Heat stress and orthostatic tolerance

Fumio Yamazaki

School of Health Sciences, University of Occupational and Environmental Health, 1-1 Iseigaoka, Yahatanishi-ku, Kitakyushu 807-8555, Japan

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Abstract

In healthy individuals, exercise and nonexercise (i.e. passive body heating) heat stress induces vulnerability in the cardiovascular system, and is apt to cause hypotension during upright posture, resulting in a reduction of orthostatic tolerance. Reduced orthostatic tolerance is linked to multiple physiological mechanisms including 1) a redistribution of blood flow from central parts of the body to skin, 2) an increase in leg venous compliance, 3) altered baroreflex function, 4) an attenuated venoarterial response in the lower extremities, and 5) a decrease in plasma volume. A combination of countermeasures such as cooling of the body, rehydration, and heat acclimation, can improve orthostatic tolerance in a hot environment. The purpose of this review was to summarize findings investigating the causes of and preventive approaches to heat stress-induced orthostatic intolerance.

Keywords: heat stress, orthostatic tolerance, blood pressure

Introduction

Physical and mental stress is a frequent occurrence in daily life including work and sports. This stress increases the strain on cardiovascular control systems1-3). Working upright in the heat is particularly stressful on the body (heat + gravitation + exercise) in terms of maintaining blood pressure within the normal range. Dynamic exercise abruptly increases metabolic heat production in active muscle4) and the excess heat production relative to heat loss during exercise increases core body temperature in an intensity-dependent manner5,6). When dynamic exercise is performed in a hot environment, the exercise and environmental heat stress aggravates the physical strain that is manifested by greater increases in body temperature and heart rate (HR) and reduced performance of exercise5-9). In addition, heat stress greatly compromises blood pressure control during orthostatic challenge10-14), gravitational acceleration15), and simulated hemorrhage via lower body negative pressure (LBNP)16-18) (Fig. 1). Lind et al.11) administered a 5-min head-up tilt (HUT) test to 43 subjects in cool (18-20°C) and hot (35 or 45°C) environments, and observed that no subject fainted in the cool environment while fainting episodes occurred in 15 (35 %) subjects in the hot environment. More recently, Keller et al.17) reported that whole-body heat stress, induced by a hot water-perfused suit, reduced orthostatic tolerance as assessed using graded LBNP, compared to normothermia. The mechanisms resulting in this response are still unclear, but would be related to a redistribution of blood flow, coupled with marked cutaneous vasodilation, increased leg venous compliance, altered baroreflex function, attenuated venoarteriolar response and decreased plasma volume (PV)19,20).

Fig. 1 Changes in mean arterial pressure, heart rate and forearm skin vascular conductance during normothermia and whole-body heating in a healthy male volunteer. Abrupt reductions in arterial pressure and heart rate (i.e. presyncopal signs) were observed during 70° head-up tilt during heating.
This review provides a brief overview of orthostatic intolerance during heat stress. For further information on topics related to cardiovascular control during heat stress, the reader is referred to several excellent reviews21-26). The purpose of this review is to present findings from human studies investigating the causes of and countermeasures to heat stress-induced orthostatic intolerance.

