

Heat Illness during Working and Preventive Considerations from Body Fluid Homeostasis

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Received March 6, 2006 and accepted May 16, 2006

Abstract: The purposes of this review are to show pathophysiological mechanisms for heat illness during working in a hot environment and accordingly provide some preventive considerations from a viewpoint of body fluid homeostasis. The incidence of the heat illness is closely associated with body temperature regulation, which is much affected by body fluid state in humans. Heat generated by contracting muscles during working increases body temperature, which, in a feedback manner, drives heat-dissipation mechanisms of skin blood flow and sweating to prevent a rise in body temperature. However, the impairment of heat-dissipation mechanisms caused by hard work in hot, humid, and dehydrated conditions accelerates the increase in body temperature, and, if not properly treated, leads to heat illness. First, we overviewed thermoregulation during working (exercising) in a hot environment, describe the effects of dehydration on skin blood flow and sweating, and then explained how they contribute to the progression toward heat illness. Second, we described the advantageous effects of blood volume expansion after heat acclimatization on temperature regulation during exercise as well as those of restitution from dehydration by supplementation of carbohydrate-electrolyte solution. Finally, we described that the deteriorated thermoregulation in the elderly is closely associated with the impaired body fluid regulation and that blood volume expansion by exercise training with protein supplementation improves thermoregulation.

Key words: Heat-related death, Industrial accidents, Thermoregulatory responses, Sports drinks, Heat acclimation, Hypovolemia, Hyperosmolality, Aging

Introduction

During the period from 2001 to 2003 in Japan, 483 individuals were reported absent from work for more than 4 d due to heat related illness. Of these 483 patients 63 died due to their heat illness¹⁾. According to the report, 50% of the heat illness incidences occurred between 14:00 and 16:00 in the months of July to August and 70% of the incidences occurred within the first three days after starting work. Eighty percent of the reported deaths occurred in the construction industry and thirty percent of deaths were over 50 yr old. To prevent heat illness, the report indicated that 1) working intensity and duration should be lowered in the aged workers

since thermoregulatory capacity is reduced with aging, 2) daily aerobic and/or resistance training are recommended since the thermoregulatory capacity increases with physical fitness, 3) beverages should be always available to workers and, especially, aged worker should be encouraged to drink it since their thirst sensation is blunted, 4) dehydration suffered during working for a day should be recovered completely within the day since hypovolemia and hyperosmolality due to prolonged dehydration reduces thermoregulatory capacity, 5) high protein diet is recommended since thermoregulatory capacity is improved by enhanced increased blood volume. In this review, we introduced the studies supporting the guideline.

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Thermoregulation during Working in the Heat

Body temperature & heat balance

Distribution of temperatures in the body is different between body core and skin surface. Body core temperature is the deep-tissue temperature of the body and remains almost constant because of well-designed negative feedback system. In contrast, skin temperature is easily influenced from environmental temperature; i.e. to maintain body core temperature, it falls and rises in a cold and a hot environments induced by cutaneous vasoconstriction and vasodilation, respectively.

The body core temperature is determined by the heat balance between production and loss during working. For example, when a 65 kg person works at a work intensity equivalent to 135 watts (i.e. carrying a package to upstairs or running at 160 m/min), the heat generated by contracting muscles is estimated 233 kcal for 30 min, and if not dissipated from the body surface, the core temperature would increase to 41.3°C. However, experimentally, the core temperature rapidly increases but eventually reaches a steady state when heat dissipation mechanisms are activated sufficiently to balance the heat production. Skin blood flow (SkBF) and sweating are two major physiological mechanisms involved in heat dissipation in humans. SkBF transfers the heat generated by the contracting muscles to the skin surface. The heat is transferred to the air according to temperature gradient between the skin and the air (non-evaporative heat loss). At high atmospheric temperature (T_a) (above 30°C), non-evaporative heat loss becomes negligible or even serves as an avenue for heat gain once T_a exceeds skin temperature. On the other hand, sweat transfers heat from the skin surface to the air when sweat evaporates (evaporative heat loss). As such, sweating is the main mechanism for heat dissipation at T_a above 30°C. Evaporative heat loss is determined by the water vapor gradient from skin to the air and is limited in a humid environment. Thus, the core temperature is controlled within a narrow range when heat balance is attained, but it increases rapidly when heat production overcomes heat dissipation such as during heavy labor in a hot and humid environment.

Thermal factors

Skin temperature as well as core temperature are continuously monitored by peripheral and central thermal sensors, respectively, through an afferent path to the thermoregulatory center in the preoptic/anterior hypothalamus², and if these temperatures are determined to be higher than set point by the thermoregulatory center, SkBF and sweat rate (SR) are increased through efferent

paths of sympathetic nervous system³. The sensitivity of this thermal reflex mediated by changes in body core temperature is 10 times greater than that by skin temperature^{4,5}. Recently, it has been suggested that 95% of cutaneous vasodilation is caused by the excitation of vasodilator nerve in the sympathetic nerves⁶ but it is unclear if this nerve is identical to sudomotor nerve or not⁷.

Non-thermal factors

Heat dissipation mechanisms are much influenced by other homeostatic systems; i.e. body fluid and/or circulatory regulations. Adolph and his colleagues⁸ first reported the interaction between body temperature and body fluid regulations in humans, suggesting that rectal temperature at rest increased by 0.25°C per 1% loss of body weight in the soldiers marching in the desert. Thereafter, most of the earlier work on the interaction of thermoregulation and body fluid balance has focused on either hypovolemia and hyperosmolality induced by dehydration.

Effects of Dehydration on Thermoregulation

Hypovolemia

Nadel *et al.*⁹ first studied the effects of isotonic hypovolemia on SkBF during 30-min exercise at 55% of maximal oxygen consumption (VO_{2max}) in normovolemia and hypovolemia achieved by diuretics administration (change $[\Delta]$ in plasma volume $[PV]=-700$ ml) in a hot environment ($T_a=35^\circ\text{C}$). They suggested that hypovolemia significantly increased esophageal temperature (T_{es}) threshold for cutaneous vasodilation by 0.42°C and decreased the maximal SkBF by 50%. Moreover, Mack *et al.*¹⁰ reported that -40 mmHg of lower body negative pressure (LBNP), a maneuver that reduced the venous return to the heart, suppressed cutaneous vasodilation in response to increased T_{es} during exercise while the cessation of LBNP released the suppression. Similarly, other maneuvers to increase the venous return to the heart; acute blood volume expansion¹¹, a supine position^{12,13}, headout-of-water immersion¹⁴, or continuous negative pressure breathing¹⁵ all enhanced cutaneous vasodilation during exercise. These results support the notion that dehydration-induced hypovolemia suppresses cutaneous vasodilation by unloading baroreceptors.

