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Heat Stress and Baroreflex Regulation of Blood Pressure

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Abstract

In healthy, noninjured, individuals, passive (i.e., nonexercising) whole-body heating has the potential to cause significant cardiovascular stress that may be second only to the cardiovascular stress associated with exercise. For example, such a heat stress can increase heart rate to well over 100 beats·min⁻¹ with cardiac output increasing upward to 13 L·min⁻¹. This increase in cardiac output is necessary to maintain blood pressure due to profound reductions in total vascular conductance associated with cutaneous vasodilation. These responses are accompanied with elevations in sympathetic activity and reductions in vascular conductance (i.e., increased vascular resistance) from noncutaneous beds. While heat-stressed, blood pressure control is compromised resulting in orthostatic intolerance. A plausible explanation for such an event is that heat stress impairs baroreflex responsiveness perhaps due to the reduced range by which baroreflexes can increase heart rate, cardiac output, sympathetic activity, and vascular resistance during a hypotensive challenge. Given that dynamic exercise has the potential to cause large increases in internal temperature, possibly a component of the response to exercise, with respect to baroreflex control of blood pressure, may be affected by the thermal load during the exercise bout. Within this context, the purpose of this review was to summarize findings investigating the effects of heat stress on baroreflex regulation of blood pressure.

Keywords

HYPERTHERMIA; BARORECEPTORS; SYMPATHETIC NERVE ACTIVITY; HEART RATE; SKIN BLOOD FLOW

Muscle temperature increases almost instantaneously with the onset of dynamic exercise, such that within the first 3 min of relatively intense (i.e., 80 W) knee extension exercise, muscle temperature can increase upward to 1°C (12). As exercise continues, depending on the intensity, muscle temperature can surpass 40°C (13,46). Elevated muscle temperature increases the temperature of the venous blood that drains the active muscle (12). This venous blood mixes with blood from other regions of the body resulting in an overall increase in internal, or core body, temperature. Thus, the exercising muscle can be viewed as the furnace that is driving the elevation in internal temperature.

Numerous studies have sought to identify the effects of exercise on baroreflex responsiveness, as addressed in the following review papers (19,25,29,34,35,38–40). However, most, if not all, of the studies cited in those review articles did not consider the potential for elevated temperature that accompanies exercise to contribute to the modification of the baroreflex. The central components governing thermoregulation are in the hypothalamus (50), and electrical

stimulation of the hypothalamus modifies the baroreceptor reflex (11,41). Thus, it seems feasible that at least a component of the effects of dynamic exercise in modifying baroreflex responses could be attributed to hyperthermia accompanying exercise.

Within the context of this background, the objective of this review is to discuss studies that investigated the effects of passive (i.e., nonexercise) induced heat stress on baroreflex responses. Perhaps in doing so, the potential for heat stress in contributing to exercise-induced changes in baroreflex responses could be elucidated, although it is recognized that this question cannot be thoroughly evaluated via passive heat stress studies alone. This review will focus on the effects of passive heat stress on 1) carotid baroreflex responses, 2) integrative baroreflex responses, and 3) postsynaptic responses. Findings from the reviewed studies may also have important implications with respect to the effects of heat stress on blood pressure control that may contribute to pronounced reductions in orthostatic tolerance (15,27).

Generally, physiological responses to perturbations are assessed when subjects are normothermic and again during heat stress conditions. Heat stress is typically administered by perfusing warm (46–48°C) water through a tube-lined suit worn by each subject. This procedure increases skin temperature to approximately 38.5°C within 5–10 min and increases internal temperature 0.7–1.5°C within 30–60 min. In some protocols, differing modes to heat the subjects were used such as exposure to a hyperthermic climatic chamber or leg immersion in warm water.

CAROTID–CARDIAC AND CAROTID–VASCULAR BAROREFLEX RESPONSES

Carotid baroreflex responsiveness is evaluated by changing carotid sinus transmural pressure via R-wave–triggered application of neck suction and neck pressure (9,30,37). The efferent responses to ramped changes in carotid sinus transmural pressure (i.e., heart rate for the carotid–cardiac reflex and mean arterial blood pressure for the carotid–vascular reflex) are then evaluated. We and others found that passive heat stress did not alter the maximal gain of the carotid–cardiac baroreflex, when the cardiac response was evaluated as heart rate, as opposed to R–R interval (2,59,60). In contrast, heat stress significantly decreased the maximal gain of the carotid–vascular baroreflex by approximately 35% (Fig. 1). Both carotid–cardiac and carotid–vascular baroreflex curves were shifted to accommodate the slight decrease in blood pressure that tends to occur and the substantial increase in heart rate that accompanied the heat stress. These data indicate that carotid baroreceptor modulation of heart rate is preserved under heat stress conditions, while carotid baroreflex regulation of blood pressure is impaired. Reduced carotid–vascular responses may be related to the possibility that the carotid baroreflex does not have an efferent limb governing skin blood flow (3,55), although recent findings challenge that conclusion (21).