**Potential mechanisms for orthostatic intolerance during heat stress**

1. **Redistribution of blood flow**

Cardiovascular control under heat-stressed conditions was elegantly studied by Rowell and colleagues in the 1960s and early 1970s24-30). These researchers investigated the cardiovascular responses to direct passive heating of the body with hot water-perfused suits, heating subjects to the limits of thermal tolerance to elicit maximal hemodynamic responses to heat stress. Cardiac output (CO) in some subjects more than doubled from baseline to the limit of thermal tolerance. This increase in CO was accomplished by an increase in heart rate (HR) and an increase in, or maintenance of, stroke volume (SV), despite a fall in central venous pressure (CVP). The increase in SV was therefore attributed to an increase in cardiac contractility. In addition, high skin and core temperatures resulted in a redistribution of blood flow from the splanchnic and renal vascular beds30). A decrease in central blood volume (CBV) with increasing body temperature also resulted in a decrease in the left atrial diameter (LAD, an index of CBV)(~1.5 mm decrease per 1°C rise of core temperature) at supine rest31,32) (Fig. 2). The decrease in atrial size could be cancelled out by head-down tilt (HDT)31,32), suggesting that raising the legs above the heart level during rest is practically important for rapid recovery from heat syncope. Compared with young subjects, older subjects had a lower CO and less blood flow from the splanchnic and renal circulation during passive heating33). As a result of these combined attenuated responses, older males had a significantly lower increase in total blood flow directed to the skin. Using this model to study thermoregulatory control, Rowell24) estimated that total skin blood flow (SkBF) in young men could increase from 0.3 l/min (~5% of CO) in normothermic conditions up to 7.6 l/min (~60% of CO) during maximal passive heat stress. In hyperthermia, therefore, cutaneous vessels become large storage spaces for blood and extensively influence venous return. Furthermore, since vasomotor control in the skin markedly contributes to changes in total peripheral vascular resistance (PVR) during heat stress, the control of SkBF plays a pivotal role in maintaining blood pressure. Although it had been thought that cerebral blood flow was relatively stable during heat stress, data obtained from transcranial ultrasonography recently showed that a decrease in arterial P_CO2 caused by hyperventilation during hyperthermia resulted in a reduction of cerebral blood flow velocity34-39). LBNP decreased cerebral blood flow velocity during whole body heating but not during normothermia18,39). These findings suggest that the heat stress-induced reduction of cerebral blood flow contributes to orthostatic intolerance.

2. **Increase in leg venous compliance**

The postural change from supine to an upright position induces a shift in blood by 500-700 ml from the upper body to the lower extremities40). Increased venous distensibility in the lower extremities increases the volume of blood pooled there and reduces the venous return to the heart during orthostatic stress. Such changes in the leg veins lead to a reduction of blood pressure with a decrease in cardiac filling. It has been thought, therefore, that leg venous distensibility is a determinant of orthostatic tolerance in normothermic humans41-43). Muscle venous volume accounts for approximately 85% of the leg venous volume in normothermia44,45). Whole-body heating induces cutaneous venodilatation in the legs and arms46,47) and decreases muscle venous volume as a percentage of the total volume of leg veins with an increase in skin venous volume. Compared with normothermic control, whole-body heating rapidly increases calf volume during the early phase of HUT, whereas whole-body cooling decreases the magnitude and the speed of change in calf volume48). Local heating to the legs in normothermia increases the blood flow in the warmed skin area and increases the speed of the change in calf volume the same way.
as that during whole-body heating. That is, the thermal modulation in leg venous distensibility is almost independent of whole-body or local heating. These findings suggest that the blood flow and venous distensibility in skin, rather than in muscle, characterize the pattern of initial change in leg volume in response to increased leg venous pressure in heat-stressed humans. HUT decreased LAD from tilted angle-dependent manner, and LAD during HUT at a given angle was decreased by whole-body heating (Fig. 2). The effects of both types of stress on LAD were additive. In a hot environment, since increased venous distensibility in the lower extremities rapidly decreases cardiac filling resulting in hypotension, a sudden change of posture to a standing position should be avoided.

3. Alteration of baroreflex function

Baroreflex function is an indispensable control mechanism for arterial blood pressure. In recent years, influences of heat stress on the baroreflex control of HR and peripheral vascular resistance (PVR) or muscle sympathetic nerve activity (MSNA) have been extensively studied in human subjects.

1) Effect of heat stress on baroreflex control of HR.

Baroreceptors in the aorta and carotid sinuses sense mechanical distension in the arterial wall by changes in arterial blood pressure. Stimulation of these receptors increases their afferent input to the cardiovascular centers and decreases HR via reduced sympathetic and increased parasympathetic nerve activity. Carotid baroreceptor-cardiac response has been evaluated noninvasively based on beat-to-beat HR response to a change in carotid arterial pressure produced by the application of negative or positive pressure using a neck chamber. With this technique, the effect of heat stress on the relationship between carotid distending pressure and HR has been examined in the supine position. Prior reports showed that whole-body heating did not alter the sensitivity of the carotid baroreflex for controlling HR, as defined by the maximal slope of the linear portion of the baroreflex curve around the operating point, irrespective of heating levels (Fig. 3). The unchanged sensitivity of arterial baroreflex control of HR during heat stress has been shown in other studies using pharmacological manipulation of arterial pressure and evaluation of the spontaneous relationship between arterial pressure and HR (i.e. sequence method).