There have been several studies suggesting that hypovolemia also suppresses sweating rate. Fortney *et al.*¹⁶ examined the effect of isotonic hypovolemia by 9% on local SR during exercise at 65–70% of VO_{2max} in a hot environment ($T_a=30^\circ\text{C}$, relative humidity [r.h.]=40%) and suggested that the T_{es} threshold for sweating remained

unchanged while SR on the chest and arm in response to increased T_{es} was significantly reduced. Moreover, Mack *et al.*¹⁰ suggested that the reduction in cardiac filling pressure by LBNP reduced SR during exercise. Dodt *et al.*¹⁷ suggested that skin sympathetic nervous activity was reduced by LBNP. In contrast, Kamiyo *et al.*¹⁸ suggested in subjects exercising at 60% of VO_{2max} in a hot environment ($T_a=30^{\circ}C$, r.h.=45%) that diuretics-induced hypovolemia ($\Delta PV=-10\%$) suppressed cutaneous vasodilation in response to increased T_{es} but not SR. Thus, it is unclear if SR is reduced by hypovolemia or not.

Hyperosmolality

Hypotonic sweat loss increases plasma osmolality (P_{osmol}). SkBF and SR were reported to decrease as P_{osmol} increased. Fortney *et al.*¹⁹ examined the effects of hyperosmolality on SkBF and SR during exercise at 70% of VO_{2max} in a hot environment ($T_a=30^{\circ}C$, r.h.=40%) and suggested that ~ 10 mosmol/kgH₂O of increase in P_{osmol} caused an upward shift of T_{es} thresholds for cutaneous vasodilation and sweating by $0.22^{\circ}C$ and decreased the sensitivity of SkBF in response to T_{es} . Takamata *et al.*²⁰ quantified the effect of P_{osmol} on the T_{es} threshold for cutaneous vasodilation and sweating in resting and passively heated subjects while immersing their lower legs in $42^{\circ}C$ water. P_{osmol} was increased by 3, 9, 15 mosmol/kgH₂O by intravenous infusion of hypertonic saline prior to passive heating. They reported that the T_{es} thresholds for cutaneous vasodilation and sweating increased linearly by $0.044^{\circ}C$ and $0.034^{\circ}C$ per 1-mosmol/kgH₂O increase, respectively.

Since the T_{es} threshold for cutaneous vasodilation increases with exercise intensity in a similar pattern to that in P_{osmol} ²¹, Takamata *et al.*²² hypothesized that the increase in the threshold with exercise intensity was caused by concomitantly increased P_{osmol} , and found that the upward shift of T_{es} threshold at a given increase in P_{osmol} in passively heated subjects was identical to that during graded exercise. Recently, Mitono *et al.*²³ found that the T_{es} threshold for cutaneous vasodilation increased with P_{osmol} when exercise intensity increased, but when the increase in P_{osmol} at high intensity of exercise was attenuated by prior hypotonic saline infusion, the T_{es} threshold was also attenuated (Fig. 1). These results support the hypothesis proposed by Takamata *et al.*²²

Interactive effects of hypovolemia and hyperosmolality

Hypotonic sweat loss induces hypovolemia and hyperosmolality. There have been few studies to investigate the interactive effects of hypovolemia and hyperosmolality on cutaneous vasodilation and sweating. Recently, we assessed the thermoregulatory responses during moderate exercise (60% VO_{2max}) in the warm ($T_a=30^{\circ}C$) in four

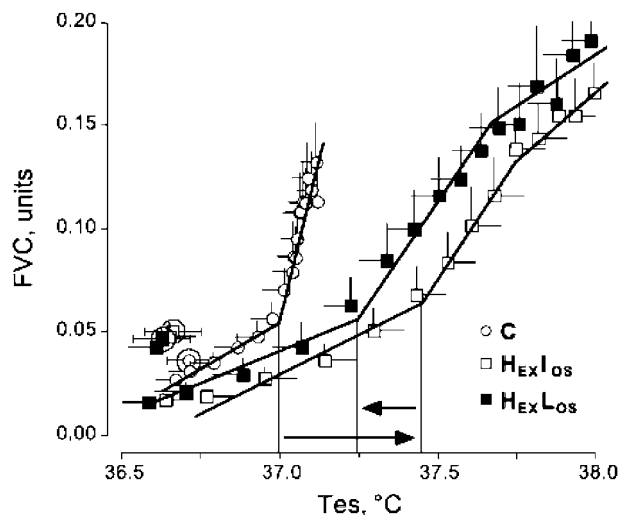


Fig. 1. Relationships between forearm skin vascular conductance (FVC) and esophageal temperature (T_{es}) during cycle ergometer exercise at 30% VO_{2max} in isoosmolality (C) and at 65% VO_{2max} in isoosmolality ($H_{EX I_{OS}}$) and hypoosmolality ($H_{EX L_{OS}}$).

Circled symbols indicate the values at rest. Values are means and SE for 8 subjects.

hydration conditions; control, normal PV with hyperosmolality, low PV with isoosmolality, and low PV with hyperosmolality, attained by combined treatment with diuretics, 24-h water restriction, and hypertonic saline infusion^{18, 24} (Fig. 2). The T_{es} thresholds for cutaneous vasodilation were higher in normal PV with hyperosmolality, low PV with isoosmolality, and low PV with hyperosmolality compared to control. The increase in T_{es} threshold was similar ($\approx 0.5^{\circ}C$) in all treatment conditions. In normal PV with hyperosmolality, maximal skin vascular conductance during exercise was similar to control but the rate of increase in skin vascular conductance per $^{\circ}C$ increase in T_{es} (sensitivity) was suppressed. On the other hand, in low PV with isoosmolality, the maximal skin vascular conductance was suppressed while the sensitivity of skin vascular conductance response remained unchanged. Finally, in the low PV with hyperosmolality condition, both of the maximal skin vascular conductance and the sensitivity were suppressed. The T_{es} threshold for sweating, the sensitivity of SR in response to increased T_{es} , and maximal SR all decreased significantly in the hyperosmotic conditions but did not in hypovolemia¹⁸. These results suggest that the suppressive effects of hypovolemia and hyperosmolality on the cutaneous vasodilation response is additive but their effect on the T_{es} threshold for vasodilation is not. Moreover, SR response is suppressed by hyperosmolality but not by hypovolemia.