INTEGRATED BAROREFLEX RESPONSES

A variety of techniques can be used to evaluate the effects of a perturbation on integrated baroreflex responses. The most widely used techniques include pharmacological manipulations of blood pressure, lower-body negative pressure (LBNP), transfer function gain analysis between blood pressure and heart rate, and evaluation of the spontaneous relationship between blood pressure and heart rate (i.e., sequencing technique). Each of these techniques has been used, occasionally with mixed results, to evaluate the effects of passive heating on integrative baroreflex responses.

To identify whether whole-body heating alters baroreflex control of muscle sympathetic nerve activity (MSNA), MSNA and beat-by-beat arterial blood pressure were recorded during acute

pharmacologically induced hypotensive and hypertensive challenges while subjects were normothermic and again during heat stress conditions (5). For both thermal conditions, MSNA increased and then decreased when blood pressure was lowered and then raised via intravenous bolus infusions of sodium nitroprusside and phenylephrine, respectively. The slope of the relationship between MSNA and diastolic blood pressure during the heat stress was similar relative to normothermia. Moreover, during these same pharmacological perturbations, no significant difference in the slope of the relationship between heart rate and systolic blood pressure was observed. These data suggest that primarily arterial baroreflex modulation of MSNA and heart rate are not altered by whole-body heating. However, the heat stress caused an upward shift of these baroreflex curves to accommodate increases in heart rate and MSNA that occur with this thermal exposure.

Although it is clear from the aforementioned study that baroreflex responses are unaltered during brief changes in arterial blood pressure, it was unclear whether similar responses would be observed during sustained changes in blood pressure. To address this question, blood pressure was elevated over a period of 20 min via steady-state infusion of three doses of phenylephrine HCl in both normothermic and heat stress conditions (6). The sensitivity of baroreflex control of MSNA and heart rate, expressed as the slope of the relationship between MSNA and diastolic blood pressure (normothermia = $-1.3 \pm 3 \text{ burst} \cdot \text{min}^{-1} \cdot \text{mm Hg}^{-1}$, heat stress = $-1.8 \pm 0.3 \text{ burst} \cdot \text{min}^{-1} \cdot \text{mm Hg}^{-1}$, $P = 0.10$) as well as the slope of the relationship between heart rate and systolic blood pressure (normothermia = $-0.6 \pm 0.1 \text{ beats} \cdot \text{min}^{-1} \cdot \text{mm Hg}^{-1}$, heat stress = $-0.5 \pm 0.2 \text{ beats} \cdot \text{min}^{-1} \cdot \text{mm Hg}^{-1}$, $P = 0.71$), respectively, were similar between thermal conditions. Thus, regardless of whether changes in blood pressure were acute or sustained, the maximal gains of integrated baroreflex control of MSNA and of heart rate were preserved. However, the baroreflex curves are shifted to accommodate the change in these variables associated with the heat stress. Consistent with those findings, Gorman and Proppe (14) showed that passive heating of baboons did not alter baroreflex regulation of heart rate during relatively acute (i.e., during 1 to 1.5 min) changes in arterial blood pressure.

Although pharmacological studies are ideal to evaluate baroreflex function under tightly controlled conditions, evaluation of efferent responses to LBNP may be a more applicable approach to investigate the effects of heat stress on baroreflex responses to orthostatic stress. To this end, we evaluated MSNA responses during LBNP while subjects were normothermic and heat-stressed (7). Progressive LBNP caused expected increases in MSNA in both thermal conditions. At higher LBNPs, MSNA was greater during heat stress relative to normothermia, although this would be expected because of a larger reduction in mean arterial blood pressure to LBNP while subjects were heat-stressed. To account for this, the MSNA responses were evaluated against the reduction in central blood volume indexed from thoracic impedance. This approach, therefore, evaluates the change in MSNA during LBNP for a given reduction in central blood volume. This analysis showed that the slope of the relationship between the reduction in central blood volume and the increase in MSNA was in fact significantly elevated in the heat-stressed conditions (Fig. 2). This finding indicates that, for a given fluid shift and accompanied reduction in central blood volume and baroreceptor unloading, there was a greater increase in MSNA during the heat-stressed condition relative to normothermia. These findings are consistent with recent findings showing that heat stress increases baroreflex control of MSNA through increased sensitivity of a “gating” mechanism, as indicated by an increase in the slope of the relationship between burst incidence and diastolic blood pressure (20). In contrast, the relationship between diastolic blood pressure and the size of the MSNA burst (i.e., baroreflex control of burst area) was not affected by heat stress. Together, these studies suggest that heat stress may actually augment baroreflex responsiveness with respect to control of MSNA.

