobin levels were measured using an RIA kit (Daiichi II myoglobin kit, Daiichi isotope, Tokyo, Japan). Plasma cortisol levels were measured using a commercially available RIA kit (Eiken, Tokyo, Japan). These parameters were measured at six temperatures: 38°C (control), 39°C, 40°C, 41°C, 42°C and 43°C.

Statistical analysis

Results are expressed as mean ± SD and statistical significance was determined using a one-way analysis of variance (ANOVA). Multiple comparisons with control values were evaluated using the Bonferroni method. Significance was established at the p < 0.05 level.

Results

Hemodynamic parameters (Table 1)

The average time required to raise the body temperature from 38°C to 43°C was 332 ± 63 min. HR increased as body temperature increased from 38°C to 43°C by approximately 73% (p < 0.05) (Table 1). MAP did not change significantly until 42°C. It subsequently decreased significantly at 43°C. CO increased by approximately 29% as the temperature increased from 38°C to 42°C. Stroke volume (SV), calculated from CO and HR, did not show any significant changes.

Muscle and skin circulation (Table 1)

SVR decreased gradually as body temperature increased. Left femoral blood flow did not show any significant changes. The left femoral blood flow fraction at 38°C was approximately 2.3% of CO and remained unchanged at 43°C.

Table 1 Changes in hemodynamic parameters according to body temperature

Body temperature (°C)	38	39	40	41	42	43
Heart rate (bpm)	136.8±34.4	150.2±34.0	163.0±28.9	173.8±27.1*	195.1±33.4*	226.1±25.0*
Mean arterial pressure (mmHg)	94.3±15.4	96.8±18.8	94.1±19.5	92.8±20.6	82.3±31.7	64.5±25.8*
Cardiac output (l/min)	2.14±0.40	2.35±0.68	2.37±0.76	2.46±0.88	2.76±1.05*	2.72±1.09
Lt. femoral A. blood flow (ml/min)	47.2±10.2	50.5±18.9	49.8±17.7	46.5±17.9	46.1±19.2	43.5±23.1
Muscle blood flow (ml/100g/min)	33.9±15.9	30.7±14.4	34.9±21.9	28.9±15.1	25.6±14.6	24.3±15.9
Subdermal blood flow (ml/100g/min)	31.2±10.2	46.6±24.2	43.4±18.6	54.7±18.4	33.4±18.6	27.0±19.7
Dermal blood flow (ml/100g/min)	4.5±4.0	4.2±4.1	3.9±3.8	3.8±3.3	3.3±2.8	2.7±1.8
Systemic vascular resistance (dyne · sec · cm ⁻⁵)	3514±810	3505±1268	3348±1092	3165±1085	2304±822*	1706±629*

mean±SD *: p<0.05 vs 38°C

Muscle blood flow measured by the hydrogen clearance method did not change significantly during heating. Subdermal blood flow tended to rise and peaked at 41°C, although this increase was not statistically significant. Dermal blood flow in the thigh measured by the laser-Doppler method, despite an increase in CO, tended to decrease as the body temperature rose.

Metabolic changes (Table 2)

Oxygen uptake ($\dot{V}O_2$) increased significantly ($p<0.05$) with induced hyperthermia, and at 43°C, uptake was 76% higher than that at 38°C. Oxygen extraction ($CaO_2-C\bar{v}O_2$) tended to increase as the body temperature rose. Femoral oxygen extraction ($CaO_2-Of\bar{v}O_2$) increased significantly at 41, 42 and 43°C.

Table 2 Metabolic effects of hyperthermia

Body temperature (°C)	38	39	40	41	42	43
Femoral artery blood lactic acid level (mg/dl)	22.8±9.9	22.0±9.5	21.6±9.4	25.2±12.0	29.8±14.0	40.8±15.4*
Femoral vein blood lactic acid level (mg/dl)	22.8±12.4	22.1±11.2	22.0±11.6	25.3±16.7	31.9±16.7	42.1±17.5*
Difference between femoral artery and vein lactic acid level (mg/dl)	0.0±8.6	0.1±4.3	0.5±6.3	0.2±3.5	2.1±7.0	1.3±9.1
$CaO_2-C\bar{v}O_2$ (Vol%)	4.00±1.04	4.44±1.68	4.46±1.60	4.36±1.34	4.80±2.20	4.75±1.31
$CaO_2-Cf\bar{v}O_2$ (Vol%)	3.91±1.46	4.49±1.40	4.64±1.27	5.50±1.22*	5.76±1.02*	5.88±1.28*
$\dot{V}O_2$ (ml/min)	78.3±21.1	91.9±34.7	91.6±29.1	102.8±31.5	118.5±55.9	136.8±46.8*

mean±SD *: p<0.05 vs 38°C

CaO₂: arterial oxygen content, Cvo₂: venous oxygen content, Cfvo₂: femoral venous oxygen content, Vo₂: oxygen uptake.