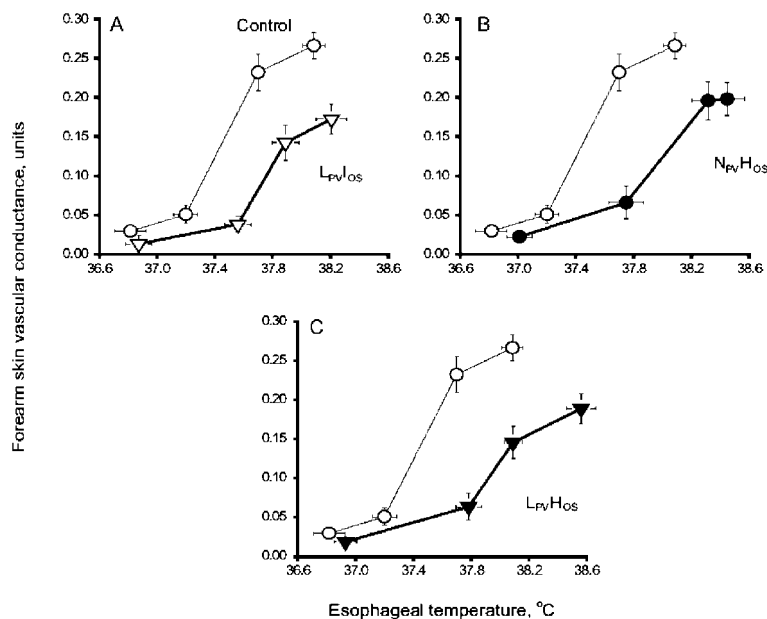


Fig. 2. Forearm vascular conductance (FVC) at a given increase in esophageal temperature (T_{es}) during exercise at 60% of VO_{2max} are shown as means \pm SE for 6 subjects.

FVC in low plasma volume and isoosmotic trial (L_{PvIos} , opened triangles; A), normovolemic and hyperosmotic trial (N_{PvHos} , closed circles; B), and low plasma volume and hyperosmotic trial (L_{PvHos} , closed triangles; C) are compared with that in control trial (Control, opened circles). The horizontal arrows are represented for the plateau value of FVC and the vertical arrows are represented for the T_{es} threshold for cutaneous vasodilation during exercise.

Heat Illness

Definitions and pathophysiology

Heat illness is caused not only by heat stress but also by body-fluid disturbance, and classified 4 categories; heat cramp, heat syncope, heat exhaustion, and heat stroke^{25, 26} as in Fig. 3. Heat cramp is thought to be due to ingesting water with no salt during restitution from thermal dehydration and is defined clinically by a painful muscle cramp. Heat syncope reflects cardiovascular failure caused by the reduced venous return to the heart due to excessive pooling of blood in peripheral dilated skin vasculatures with/without by hypovolemia due to excessive sweat loss. Heat exhaustion is caused by severe fluid and salt loss due to a large amount of sweat loss that results from exposure to high environmental heat or hard work or exercise and is defined by the clinical symptoms that involve high body core temperature (but $<40^{\circ}\text{C}$) and signs of cerebral ischemia such as weakness, discomfort, anxiety, dizziness, fainting, and headache. Heat stroke shows the most severe heat related disturbance that

sometimes becomes fatal. It is defined as a body core temperature greater than 40°C accompanied by hot and dry skin indicating impaired thermoregulation. Heat stroke is also associated with delirium, convulsions, or coma, indicating impaired central nervous system function.

Lipopolysaccharide and prognosis of heat stroke

Hales *et al.*²⁶ have introduced a new hypothesis concerning the mechanisms of heat stroke. They suggested that heat-induced splanchnic vasoconstriction makes intestinal cells ischemic leading to a break in the intestinal luminal barrier against gram-negative bacteria allowing lipopolysaccharide (LPS) from the cell wall of the bacteria to enter the circulating blood. Since LPS are known pyrogens, they cause a febrile response (fever) by suppressing heat dissipation and/or increasing heat production. The additional increase in body core temperature makes the condition worse. Experimentally, in animal models, the vascular resistance of splanchnic arteries increased with a rise in rectal temperature, but rapid splanchnic vasodilation generally occurs as rectal temperature

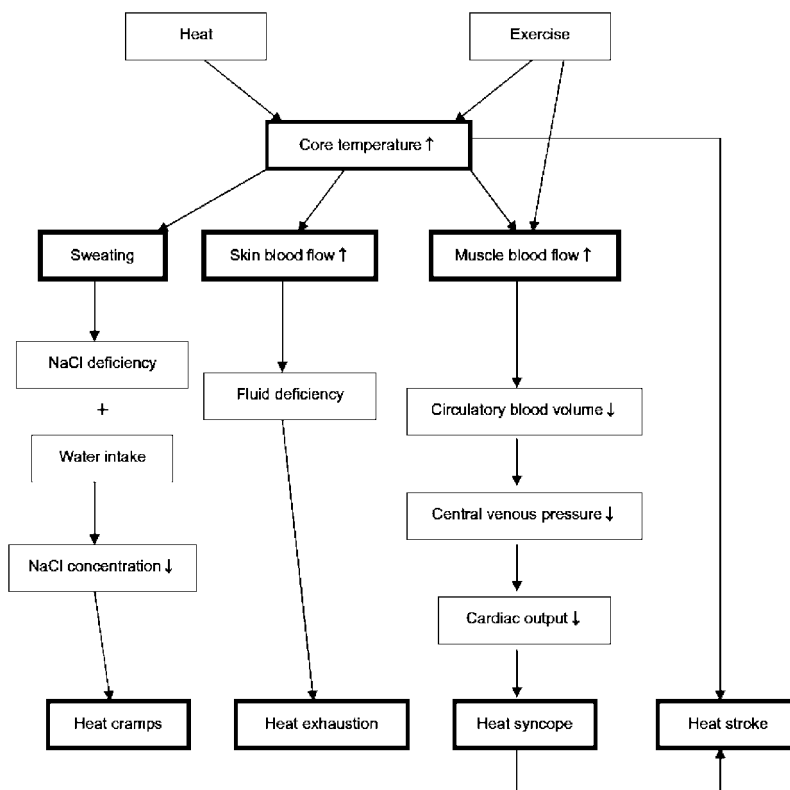


Fig. 3. Associations between physiological responses during exercise in a hot environment and pathophysiological mechanisms for heat-related illnesses.

reached 41°C and is followed by a rapid fall in arterial blood pressure^{27, 28}). As LPS enter the circulating blood from the intestinal lumen due to increased permeability, endotoxin shock occurs²⁸). In humans, Brock-Utne *et al.*²⁹) examined LPS concentration in blood sampled from heat stroke patients in an ultra marathon race (distance=89.5 km) and reported that patients with high level of LPS were more severe than that those with low level of LPS. These results suggest that the increase in LPS in blood above 40°C of core temperature makes the heat illness worse by infection in addition to the impairment of thermo and cardiovascular regulations.