In subjects with lower orthostatic tolerance, however, the sensitivity of HR response to spontaneous changes in arterial pressure was significantly reduced during passive heating (~0.6°C increase in core temperature and ~22 beats/min increase in HR from normothermic baseline levels). Disparate findings regarding the effect of heat stress are due to different representations of cardiac response. That is, when RR intervals were used as an index of cardiac effector response, heat stress reduced the sensitivity of baroreflex control for cardiac intervals with the neck chamber technique and sequence method, because the relationship between HR and RR intervals is a hyperbolic function. Because beat-to-beat changes in RR intervals closely relate to cardiac vagal efferent activity, the use of RR intervals is thought to be better for elucidating the modulation of vagal control of cardiac baroreflex function. However, if SV and PVR are almost constant during brief pressure perturbations, the HR changes are related linearly to the arterial pressure (i.e. arterial pressure = HR × SV × total PVR), and the use of HR may be better for evaluating baroreflex sensitivity in the maintenance of arterial pressure. In a study...
using transfer gain analysis in beat-to-beat changes in arterial pressure and HR\(^5\)\(^8\), severe passive heating (~0.9°C increase in core temperature, ~26 beats/min increase in HR) reduced dynamic baroreflex regulation of HR within the high-frequency range (0.2-0.3 Hz) by approximately 50% without significantly affecting the gain within the low-frequency range (0.03-0.15 Hz), suggesting a heat stress-induced reduction in the vagal cardiac controlling function. Collectively, it is thought that the sensitivity of sympathetic baroreflex control of HR is not reduced during passive heating, but the sensitivity of parasympathetic baroreflex control of HR is reduced under severe heat stress, while vagal activity is intensively inhibited. Healthy subjects with lower orthostatic tolerance show a significant reduction in the sensitivity of parasympathetic baroreflex control even when mildly heat-stressed.

In prior studies\(^5\)\(^0\)-\(^5\)\(^2\),\(^5\)\(^9\), a rise in the operating point relative to the responding range in the arterial baroreflex response curve under heat stress has been reported (Fig. 3). The rise suggests that the capacity for a tachycardiac response to the rapid onset of hypotension is reduced and the capacity for a bradycardiac response to sudden hypertension is increased. To address whether the reduced responsiveness of HR to rapid hypotensive stimulation is due to a slowing of the response, Yamazaki et al.\(^6\)\(^0\) examined the effect of whole-body heating on the response time of HR and blood pressure following 5 s of neck pressure (NP) at 40 mmHg during supine rest. Whole-body heating increased significantly from the onset of NP until the peak of the tachycardiac response (3.93±0.35 s in normothermia and 5.20±0.24 s during heating), and from the onset of NP until the peak of the blood pressure response (6.75±0.51 s in normothermia and 9.39±0.62 s during heating). These results suggest that heat stress prolongs the response time of carotid-cardiac and carotid-vasomotor baroreflexes. This sluggish responsiveness may affect the feedback control system for blood pressure and impair the ability to maintain blood pressure during orthostatic stress in a hot environment. The heat stress-induced instability in the feedback control system is also represented by increased variability of blood pressure during HUT\(^6\)\(^1\).