Arterial and venous lactic acid concentration increased significantly as the temperature increased to 43°C. However, the difference in lactic acid concentration between femoral arterial and venous blood did not increase significantly.

Table 3 Changes in biochemical parameters according to body temperature

Body temperature (°C)	38	39	40	41	42	43
Plasma myoglobin level (ng/ml)	5.87±1.35	6.00±1.38	6.11±1.29	5.81±1.42	5.85±1.86	6.16±1.77
Plasma cortisol level (μg/dl)	11.5±7.9	9.8±10.7	8.4±9.0	6.0±4.1	5.9±2.7	6.7±2.2
plasma cAMP level (pmol/ml)	10.2±4.1	11.2±3.6	13.1±4.2	16.0±6.6	23.5±15.5*	31.0±8.4*
Plasma cGMP level (pmol/ml)	12.6±6.7	11.4±5.9	12.2±4.7	11.8±4.1	12.2±3.9	11.9±3.4

mean±SD *: p<0.05 vs 38°C

Biochemical changes (Table 3)

Plasma myoglobin concentration did not change significantly, while plasma cortisol concentration tended to decrease during induced hyperthermia. Plasma cAMP concentration increased as body temperature rose, such that cAMP concentration at 42°C was significantly higher than that at 38°C, and reached a peak at 43°C (Fig. 1).

Aminogram changes (Fig. 2, 3)

Arginine (AGR), glutamine (GLN), valine (Val), leucine (LEU), isoleucine (ILEU),

Figure 1. Changes in plasma cAMP and cGMP concentration. Points represent mean±SD.

Figure 2. Changes in arterial blood amino acid concentration and Fisher ratio. ARG: Arginine, GLN: Glutamine, VAL: Valine, LEU: Leucine, ILEU: Isoleucine, TYR: Tyrosine, PHE: Phenylalanine, Total A. A.: Total amino acids, bars represent mean $\pm$ SD.

Figure 3. Changes in differences between femoral artery and vein amino acid concentrations during hyperthermia. ARG: Arginine, GLN: Glutamine, ALA: Alanine, VAL: Valine, LEU: Leucine, ILEU: Isoleucine, TYR: Tyrosine, PHE: Phenylalanine, TAA: Total Amino Acids, bars represent mean $\pm$ SD.

tyrosine (TYR), phenylalanine (PHE), and total amino acid levels were all significantly higher at 43°C compared to the levels at 38°C (**Fig. 2**). However, the Fisher ratio, which is the ratio between branched chain amino acids (BCAA) and aromatic amino acid (AAA) did not change significantly. The rise in body temperature from 38°C to 43°C resulted in a significant increase in the arterio-venous amino acid gradient for GLN, alanine (ALA), VAL, LEU,

and ILEU. The concentration of all amino acids in the arterial blood was higher than that in the venous blood.

Discussion

The present results demonstrate that blood flow in the hindlimb of mongrel dogs does not increase despite the increased CO associated with induced hyperthermia. Laser-Doppler blood flow meter failed to show any increase in dermal blood flow. Subdermal blood flow in the hindlimb measured by hydrogen clearance method tended to increase with hyperthermia up to 41°C. However, neither this increase nor the increase in muscle blood flow of the hindlimb was statistically significant. These findings agree with the results reported by Hales et al⁹⁾. In a similar human study, Detry et al¹¹⁾ found that forearm blood flow measured by volumetry increased during hyperthermia. However, forearm blood volume did not increase during hyperthermia, when epinephrine, which is believed to reduce dermal blood flow, was administered. Therefore, they concluded that the increased dermal blood flow contributed to the increased forearm blood flow. These contradictory results may reflect differences between the species¹²⁾.

No significant changes were observed in the femoral arterio-veno lactic acid difference, an increase in which indicates anaerobic metabolism. $\dot{V}O_2$ in the present study increased and the femoral oxygen extraction increased significantly during hyperthermia, which indicates that the metabolic state of the muscle was accelerated without an anaerobic reaction. Therefore, we concluded that lactate metabolism and oxygen kinetics of the muscle did not move to an anaerobic state in response to induced hyperthermia up to 43°C under general anesthesia. These results agree with those of Ito et al.¹³⁾, who used ³¹P-MRS to investigate changes in energy metabolism in response of the mouse hindlimb to local heating with hot air (39-51°C). In their study, the phosphocreatine, ATP and inorganic phosphate levels were unchanged from 39 to 42°C.