Body Fluid Recovery

Blood volume in dehydration and exercise

The plasma water loss due to sweating is buffered by a fluid shift from the interstitial and intracellular fluid spaces (ICF). Hypovolemia decreases capillary pressure while increases capillary colloid osmotic pressure, which allow water to move from the interstitial to intravascular fluid space according to the changes in the Starling's forces. In addition, hyperosmolality in the extracellular fluid space (ECF) moves

water from ICF to ECF according to the osmotic gradient between the two spaces³⁰). As a result, a large amount of plasma water loss is buffered.

During exercise, since osmotic active substances of metabolites may be accumulated in the ICF of contracting muscles, additional fluid shift into muscle ICF occurs according to the osmotic gradient between the intra- and extravascular spaces³¹). The volume shifted to the contracting muscles is estimated to be around 1 liter during maximal cycle ergometer exercise³²). However, this volume is greater than the decrease in PV, indicating that fluid shifts into the vascular compartment must also occur. Lundvall *et al.*³²) reported that the decrease in PV was only a half of the volume shifted to the contracting muscles. These results suggest that hypovolemia and hyperosmolality are caused not only by dehydration but also by exercise itself although they are attenuated by fluid shift from other fluid compartments, both of which suppress heat dissipation mechanisms during exercise.

Fluid supplementation

Hypovolemia and hyperosmolality due to dehydration are not recovered completely before the lost body fluid is

restituted by ingesting fluid during voluntary drinking. Nose *et al.*³³⁾ assessed the effects of diluted sodium chloride solution on the restitution of fluid balance following thermal dehydration, and suggested that subjects recovered 82% of the lost body water (2.3% body weight) and 174% of PV loss when they ingested 0.45% of NaCl solution ad libitum for 3 h while only 68% and 78%, respectively, when they ingested tap water. Since P_{osmol} was elevated throughout the rehydration period with NaCl solution but returned to the control level by 30 min with tap water. They suggested that the maintenance of high P_{osmol} with NaCl solution retained ingested fluid in ECF by maintaining high plasma level of antidiuretic hormone as well as by preventing fluid shift to ICF. Also, they suggested that the high P_{osmol} maintained dipsogenic stimulation to thirst sensors in the hypothalamus to enhance fluid intake.

The recovery of body fluid by ingesting water improves thermoregulatory regulation. We recently examined the effects of PV recovery on the relationship between T_{es} and forearm SkBF during exercise at 60% $\text{VO}_{2\text{max}}$ in a hot environment ($T_{\text{a}}=30^{\circ}\text{C}$, r.h.=50%) in three groups; control, after thermal dehydration of 2% body weight, and after ad libitum rehydration with 0.45% NaCl solution for 2 h³⁴⁾. Dehydration decreased PV by 200 ml and increased P_{osmol} by 4 mOsm/kgH₂O, while rehydration recovered PV to the control level but P_{osmol} remained elevated at the same level as in dehydration. Dehydration increased the T_{es} threshold for cutaneous vasodilation and reduced maximal SkBF by 30%, but after rehydration, they returned to those in control. Although P_{osmol} did not recover, even a slight PV recovery was sufficient to release the inhibition of cutaneous vasodilation. Montain and Coyle³⁵⁾ studied body temperature regulation during prolonged exercise at 65% of $\text{VO}_{2\text{max}}$ for 120 min in a hot environment ($T_{\text{a}}=33^{\circ}\text{C}$, r.h.=50%) without fluid or with ingesting a carbohydrate-electrolyte solution during exercise. By the end of exercise, in the trial without fluid, PV decreased by 3% (100 ml) and P_{osmol} increased by 12 mOsm/kgH₂O compared those in the trial with carbohydrate-electrolyte solution, resulting in reduced cardiac stroke volume and cardiac output. T_{es} in the trial without fluid increased to 38.1°C and 38.6°C at 60 min and 120 min of exercise, respectively, whereas T_{es} in the trial with solution was around 38.1°C at 60 min of exercise but remained unchanged until the end of exercise. These results suggested that PV recovery with fluid replacement attenuates hyperthermia.

Excessive salt intake may have no advantage for thermoregulation during exercise though it retains more body fluid. Nielsen *et al.*³⁶⁾ examined the effects of three hydration

states on plateau T_{es} during exercise at 50% of $\text{VO}_{2\text{max}}$ in a hot environment; 1.5 l water intake, 1.0 l 2% NaCl solution intake, and dehydration by 1 kg body weight with exercise or sauna, prior to the test trial. They suggested that cardiac output in the trial after 2% NaCl trial was higher than that in the trial after dehydration but remained at the same level as that in the trial after water intake, and also that plateau T_{es} was extremely high in the trial after 2% NaCl intake compared to that in the trial after water intake and remained at the same level as that in the trial after dehydration. Montain and Coyle³⁵⁾ examined the effects of PV expansion by Dextran infusion on thermoregulation during exercise and suggested that the infusion maintained PV, cardiac stroke volume and cardiac output higher than those without infusion during 2-h exercise, but T_{es} increased at the same rate between the trials. These results suggest that hyperosmolality due to excessive intake of salt or infused osmotic contents before and during exercise causes hyperthermia despite of hypervolemia.

Energy supplementation

Carbohydrate (CHO) depletion often causes fatigue during exercise. Muscle glycogen utilization during exercise primarily depends on exercise intensity and is the highest during the early period after the start of exercise³⁷⁾. During exercise in the heat, the catabolic rate of CHO increases due to enhanced CHO oxidation rate, leading to enhanced muscle glycogen utilization and increased lactate concentration in the muscle and blood³⁸⁾. The high catabolic rate of CHO in the heat is associated with higher plasma adrenaline concentration as well as increased muscle temperature³⁸⁾. Dehydration is also thought to accelerate muscle glycogen utilization³⁹⁾. CHO ingestion during exercise is reported to enhance glucose uptake by the contracting muscles resulting in prolonging exercising time by delaying glycogen depletion in the muscles and the maintaining blood glucose level for fuel delivery to the brain³⁷⁾, resulting in improving endurance performance. To maximize muscle glycogen storage, CHO should be administered at least by 3 h before exercise⁴⁰⁾.