As described above, the cardiovascular system under hyperthermic conditions adjusts the SkBF to increase heat dissipation, resulting in a reduction in the volume of blood available to the heart and other splanchnic organs. Therefore, the size of the atria in subjects, tilted at a given angle, is smaller during whole-body heating than during normothermia\(^9\)\(^2\)\(^0\), suggesting that heat stress decreases venous return to the heart and therefore increases the unloading of cardiopulmonary baroreceptors during an orthostatic challenge. To elucidate the combined effects of orthostatic and heat stress on arterial baroreflex function in controlling HR, Yamazaki and Sone\(^5\)\(^1\) investigated whether, during 70° HUT, arterial baroreflex control of HR is modified by whole-body thermal stress. The sensitivity of the arterial baroreceptor-cardiac response was calculated from the spontaneous changes in beat-to-beat arterial pressure and HR during normothermia and whole-body heating. The sensitivity of HR response significantly decreased with HUT under both thermal conditions; the decreased rate of sensitivity was greater during heating (~63±4%) than normothermia (~47±4%). The heating-induced reduction in sensitivity during orthostatic stress might be due to an exaggerated inhibition of parasympathetic activity, because the sensitivity of spontaneous baroreflex control of HR declined with the decreasing spectral power of RR interval variability in the high-frequency range during graded LBNP\(^6\)\(^2\). Spontaneous baroreflex sensitivity is reportedly modified by closed-loop influences\(^6\)\(^3\), but the combined effect of orthostatic and heat stress on open-loop characteristics of the arterial baroreflex function remains unclear.

2) Effect of heat stress on baroreflex control of peripheral vasomotion

Neural control of peripheral vasomotion becomes an important factor in preventing an excess drop in blood pressure due to the redistribution of blood caused by orthostatic stress. To identify whether heat stress impairs baroreflex control of total PVR during orthostatic stress, subjects were exposed to HUT at angles from 15° to 60° in both normothermic and whole-body heating conditions\(^4\). Whole-body heating reduced total PVR with increasing SkBF and decreased the LAD, and also shifted downwards the line reflecting the linear relationship between total PVR and LAD during graded HUT. Additionally, the slope of the line was less steep for whole-body heating than for normothermia. These results suggest that heat stress impairs the sensitivity of integrative (arterial + cardiopulmonary) baroreflex control of total PVR. When vascular conductance instead of vascular resistance was used as an index of vasomotor response, however, heat stress did not significantly change the sensitivity of integrative baroreflex control\(^2\)\(^0\). Thus the influence of heat stress on baroreflex sensitivity of peripheral vasomotion is still open to further discussion concerning an interpretation of the results.

Since peripheral vasomotion is under baroreflex control via vasomotor sympathetic nerve activity, impaired functioning of the system controlling vasomotor sympathetic nerve activity can induce hypotension in the early phase of orthostatic stress. To test the hypothesis that heat stress reduces the baroreflex response during falling arterial pressure for a short period in humans, MSNA was analyzed during early phase II (the period of falling arterial pressure) of the Valsalva maneuver in normothermic and heating conditions (~0.8°C rise in core temperature and ~23 bursts/min increase in MSNA)\(^6\)\(^4\). The baroreflex slopes of MSNA and HR against mean arterial pressure in phase II decreased 30±8% and 24±9% respectively during heat stress\(^6\)\(^4\), suggesting that heat stress reduces the baroreflex responses of MSNA and HR during a period
of rapid decline in blood pressure. In contrast, it has been reported that arterial baroreflex responses of MSNA were increased by mild heat stress (~0.4°C rise in core temperature and ~13 bursts/min increase in MSNA)\(^5\). Cui et al.\(^3\) caused a change in arterial blood pressure by injecting a bolus of sodium nitroprusside and phenylephrine to assess arterial baroreflex sensitivity of MSNA during both normothermic and heat-stressed conditions in the supine position. They observed that whole-body heating did not alter arterial baroreflex sensitivity for controlling MSNA, but heat stress caused an upward shift of the baroreflex curves expressing MSNA-diastolic blood pressure. When MSNA responses were evaluated against the reduction in CBV indexed from thoracic impedance or CVP during MSNA responses were evaluated against the reduction in CBV indexed from thoracic impedance or CVP during orthostatic stress, the slopes reflecting the linear relationship between the reduction in CBV and the increase in orthostatic stress, the slopes reflecting the linear relationship during 10° head-down and head-up tilt \(^6\) under mildly heat-stressed conditions. Thus, the findings, regarding the influence of heat stress on arterial and cardiopulmonary baroreceptor control of MSNA, are inconsistent, perhaps due to different experimental conditions and different methods of analyzing baroreflex sensitivity.