In the aminogram, PHE and TYR were taken into skeletal muscle during protein synthesis and released during skeletal muscle breakdown. The changes in concentration reflect the increase and decrease of protein degradation and synthesis, respectively¹⁴⁾. No significant changes in PHE and TYR were observed in response to hyperthermia in the present study, suggesting that no skeletal muscle degradation occurred. Since the arterial Fisher ratios before and after heating did not change significantly, the amino acid metabolism in skeletal muscle during induced hyperthermia was considered to remain unchanged¹⁵⁾. In addition, amino acid levels in femoral arterial blood increased more than those in femoral venous blood at 43°C and no significant changes were observed in the plasma myoglobin concentration at the temperature of 43°C. These findings suggest that no muscle breakdown occurred during hyperthermia.

Several reports have suggested that plasma cortisol concentration is influenced by hyperthermia^{16,17)}. Oda et al¹⁶⁾ reported that cortisol levels increased remarkably during

hyperthermia in mongrel dogs under pentobarbital anesthesia. However, in their study, plasma cortisol levels remained stable. Tanioka et al. reported similar results¹⁷⁾. They suggested that morphine suppresses the hormonal response to ACTH and cortisol during hyperthermia. These differences in hormonal responses to hyperthermia might be explained by the use of different anesthetic methods.

The increased plasma cAMP level is believed to stimulate an increase in cardiac output and decrease in systemic vascular resistance. In the present study, plasma cAMP levels increased significantly during hyperthermia, whereas cGMP levels did not increase significantly. cAMP and cGMP levels are regulated by the balance between their synthesis by adenylate and guanylate cyclase (AC, GC), respectively, and their degradation by phosphodiesterase (PDE). Hyperthermia tends to alter the metabolism of one of these steps. Loten et al.¹⁸⁾ reported that the stability of low-Km PDE, one of the type III PDEs that specifically degrades cAMP, decreases dramatically at 40°C. Mancebo¹⁹⁾ and Jenq²⁰⁾ found that AC activity reaches an optimal level at 37°C, and becomes inactivated at 56°C. This suggests that AC activity may predominate over PDE activity during hyperthermia at 40–43°C, causing cAMP to increase. Milewich²¹⁾ reported that GC activity completely ceases at 60°C. cGMP-specific PDE gradually loses its enzymatic activity at 50°C²²⁾, while between 10°C and 42°C, its reaction rate increases as the temperature rises. This may be one of the reasons why cAMP increased significantly as body temperature rose from 38°C to 43°C in the present study, whereas no significant change was detected in cGMP.

In a clinical study of hyperthermia in humans²³⁾, plasma norepinephrine concentration increased during induced hyperthermia, reaching a maximum value of 530–1700 pg · ml⁻¹ at the highest temperature (41.5–41.8°C). The positive chronotropic and inotropic effects of norepinephrine were caused chiefly by activating AC and increasing cAMP²⁴⁾. We speculate that the increased cAMP levels were induced by norepinephrine.

In conclusion, SVR decreased and CO increased remarkably during experimental hyperthermia in mongrel dogs. Based on the results of the present study, we speculate that the cause of hyperdynamics during hyperthermia is due to increased cAMP concentration induced by heating. Although, blood flow in muscle and skin did not increase, the oxygen supply remained sufficient to maintain normal muscle metabolism during induced hyperthermia.

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人為的高体温のイヌ皮膚，筋の血流量および代謝に 及ぼす影響

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要 旨： 人為的高体温時（38℃～43℃）の皮膚および筋の血流量と酸素需給の変化を，雑種成犬18頭の後肢を用いて検討した．高体温時には心拍出量増加と体血管抵抗減少がみられたが，筋，真皮の血流量は有意の変化はなく，皮下組織の血流量増加も有意ではなかった．大腿動静脈の酸素含量較差は体温上昇とともに有意に増加したが，乳酸濃度較差は増加しなかった．血漿中の cAMP 濃度は体温上昇とともに有意に増加したが，cGMP 濃度は増加しなかった．高体温時により動脈血中の遊離アミノ酸は有意に増加したが，大腿動静脈間で濃度を比較すると動脈のほうが高値を示した．

これらの結果から，麻酔下の人為的高体温時には，筋の血流量は増加しないが，酸素供給は筋の代謝を正常に維持するのに十分であり，骨格筋の分離も亢進しないことが示された．また，高体温時の高心拍出量状態は，加温により引き起こされた cAMP 増加と関係がある可能性が示唆された．

キーワード： 高体温，血流量，cAMP