On the other hand, fructose has been noted during the last decades because of its several advantages for metabolisms. The first, pre-exercise administration of fructose does not induce hyperinsulinemia which is found in pre-exercise administration of glucose and results in a transient hypoglycemia during exercise^{41, 42)}. Furthermore fructose ingestion before exercise enhances fat utilization^{43, 44)} and conserves muscle glycogen⁴⁵⁾ during pro-longed exercise. However, several disadvantages also were reported

about fructose ingestion; the slower oxidation rate^{43,44} and greater gastrointestinal distress than glucose⁴⁶. The effects of fructose supplementation on endurance performance are inconsistent. However, pre-exercise ingestion of fructose is available for energy source of CHO at least as well as glucose without dumped endurance performance, despite the disadvantages above mentioned.

Gastric emptying and intestinal absorption

Gastric emptying increases in proportion to gastric volume up to 600 ml⁴⁷. Above this volume, a further increase in gastric emptying is absent. The rate of gastric emptying is approximately 40 ml/min when ingesting 750 ml distilled water⁴⁸. The emptying time depends on the calorie content of the solution⁴⁷; 30 ml/min (1.8 l/h) in 6% CHO solution and 25 ml/min (1.5 l/h) in 10% CHO solution, where CHO delivery to the gastro-intestinal tract is estimated 110 g/hr in 6% CHO solution and 150 g/h in 10% CHO solution⁴⁸. In addition, osmolality in the fluid does not seem to be a major factor to limit gastric emptying. For example, Vist and Maughan⁴⁹ reported that gastric emptying rates of 600-ml solutions were faster for diluted (40 g/l) glucose (230 mosmol/kgH₂O) or glucose polymer (42 mosmol/kgH₂O) than those for concentrated (188 g/l) glucose (1,300 mosmol/kgH₂O) or glucose polymer (237 mosmol/kgH₂O). However, the gastric emptying rate was no different between for the diluted glucose and glucose polymer, while it was slightly faster for the concentrated glucose polymer than that for the concentrated glucose. Considering that the maximal SR in most of endurance athletes is 1.5 l/h–2.0 l/h³⁰ and also that the maximal rate of exogenous CHO oxidation exceeds far 60 g/h⁵⁰, the delay in gastric emptying rate due to increased calorie in the solution is negligible compared with the merits of water and calorie recovery during exercise. However, severe dehydration >4% of body weight, high ambient temperature >49°C, and high intensity exercise >80% VO_{2max} are suggested to prolong the gastric emptying time⁴⁸. Thus, 6–10% CHO solution, commercially most available, does not induce a significant increase in gastric emptying time except for the extreme conditions.

In the small intestine, water is absorbed passively according to osmotic gradient between the lumen and the interstitial fluid space. So, theoretically, low osmotic solutions are likely absorbed more rapidly than high osmotic solutions. However, since the active Na⁺-glucose co-transporters in the intestinal cell membrane are suggested to accelerate the production of osmotic gradient between the lumens and the interstitial fluid space of intestine, water absorption increases by 6- to 10-fold by adding 2–6% CHO to saline⁴⁸. However, when

glucose concentration in the solution is over 8%, net water absorption rate in the intestine starts to decline and subjects sometimes experience gastrointestinal discomfort⁴⁸. From these results, they recommended that the concentration of CHO in saline should be around 6%.

Timing of intake

Drinking beverages prior to exercise or work may decrease heat accumulation in the body by attenuating hypovolemia and hyperosmolality. Montain and Coyle⁵¹ examined the effects of the timing of fluid ingestion on thermoregulation during exercise. Endurance-trained cyclists performed 140 min of cycle ergometer exercise at 62% VO_{2max} in a hot environment (T_a=33°C; r.h.=51%) in four trials; starting to drink 1,173 ± 44 ml of CHO solution, equivalent to 3% body weight, at 0 min, 40 min, or 80 min after the start of exercise, within 10–15 min or consumed the same total volume in small aliquots throughout exercise. They showed that fluid intake at 0 min significantly attenuated increases in T_{es} and heart rate from 40 min to 120 min of exercise compared with those in other trials, but T_{es} and heart rate at 140 min of exercise were similar among the trials. The results suggest that drinking CHO solution at the onset of exercise are more effectively suppresses the increases in T_{es} and heart rate than drinking in the later time of exercise.

Furthermore, previous reports indicated some adverse impacts of oropharyngeal stimulations due to drinking on body fluid regulation and cardiovascular system in dehydrated subjects. It is well-known that the stimulation of oropharyngeal reflexes by drinking such a small amount of water so as not to change PV and P_{osmol} reduces thirst sensation and plasma vasopressin secretion^{52, 53}. These responses have been thought to be a feed-forward mechanism to prevent over-hydration by drinking too much water^{52, 54}. However, as reported by Takamata *et al.*⁵³, SR response was suppressed by hyperosmolality in passively heated humans, but drinking water (even a small amount) released the suppression of SR responses in dehydrated subjects, suggesting that frequent drinks of a small amount of water do not restore body fluid balance but causes a greater loss of body fluid by increasing SR.

Moreover, we recently examined that the effects of oropharyngeal stimulations due to drinking on maintenance of arterial blood pressure during exercise in dehydrated humans⁵⁵. Subjects were asked to drink 200-ml warmed water at around 30 min of moderate exercise under a warm environment (T_a=30°C; r.h.=50%) in euhydrated and dehydrated conditions, simultaneously monitoring cutaneous vascular conductance and mean arterial pressure. We reported

that cutaneous vascular conductance decreased by 30% in dehydrated conditions compared with that in euhydrated condition before drinking, but it rapidly increased by 20% immediately after drinking in dehydrated conditions, followed by a fall in mean arterial pressure by 5 mmHg (Fig. 4). However, there occurred no changes in cutaneous vascular conductance and mean arterial pressure in euhydration. Because PV and P_{osmol} did not change during the period, oropharyngeal stimulation by drinking released the dehydration-induced suppression of cutaneous vasodilatation and reduced mean arterial pressure during exercise, suggesting that drinking in the late time of prolonged exercise causes transient hypotension and possibly makes subjects feel fatigue.

These results suggest that some large amount of fluid supplementation in the early period of working, before feeling thirst sensation, is recommended. Moreover, frequent small amount of fluid supplementation is not recommended.

Heat Acclimation

Improvements of thermoregulation

After repeated heat exposure or exercise training in a hot environment, the increases in heart rate and core temperature are attenuated with increased SkBF and sweating, resulting in prolonged exercising time⁵⁶. The increased SkBF and sweating responses are characterized by the low T_{es} threshold for cutaneous vasodilatation and sweating^{57, 58} and their enhanced sensitivity to increased T_{es} ^{57, 59}. The magnitude of adaptation depends on the intensity, duration, and frequency of heat exposures, but the most effective maneuver to acquire the adaptation should include 'exercise in the heat'⁵⁶. In general, the full adaptations are obtained after successive 10–14 d exposures to heat, while one-week intervals between each heat exposure induces no significant adaptation⁶⁰. Heat acclimation is transient and gradually disappears if not maintained by continued or repeated heat exposures. In the permanent residents of the tropical zone, basal metabolic rate (or basal heat production) is lower than those in more temperate zones⁶¹.