Heat stress may hinder translation from sympathetic activation to vasoconstriction, because passive heating has been shown to attenuate \(\alpha\)-adrenergic vasoconstriction in isolated dog veins\(^7\) as well as \textit{in vivo} and \textit{in vitro} rat preparations\(^8\). In human studies, both local (37-42°C of skin temperature) and whole-body heating decreased the sensitivity of the cutaneous vessels to constrict in response to norepinephrine (NE), as indexed by a significant elevation in the dose of NE required to elicit 50% maximal vasoconstriction (i.e., \(EC_{50}\))\(^9\), although a follow-up study showed that local skin heating to 40°C did not attenuate cutaneous vasoconstriction in response to NE doses compared with a 34°C control condition\(^10\). Cui et al.\(^3\) demonstrated that whole-body heat stress reduced mean arterial pressure and total PVR response to venous infusion of phenylephrine, leading to speculation that heat-induced attenuation of \(\alpha\)-adrenergic vasoconstriction may contribute to accompanying orthostatic intolerance.

4. Modification of local vascular response

Cutaneous vasoconstriction during orthostatic stress occurs more remarkably in legs than in arms at the heart level\(^2\)\(^3\)\(^4\). The greater cutaneous vasoconstrictor response in the legs, compared with the arms, is partly attributable to higher \(\alpha_1\)- and \(\alpha_2\)-adrenoceptor reactivity at a given level of adrenergic sympathetic activity\(^7\). In addition to adrenergic sympathetic mechanisms, the different vasoconstrictor responses between the legs and arms during orthostatic stress are derived from the participation of a local response (i.e. vеноarteriolar response) mechanism\(^7\)\(^8\)\(^9\). Vеноarteriolar response in the skin does not occur through \(\alpha\)-adrenergic mechanisms, and the response is due to myogenic mechanisms associated with changes in vascular pressure, or is a neurally-mediated nonadrenergic response\(^10\). The enhanced cutaneous vasoconstrictor response in the legs, during HUT at the lower angles (15°-45°), was diminished by whole-body heat stress\(^10\). It is thought that the diminished vasoconstriction was partly caused by modulation of the local vascular response during heat stress, because both whole-body heating and local heating significantly attenuated cutaneous vеноarteriolar responses in the forearm\(^1\)\(^2\)\(^3\)\(^4\)\(^5\) and the calf\(^7\). The heat stress-induced reduction of the cutaneous vasoconstrictor response in the lower body, during orthostatic stress, acts to decrease the total PVR and increase blood pooling.

5. Decrease in PV

A positive correlation between PV and orthostatic tolerance in normothermic individuals has been reported\(^5\). Restoration of PV during dehydration is linked to improved orthostatic tolerance\(^6\)\(^7\). Furthermore, acute PV expansion preserves LBNP tolerance during whole-body heat stress\(^8\). These reports suggest that blood volume serves as a determinant for orthostatic tolerance during normothermia and hyperthermia. Upright posture induces a redistribution of blood from the cranial portion to the inferior portion of the body as well as a filtration of fluid through capillary walls, resulting in decreased circulating PV\(^9\)\(^1\)\(^0\). For example, PV was shown to decrease ~16% via a transcapillary fluid shift during 90° HUT for 35 min in the normothermic condition\(^1\); and blood volume decreased 5.7% while quietly standing for 20 min, compared with sitting\(^1\). Thermal stress-induced changes in intravascular pressure influence fluid permeability through capillary walls\(^3\)\(^4\). Additionally, heat stress-induced sweating exaggerates hemococoncentration during orthostatic stress\(^7\). Thus, both upright posture and heat stress act to decrease PV, resulting in reductions in orthostatic tolerance and aerobic exercise performance\(^7\)\(^9\). It has been suggested that reduced plasma renin activity and activation of the renin-angiotensin-aldosterone system\(^6\)\(^7\)\(^8\) decreases orthostatic tolerance due to a decrease of PV retention. Fig. 4 shows an overall schematic for the influences of upright posture, environmental heat and prolonged exercise on the blood pressure control system.