Integrated baroreflex function can be assessed by transfer function analysis between blood pressure and heart rate spectral variability (42). In its simplest form, this method analyzes the dynamic relationship between spontaneous changes in arterial blood pressure with corresponding changes in heart rate. Baroreflex regulation of heart rate can then be assessed within defined frequency ranges of oscillations in blood pressure. The most widely used frequency ranges for humans are the low-frequency range (0.03–0.15 Hz) and the high-frequency range (0.2–0.3 Hz), when breathing is fixed at approximately 0.25 Hz (15 breaths·min⁻¹). Spectral analysis of heart rate and systolic blood pressure revealed that the heat stress significantly reduced heart rate and systolic blood pressure variabilities within the high-frequency range, reduced systolic blood pressure variability within the low-frequency range, and increased the ratio of low- to high-frequency heart rate variability (i.e., an index of cardiac sympathetic activity) (4). Transfer function gain analysis showed that the heat stress significantly reduced dynamic baroreflex regulation of heart rate within the high-frequency range by approximately 50% without significantly affecting the gain within the low-frequency range (Fig. 3). Thus, within the respiratory frequency range, for the same magnitude of change in blood pressure, there was less of a change in heart rate during the heat stress.

Several investigations have used the sequence technique (16) to assess spontaneous baroreflex control of heart rate in the time series in heat-stressed subjects (26,58,60,61). This method calculates the slope between blood pressure and heart rate from sequences of three or more cardiac cycles in which blood pressure and interbeat interval are simultaneously increasing or decreasing. Generally, heat stress did not change baroreceptor control of heart rate in any of these investigations (26,58,60,61), although differing conclusions could be made if these findings were analyzed as baroreflex control of R–R interval (26). Justification for the differences in conclusion regarding the effects of heat stress on baroreceptor control of heart rate between transfer function analysis (4) relative to sequencing technique analysis (26,58,60,61) are not readily clear, except that with the transfer function technique, spontaneous baroreflex control of heart rate is calculated within specific frequency ranges across all cardiac cycles, whereas with the sequencing technique time series analysis is performed on only 20–30% of the cardiac cycles (26,60). Nevertheless, we observed that when greater changes in blood pressure are imposed pharmacologically (5), relative to that which occurs spontaneously with respiration, or during large changes in carotid sinus transmural pressure (Fig. 1), heat stress does not affect baroreceptor control of heart rate.

POSTSYNAPTIC ADRENERGIC VASOCONSTRICTOR RESPONSES

An integral component of any baroreflex is the end organ response to increased nerve activity and subsequent neurotransmitter release (in the case of a hypotensive challenge). Interestingly, Kregel et al. (24,32,33) showed that vasoconstrictor responses to α -adrenergic agents were significantly attenuated in heated rats. Similar findings have been shown from isolated dog vessels (1,17,51), although this observation is not consistently found in isolated rat vessels (31,36). Finally, in humans, venoconstriction of hand veins, evoked by deep breathing, mental stress, or ammonia inhalation, was attenuated when the veins were directly heated, as well as when internal temperature was elevated without the veins being directly heated (62). From these findings, it is plausible that heat stress attenuates adrenoceptor vasoconstrictor responsiveness. Thus, despite apparently normal or perhaps elevated sympathetic responsiveness to baroreceptor unloading, as indexed from MSNA (Fig. 2), attenuated postsynaptic vasoconstrictor responsiveness may contribute to reduced baroreflex sensitivity observed during the carotid–vascular assessment (Fig. 1).