Blood volume expansion

Heat acclimation changes body fluid regulation, such as by reducing sodium concentration of sweat ($[\text{Na}^+]_{\text{sweat}}$) and by increasing thirst sensation to match body fluid loss, to expand total body water and blood volume⁶². Blood volume fluctuates with seasonal variation of T_{a} : 5% expansion in the hottest months and ~3% contraction in the coldest months⁵⁶. We recently reported that 3.5% PV expansion

occurred after 10-d endurance training (at 60% $\text{VO}_{2\text{max}}$ for 1 h/d) in warm environments ($T_{\text{a}}=30^{\circ}\text{C}$) with concomitant improvement of thermoregulatory responses⁵⁷. More recently, Ichinose *et al.*⁵⁹ suggested that the increases in blood volume and cardiac stroke volume after endurance training for 10 d are closely associated with the enhanced sensitivity of cutaneous vasodilatation to increased T_{es} during exercise in a hot environment. These results suggest that fluid expansion is closely associated with the improvements of thermoregulatory responses.

Regarding the mechanisms for fluid volume expansion after heat acclimatization, Convertino *et al.*⁶³ suggested that 8% blood volume expansion (=457 ml) after 8-d endurance training at 65% $\text{VO}_{2\text{max}}$ for 2 h/d was caused by facilitated Na^+ and H_2O retention due to nine folds increases in plasma rennin activity and vasopressin during exercise, and also by chronic increase in plasma albumin content after exercise to retain plasma water in the intravascular space. Nagashima *et al.*⁶⁴ suggested that PV increased by 170 ml at 22 h after single intense exercise (85% $\text{VO}_{2\text{max}}$), which was accompanied by an increase in plasma albumin content. Furthermore, they suggested that the expansion was caused by enhanced albumin synthesis⁶⁵.

Allan and Wilson⁶⁶ suggested that SR increased by 70% after the acclimation by immersing subjects in a 40-°C water bath for 1 h daily for 3 wk. They also suggested that $[\text{Na}^+]_{\text{sweat}}$ before acclimation varies inter-individually, ranging 30 to 60 mEq/l, but which was positively correlated with SR ranging 0.6 and 1.2 mg/cm²/min. However, after acclimation, the relationship moved downward; $[\text{Na}^+]_{\text{sweat}}$ decreased to 10 and 35 mEq/l at the same SR. Hypotonic sweat loss is advantageous for maintaining PV because the larger amount of free water loss in sweat causes a greater increase in ECF osmolality that facilitates water movement from the ICF to ECF space according to the osmotic gradient between the spaces³⁰. For example, 90% of sweat loss comes from ECF in a subject secreting 100 mEq/l of $[\text{Na}^+]_{\text{sweat}}$, while only 40% in a subject secreting 15 mEq/l of $[\text{Na}^+]_{\text{sweat}}$. Moreover, when sweat loss is 2,000 ml the subject secreting 100 mEq/l of $[\text{Na}^+]_{\text{sweat}}$ loses 347 ml of PV while only 160 ml in the subject secreting 15 mEq/l of $[\text{Na}^+]_{\text{sweat}}$.

Greenleaf *et al.*⁶⁷ studied the mechanisms for increased thirst sensation during heat acclimation. They asked subjects to performed a cycle ergometer exercise at 75 W in a hot environment for 2 h/d for 8 consecutive days ($T_{\text{a}}=40^{\circ}\text{C}$, r.h.=50%) and a similar regimen in a thermoneutral environment ($T_{\text{a}}=24^{\circ}\text{C}$, r.h.=50%). They showed that voluntary fluid intake during the 2 h of exercise was around 180 ml/h and remained at the level throughout 8 d in the thermoneutral

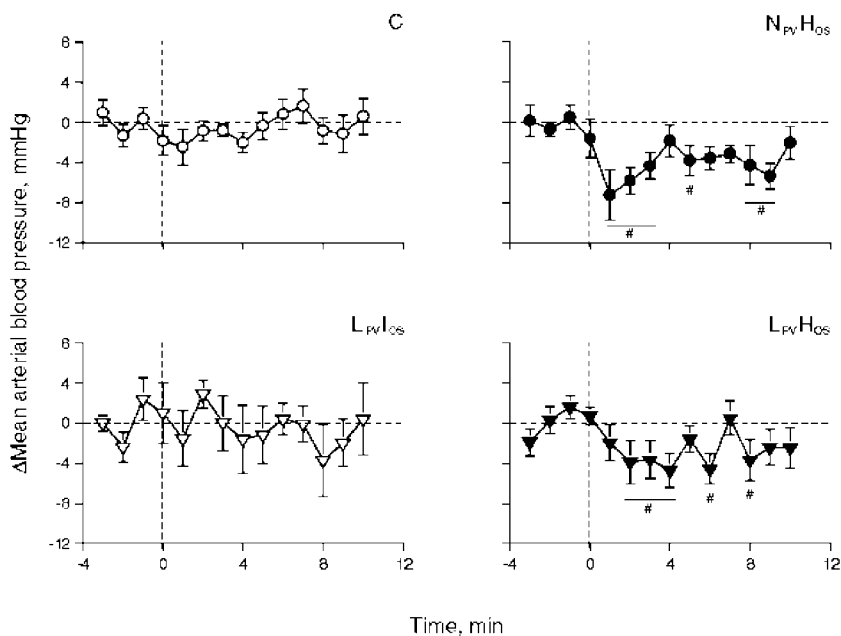


Fig. 4. Changes in mean arterial pressure after drinking are presented as the differences from the baseline for 3 min before drinking in control trial (C, opened circles; upper left), low plasma volume and isoosmotic trial (L_{PV}I_{0S}, opened triangles; lower left), normovolemic and hyperosmotic trial (N_{PV}H_{0S}, closed circles; upper right), and low plasma volume and hyperosmotic trial (L_{PV}H_{0S}, closed triangles; lower right).

#, Significant difference from the baseline within each trial at the level of $P < 0.05$.

group, but it increased from 450 ml/h on day 1 to about 1,000 ml/h on days 5–8 in the acclimation group. Since the changes in plasma sodium concentration, P_{osmol} , and AVP were minimal in both groups, they suggested that the loss of body fluid volume and the enhanced rennin-angiotensin system were closely associated with the enhanced fluid intake in the acclimation group.