Countermeasures to orthostatic intolerance during heat stress

1. Cooling of the body

A variety of countermeasures have been utilized to reverse heat stress-induced decreases in orthostatic tolerance. One way to improve orthostatic tolerance during heat stress is to cool the body. Cooling can be done with an air conditioner, fan, ice packs, cool jacket, etc. In experimental settings, cooling the skin surface without decreasing core temperature, using a cold water-perfused suit, increased total PVR, SV and blood pressure during HUT\(^7\). Acute skin surface cooling immediately before
upright tilting in heat-stressed individuals improved orthostatic tolerance relative to heat stress without cooling\(^{102}\). This effect is likely related to profound cutaneous vasoconstriction and the associated redistribution of blood flow from the cutaneous circulation to the central circulation, resulting in increased CVP\(^{103,104}\), pulmonary capillary wedge pressure\(^{104}\), and baroreflex sensitivity\(^{52,61}\) during cold stimulus.

2. Rehydration

Roles of fluid intake for the recovery of body fluid after and during prolonged exercise under heat-stressed conditions have been well described\(^{105-109}\). Fluid intake is also required for reducing hemoconcentration during orthostatic stress. Orally-ingested water is absorbed in the intestine passively according to an osmotic gradient between the lumen and the interstitial fluid space, resulting in an increase of PV in less than 20 min\(^{110}\). Hinghofer-Szalkay et al.\(^{111}\) have reported that drinking an isotonic NaCl beverage (290 mosmol/kg) increased PV twice as much as drinking a hypotonic beverage (<10 mosmol/kg) during supine and HUT. Oral intake of an isotonic 0.9% NaCl drink was found to be effective in restoring gravitational acceleration tolerance following the withdrawal of 400 ml of blood\(^{112}\). The Japan Sports Association has recommended the frequent intake of 0.1-0.2% NaCl solutions for the replenishment of fluid and salt loss due to thermal sweating in heat\(^{113}\).

3. Heat acclimation

Heat stroke frequently occurs when hot weather appears suddenly in between days of rainy or muggy weather\(^{113}\). In addition, among fatalities due to heat stroke in the work place, 42% of the total number of incidents (n=72) in 2008 to 2010 occurred within the first 3 days of work initiated in a warm environment\(^{114}\). When six unacclimated subjects were repeatedly given a prolonged exercise load followed by a 20-min HUT at 33.9˚C for 8 days, fainting episodes during HUT occurred in 80% (n=5) of subjects on the first day of repeated exercise-heat exposure, and tended to decrease after that (2 subjects on the 2nd day, and 1 subject on the 3rd day)\(^{115}\). These reports indicate the need for physical acclimation to heat for the prevention of heat stroke and orthostatic hypotension. The heat-acclimation-associated decreases in heat stroke and fainting episodes are related to 1) reduced cardiovascular strain presented as a decreased HR\(^{115-117}\), 2) reduced body temperature due to an increase in the rate of sweating\(^{115-117}\), and 3) increased blood volume\(^{118-121}\).

It is also important that workers, athletes and the general public are educated regarding the physiological mechanisms of orthostatic intolerance and heat illness, and specific countermeasures. Additionally, among people with chronic illness and hypertension, daily care is required for the prevention of orthostatic hypotension during heat stress.

In summary, heat-stressed individuals are apt to develop hypotension during upright posture and show lower or-
thostatic tolerance. Reduced orthostatic tolerance is due to 1) redistribution of blood flow from central parts of the body to the skin, 2) an increase in leg venous compliance, 3) altered baroreflex function, 4) an attenuated vasoactive response in the lower extremities, 5) a decrease in PV, and other physiological mechanisms. A combination of countermeasures including body cooling, rehydration, and the allowing of a period (3 days or more) for heat acclimation, can improve orthostatic tolerance in a hot environment.

References

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