Under heat stress conditions, skin blood flow of humans can increase from approximately 300 to 7500 mL·min⁻¹, having the capacity to receive more than 50% of cardiac output in this thermal condition (43,44). Although while heat-stressed, the skin serves as a large reservoir

whereby vascular conductance can be decreased, the extent of the influence of baroreceptors on the control of skin blood flow is unclear (3,8,10,18,23,45,52–56). For example, during a hypotensive challenge leading up to and at the onset of syncopal symptoms, decreases in cutaneous vascular conductance are relatively minor (Fig. 4), resulting in cutaneous vascular conductance remaining substantially elevated (i.e., four- to sixfold) when compared to preheat stress conditions (18,49). A possible explanation for this observation may be that heat stress impairs cutaneous vasoconstrictor responsiveness, which we sought to identify (57). Subjects were exposed to both local cutaneous heating and indirect whole-body heating (i.e., increasing internal temperature but not local temperature at the site of skin blood flow assessment). In both normothermic and heated conditions, varying doses of the α -adrenergic agonist norepinephrine were locally administered to the dermal space via microdialysis. Skin blood flow was measured above the microdialysis membranes, and dose–response curves were constructed. We found that both local and indirect whole-body heating significantly decreased the sensitivity of the cutaneous vessels to constrict to norepinephrine, as indexed by a significant elevation in the dose of norepinephrine required to elicit 50% of maximal vasoconstriction (i.e., EC_{50}). Moreover, in both heated states, skin blood flow did not return to preheated levels even at the highest dose of norepinephrine, despite saturation of the dose–response relationship. This latter finding indicates that, at maximal vasoconstrictor response to exogenous norepinephrine, α -adrenergic vasoconstriction does not fully compensate for local heating– and whole-body heating–induced cutaneous vasodilation. These findings are consistent with the findings of Zitnik et al. (62) who investigated the effects of local and whole-body heating on constrictor responses in the isolated hand vein. Subsequent studies have led to the hypothesis that substances released in association with local heating– and reflex-induced active cutaneous vasodilation, perhaps nitric oxide and/or peptide(s) released in association with stimulation of sympathetic cholinergic nerves, may have a sympatholytic effect, thereby attenuating cutaneous adrenergic vasoconstriction for a given neural vasoconstrictor signal (28,47,48,57).

Kregel and Gisolfi (24) showed that the pressor response to systemic infusions of norepinephrine was attenuated in the heat-stressed rat. We sought to identify whether similar responses could be identified in the heat-stressed human. This objective was accomplished via systemic infusion of varying doses of the α_1 -adrenergic agonist phenylephrine while subjects were normothermic and whole-body heat-stressed. We found that the elevation in mean arterial blood pressure and the total peripheral resistance at the two highest doses of phenylephrine were significantly attenuated during the heat stress (Fig. 5). When total vascular conductance (reciprocal of total vascular resistance) was calculated, heating similarly attenuated the reduction in vascular conductance during phenylephrine administration. These data indicate that α_1 -mediated elevations in arterial blood pressure are attenuated in the heat-stressed human.

Data from the aforementioned studies left unanswered whether attenuated increases in total vascular conductance to systemic phenylephrine was exclusively a result of attenuated cutaneous vasoconstriction, or whether heating also impairs vasoconstrictor responses to adrenergic agents in other vascular beds such as muscle. As such, we recently sought to identify the effects of increasing muscle temperature on vasoconstrictor responses to α -adrenergic agents (22). To accomplish this objective, leg muscle blood flow (clearance of ^{133}Xe injected in the muscle) and muscle vascular conductance were measured during intra-arterial infusion of varying concentrations of the α_1 -selective agonist phenylephrine and the α_2 -selective agonist BHT-933 while the muscle was normothermic and after muscle temperature was elevated approximately 4°C via local heating. The reduction in muscle vascular conductance to either drug was not attenuated by local heating, thereby countering the hypothesis that heating attenuates postsynaptic vasoconstrictor responsiveness in muscle. Combined, these data suggest that heat stress attenuates cutaneous vasoconstrictor responsiveness, while muscle vasoconstrictor responsiveness is apparently preserved. The effects of heat stress on

postsynaptic vascular responsiveness to other organs/structures such as the renal and splanchnic vascular beds remain to be determined.

SUMMARY

On the basis of the collection of studies evaluating the effects of heat stress on baroreflex responses, four key observations can be summarized. First, the majority of studies find that heat stress does not alter the baroreflex control of heart rate. The exceptions are from a few studies in which the change in heart rate is attenuated during relatively small spontaneous oscillations in blood pressure (4,26). Possibly, these observations are due to reduced cardiac vagal activity associated with heating (4). When greater changes in baroreceptor loading were caused either mechanically (Fig. 1) (2) or pharmacologically (5), the baroreflex gain of the blood pressure–heart rate relationship was unchanged during whole-body heating. Second, baroreflex control of MSNA is not attenuated by heat stress but is either unchanged or elevated. Third, cutaneous postsynaptic vasoconstrictor responses are attenuated by local and indirect whole-body heating, whereas muscle vasoconstrictor responses are not impaired when muscle temperature is elevated approximately 4°C. Fourth, heat stress consistently shifts the baroreflex curve to the prevailing heart rate, MSNA, and blood pressure, similar to that which occurs during exercise (38). The contribution of heat in mediating a component of exercise-induced changes in baroreflex responses remains to be elucidated.