Taken together, the following mechanisms probably contribute to the body fluid expansion during heat acclimation: 1) increased plasma rennin activity and vasopressin release by exercise, 2) increased albumin synthesis after exercise, 3) decreased $[\text{Na}^+]_{\text{sweat}}$, and 4) increased voluntary fluid intake.

Blunted hyperosmotic suppressions of thermoregulatory responses

As stated above, hyperosmolality suppresses thermoregulatory responses and P_{osmol} increases with exercise intensity. The blunted hyperosmotic suppression of thermoregulation after heat acclimatization was first reported by Takamata *et al.*⁶⁸⁾ They measured sweating and cutaneous vasodilation responses during passive heating in hyperosmotic and normosmotic conditions, and compared the responses between heat-acclimated and non-heat-

acclimated groups of young men. They suggested that the sensitivity of the upward shift of T_{es} thresholds for sweating and cutaneous vasodilation at a given increase in P_{osmol} was reduced in heat-acclimated subjects in whom an increase in P_{osmol} at a given loss of sweat was enhanced due to low $[\text{Na}^+]_{\text{sweat}}$. These results suggest that the hyperosmotic suppression of sweating and cutaneous vasodilation was attenuated after heat acclimation with reduced $[\text{Na}^+]_{\text{sweat}}$.

To examine the hypothesis that the hyperosmotic suppression of cutaneous vasodilation was blunted after endurance training, Ichinose *et al.*⁵⁸⁾ measured SkBF and local SR responses to 20-min cycle ergometer exercise at 70% $\text{VO}_{2\text{max}}$ in a warm environment of 30°C of T_{a} and 50% r.h. in isoosmotic and hyperosmotic conditions, and compared the results before and after training. They suggested that the upward shift of T_{es} threshold for cutaneous vasodilation at a given increase in P_{osmol} was reduced after training whereas that for sweating remained unchanged (Fig. 5). Since the reduction in each subject was significantly correlated with the increase in PV after training, they suggested that the stretch of baroreceptors due to PV expansion^{57, 58)} was involved in the reduction. However, they also suggested that there was no causal relationship between the reduction in osmotic suppression of cutaneous vasodilation and plasma

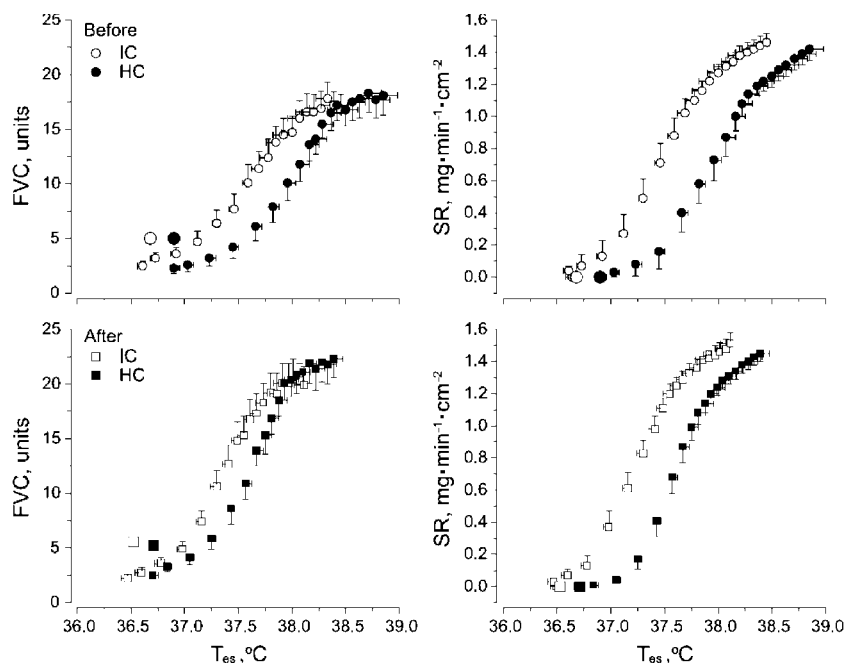


Fig. 5. Forearm vascular conductance (FVC; left) and local chest sweat rate (SR; right) responses at a given increase in esophageal temperature (T_{es}) at rest and during exercise at 70% of pretraining $\dot{V}O_{2max}$ in isoosmotic and hyperosmotic conditions before (top) and after endurance training (ET; bottom).

Large symbols indicate the averaged values during resting period. IC and HC represented isoosmotic and hyperosmotic conditions, respectively. Values are means \pm SE for 9 subjects.

expansion but they were caused by different mechanisms associated with heat acclimation.

The Elderly

Impaired thermoregulatory and body fluid regulations

The vulnerability to the heat stress in the elderly is caused by reduced heat dissipation mechanisms and impaired body fluid regulation in the elderly, resulting in less total body as well as local SR in response to passive heating or exercise are lower than those in young adults⁶⁹. The idea that sweat gland function deteriorates with aging seems to be supported by the findings that SR per a single gland and the sweat gland densities responding to hyperthermia and pharmacological stimulation decreased in the elderly⁷⁰. Recently, it has been suggested that older subjects with matched $\dot{V}O_{2max}$ to younger subjects showed lower SkBF response to total body or local passive heating as well as exercise in a hot condition than younger subjects^{71,72}. Kenney *et al.*⁷² blocked the local release of norepinephrine on the forearm with bretylium tosylate in subjects exercising at an air temperature of 36°C, and suggested that the limited cutaneous vascular response to hyperthermia by exercise

in older men was mainly caused by decreased sensitivity of active vasodilator system to increased T_{es} .

Okazaki *et al.*⁷³ have recently shown that the improved sensitivities of cutaneous vasodilation and sweating responses at a given increase in T_{es} after 18-wk endurance or resistance training in the elderly were positively correlated with the increase in blood volume, suggesting that the reduced heat dissipation mechanisms is closely associating with body fluid regulation (Fig. 6). Mack *et al.*⁷⁴ compared osmotic control of thirst and free water clearance in the elderly with those in the young by assessing rehydration process for 3 h after -2.4% body weight loss, and measured PV, P_{osmol} , renal function, and thirst before and after dehydration and during rehydration. In the elderly, PV before dehydration was lower (43.1 ± 1.6 vs. 48.1 ± 2.5 ml/kg), P_{osmol} was higher (287 ± 1 vs. 281 ± 2 mosmol/kgH₂O), and perceived thirst was lower than those in the young. During rehydration, the osmotic threshold for thirst increased in the elderly, resulting in less total fluid intake during rehydration than in the young (8.9 ± 2.0 vs. 16.6 ± 4.1 ml/kg). However, the relation between thirst and the rate of fluid intake was maintained in the elderly. These are identical to the results reported by Phillips *et al.*⁷⁵ reported that thirst sensation after 24-h water deprivation

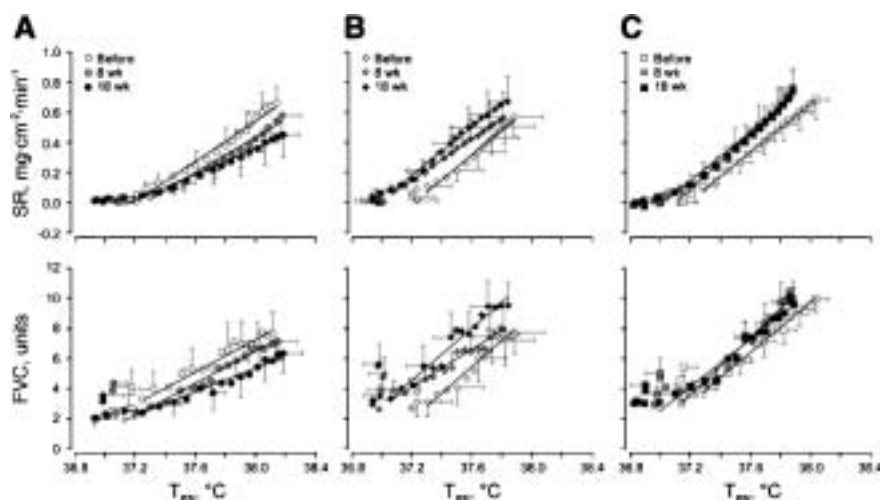


Fig. 6. Sweat rate (SR) and forearm skin vascular conductance (FVC) responses as a function of an increase in esophageal temperature (T_{es}) during exercise at the intensity of 60% of pretraining VO_{2max} in a warm environment (ambient temperature=30°C; relative humidity=50%).

A: control (C; circles). B: resistance training (RT; diamonds). C: aerobic training (AT; squares). Open symbols, before training; gray symbols, 8-wk training; solid symbols, 18-wk training. Values are shown as means \pm SE.

was attenuated in the elderly. Moreover, there have been several studies suggesting that sodium retention mechanisms are reduced in the elderly; higher $[Na^+]_{sweat}$ due to impairment of the salt reabsorptive ability of sweat gland ducts⁶⁹⁾ and the decrease in renal concentrating ability in aging rats due to the impaired responsiveness of the kidney to AVP⁷⁶⁾. These results suggest that the reduced heat dissipation mechanisms in the elderly are partially explained by impaired body fluid regulation.

Effects of exercise training

Although thermoregulatory responses are improved by exercise training in young subjects, there have been few studies to assess in the elderly whether body fluid regulation is involved in or not. Okazaki *et al.*⁷³⁾ assessed the effects of 18-wk exercise training on thermoregulatory responses and blood volume in the elderly, divided into three training regimens; control, aerobic training (50–80% VO_{2max} 60 min/d, 3 d/wk), and resistance training (knee extension and flexion at 60–80% of 1 RM \times 8, 2–3 sets/d, 3 d/wk, RT) (Fig. 6). After 18 wk of training, VO_{2max} increased by 20% in aerobic training and 10% in resistance training while blood volume remained unchanged in both trials. In addition, T_{es} thresholds for cutaneous vasodilation and sweating, determined during 30-min exercise of 60% VO_{2max} at 30°C, decreased in aerobic

and resistance training but not in control. In contrast, the sensitivities of forearm skin vascular conductance and sweating rate responses to increased T_{es} remained unchanged in all trials. However, because the sensitivities of thermoregulatory responses were increased in subjects with increased PV, blood volume expansion might be critical in the improvements of thermoregulatory responses in older men.

Effects of supplementation

More recently, they examined effects of protein and carbohydrate supplementation during aerobic training (60–70% of VO_{2max} , 60 min/d, 3 times/wk, for 8 wk) on improvements of PV and thermoregulatory capacity in the elderly⁷⁷⁾, divided into two groups according to supplementations; protein-carbohydrate and placebo. Subjects supplemented protein and carbohydrate (3.1 kcal/kg, 0.18 g protein/kg) in the protein-carbohydrate group while placebo (0.5 kcal/kg, 0 g protein/kg) in the placebo group within 10 min after each training. Subjects performed 20-min exercise test at 60% of pre-training VO_{2max} in a warm condition ($T_a=30^\circ C$) before and after the training period, while measuring thermoregulatory responses. Then they reported that after 8-wk training, PV and stroke volume during exercise in the protein-carbohydrate group increased by 6% and 11%, respectively, but did not in the placebo group,

resulting that the sensitivity of an increase in forearm vascular conductance at a given increase in T_{es} increased by about twofold in the protein-carbohydrate group but did not in the placebo group. Thus, protein and carbohydrate supplementation take advantages for the improvements of thermoregulatory capacity after aerobic training in elderly, included with the expansions of PV and stroke volume and the enhancement of heat dissipation system.

Practical Considerations

First, we recommend drinking beverage during working. When a person does physical labor outside in the summer, he/she may secrete 1.5–2.0l of sweat per hour and NaCl loss in sweat is about 1.2–3.5 g per hour. Assuming that the intensity of his/her labor is equivalent to moderate exercise at 135 watts and 50% of total energy requirements comes from glucose, about 80 g glucose per hour may be consumed. To prevent hyponatremia and/or hypoglycemia, they should ingest the same volume of fluid as sweat loss containing more than 1.2 g/l (20 mEq/l) of NaCl and 60–80 g/l (5.7–7.4%) of glucose. Commercially available beverages have compositions that meet these requirements. They should start to ingest in the early period of work before they feel thirsty, and it is recommended that the amount per one drink is some large.

Second, if work lasts over a long period in the summer, an employer should reduce work intensity until workers acclimate to the hot conditions for at least the first 2–3 d. Every worker should work at an appropriate intensity based upon an individual's level of physical fitness; i.e. setting work intensity lower for the elderly than that for the young.

Finally, several special attentions should be paid to the elderly who work in the heat. The elderly should drink a given amount of beverage every 20 or 30 min even though they do not feel thirsty. Moreover, in the elderly, ingesting protein supplements during and after a work period would accelerate body fluid expansion resulting in enhancing heat dissipation and a reduced risk of developing heat illness.

Acknowledgements

We acknowledge to Dr. Gary W. Mack, Department of Exercise Sciences, Brigham Young University, and Dr. Akira Takamata, Department of Life Science and Human Technology, Faculty of Human Life and Environment, Nara Women's University, for their critical reading of this review.

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