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FIGURE 1.

Carotid–cardiac (*left panels*) and carotid–vascular (*right panels*) baroreflex responses during normothermia (*solid lines*) and whole-body heat stress (*dashed lines*). Whole-body heat stress did not alter the maximum gain of the carotid–cardiac baroreflex (*lower left panel*), whereas this heat stress significantly ($P < 0.01$) reduced the maximum gain of the carotid–vascular baroreflex by approximately 35% (*lower right panel*). Notice how the heat stress shifted the carotid–cardiac baroreflex curve to the prevailing elevated heart rate (*upper left panel*) that occurs during this thermal exposure. The operating point, defined as the heart rate or blood pressure before perturbing the carotid sinus are depicted as *open symbols*. bpm indicates beats per minute; mm Hg, millimeters of mercury; ECSP, estimated carotid sinus pressure; MAP, mean arterial blood pressure. Figure used with permission Crandall (2).

FIGURE 2.

Linear regression between muscle sympathetic nerve activity (MSNA) and an index of central blood flow (thoracic impedance) during progressive lower-body negative pressure (LBNP) for a representative subject. *Squares* depict baseline MSNA and thoracic impedance before LBNP. The average slope of this relationship across all subjects was significantly elevated by heat stress (normothermia = $235 \pm 103 \text{ units} \cdot \text{min}^{-1} \cdot \Omega^{-1}$, heat stress = $523 \pm 230 \text{ units} \cdot \text{min}^{-1} \cdot \Omega^{-1}$, $P < 0.01$). r indicates the correlation coefficients for this subject's data. Figure used with permission from Cui et al. (7).

FIGURE 3.

Effects of whole-body heat stress (*solid line*) on transfer function gain and coherence values during fixed breathing (A and B) and spontaneous breathing (C and D) protocols. Regardless of whether breathing was fixed or spontaneous, heat stress significantly reduced the transfer function gain between spontaneous changes in systolic arterial blood pressure and corresponding changes in heart rate within the high-frequency range (0.2–0.3 Hz) relative to when the subjects were normothermic (*dashed lines*). Heat stress did not significantly affect transfer function gain between systolic blood pressure and heart rate in the low-frequency range (0.03–0.15 Hz). Regardless of breathing protocol or frequency range, heat stress did not significantly affect coherence. Reduced cardiac vagal neural activity due to heat stress is the likely cause for reduced transfer function gain between systolic blood pressure and heart rate within the high-frequency range. Figure used with permission from Crandall et al. (4).

FIGURE 4.

Mean arterial blood pressure (MAP; *dashed line*) and cutaneous vascular conductance (CVC; *solid line*) responses when a representative subject was normothermic (leftmost data set) and during 30-mm Hg lower-body negative pressure (LBNP) while the subject was heat-stressed. Numerical values above the CVC data indicate an index of skin blood flow (SkBF) derived from laser Doppler flowmetry. Notice that, at the onset of syncopal symptoms (i.e., presyncope) and corresponding large reductions in MAP, SkBF and CVC remained three- to fourfold higher relative to when the subject was normothermic. These data depict what could be construed as an inadequate reduction in CVC leading up to and at the onset of syncopal symptoms, given that, during heat stress, a large fraction of cardiac output is directed to the skin.

FIGURE 5.

Change in mean arterial blood pressure (*upper panel*), systemic vascular resistance (*middle panel*), and systemic vascular conductance (*lower panel*) to systemic infusions of three graded doses of the α_1 agonist phenylephrine. Before drug administration, heat stress (*closed circles*) significantly reduced systemic vascular resistance, significantly increased systemic vascular conductance, without significantly affecting mean arterial blood pressure. Notice the pronounced differences in the elevation in mean arterial blood pressure and systemic vascular resistance during graded infusions of the same concentrations of phenylephrine. *Significant differences ($P < 0.05$) between thermal conditions for that dose of phenylephrine. Figure used with permission from Cui et al. (6).