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Human Cardiovascular Responses to Passive Heat Stress

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Abstract

Heat stress increases human morbidity and mortality compared to normothermic conditions. Many occupations, disease states, as well as stages of life are especially vulnerable to the stress imposed on the cardiovascular system during exposure to hot ambient conditions. This review focuses on the cardiovascular responses to heat stress that are necessary for heat dissipation. To accomplish this regulatory feat requires complex autonomic nervous system control of the heart and various vascular beds. For example, during heat stress cardiac output increases up to twofold, by increases in heart rate and an active maintenance of stroke volume via increases in inotropy in the presence of decreases in cardiac preload. Baroreflexes retain the ability to regulate blood pressure in many, but not all, heat stress conditions. Central hypovolemia is another cardiovascular challenge brought about by heat stress, which if added to a subsequent central volumetric stress, such as hemorrhage, can be problematic and potentially dangerous, as syncope and cardiovascular collapse may ensue. These combined stresses can compromise blood flow and oxygenation to important tissues such as the brain. It is notable that this compromised condition can occur at cardiac outputs that are adequate during normothermic conditions but are inadequate in heat because of the increased systemic vascular conductance associated with cutaneous vasodilation. Understanding the mechanisms within this complex regulatory system will allow for the development of treatment recommendations and countermeasures to reduce risks during the ever-increasing frequency of severe heat events that are predicted to occur.

Introduction

Regardless of the cause, global surface temperatures are rising (155) and the frequency, intensity, and duration of heat waves are projected to increase in the coming decades (156,232). This, coupled with the “urban heat island” effect (22,158), can pose a significant threat to human health (86); most recently evident in the 2012 North American heat wave in which 82 heat-related deaths occurred across the US and Canada. Consistent with that observation, there are dozens of related epidemiological observations demonstrating increases in morbidity and mortality in humans during heat waves (e.g., (2,8,9,55,56,63,78,79,94,114,115,120,122,123,126,130–132,160,161,237,238,278); perhaps the most severe in modern history is the 13,700 deaths attributed to the 2003 heat wave in

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France (205). Thus, it should not be surprising that a PubMed review of the terms “heat wave” and “morbidity” or “mortality” in the title or abstract revealed approximately 200 citations on these topics, emphasizing the dangers of heat waves. Clearly, heat exposure poses a threat to human health and well-being, the incidence of which is projected to increase especially in outdoor workers and vulnerable populations (66,147,176).

When environmental and/or physiological conditions exist where heat gain outweighs heat loss, internal (i.e. core) body temperature increases. Increasing internal temperature by ~3°C above “normothermia” (e.g., from 37 to 40°C) can severely strain physiological systems and even lead to death (11). As a protection against such a response, humans have important regulatory mechanisms aimed to maintain internal temperature within a relatively narrow range. In fact, as little as a 0.3°C increase in internal temperature can initiate critical heat loss responses, namely, cutaneous vasodilation and sweating (13,75). These heat dissipating responses are accompanied by important, even critical, autonomic, and cardiovascular adjustments, which, if they were not present, may compromise thermoregulation, blood pressure control, and organ perfusion. These adjustments include increases in cardiac output through a combination of elevations in heart rate and cardiac contractility, as well as elevations in sympathetic activity necessary to reduce blood flow and blood volume from noncutaneous regions (38,135,162,212,221). Importantly, individuals with impaired heat dissipating mechanisms, including those with impaired thermoregulatory and/or cardiovascular responses to heat stress (e.g., the elderly, various diseases, and certain medications) will have a greater risk for heat-related morbidity and mortality (2,8,12,27,41,51,55,56,63,77,85,111–114,126,131,161,209).

The objective of this review article is to present a current understanding of human cardiovascular responses specifically to passive heat stress, which is defined as heat stress that occurs through increases in heat gain via exogenous sources at a time when metabolism remains at relatively basal levels. This is in contrast to studies evaluating responses to exercise-induced heat stress (i.e., significant increases in metabolism during exercise often coupled with elevated environmental temperatures). Exercise-induced heat stress has important work performance implications but these are outside the scope of this review article, as exercise induces a myriad of other physiological responses not associated with elevated environmental or internal body temperatures. Hence, understanding the physiological responses to passive heat stress permits mechanistic investigations to evaluate the various responses and adaptations to thermal stress.

Methods of Passive Heat Stress

The literature is filled with a variety of methods to passively heat stress individuals, for both research and clinical purposes. Below we list the techniques most commonly used in research. Each technique has both advantages and disadvantages. Some of the techniques result in uncompensable responses while others have a degree of compensability (i.e., the body can maintain a euthermic temperature by engaging thermoregulatory effectors). Importantly, the results from a particular research protocol may be influenced by the technique employed. Therefore, the method of heating should be considered when interpreting, and thus comparing, such research findings.

Water is inexpensive, plentiful, and an excellent carrier and conductor of heat, resulting in its wide use to passively heat individuals. Whole-body water immersion is the simplest, and perhaps the fastest, mode of passive heat stress used in research settings. Upon immersion in a container of hot water, skin temperature rapidly equilibrates to the water temperature and heat is rapidly transferred to the core, increasing internal temperature. Despite this temporal benefit, however, water-induced increases in hydrostatic pressure cause a central displacement of blood and a corresponding diuresis. These nonheating effects typically limit the use of this technique to only those studies where measurements are not influenced by central baroreceptor loading and diuresis induced dehydration. Technical issues related to biomedical electrical monitoring are amplified by the water medium. Another factor that needs consideration is that immersion in high water temperatures, ≃41°C (23), increase skin temperatures to levels which could be considered “nonphysiological,” unless one is studying responses to a recreational spa or hot bath (87). Nevertheless, such high skin temperatures likely influence both cardiovascular and thermoregulatory responses for a given increase in internal temperature (98,139,166,167,188,189,221,231,265,268,269).

The immersion of just the lower limbs, typically below the knee, in warm water can also be used to passively heat individuals. Often the portions of the body that are not immersed are covered with blankets, or insulated and/or water impermeable garments, to impede heat loss and thus speed heating. Although the rate of heating is slower than whole-body immersion, there are a number of advantages of this modality over whole-body immersion; foremost are more “typical” skin temperatures in the nonimmersed areas, less central fluid displacement, and the capability to instrument skin with electrical devices. With this approach, increases in skin blood flow in the areas not exposed to the water occur exclusively via reflex vasodilation, since the assessed areas are not in contact with the heating source.

Since approximately the 1960s, it has become common to heat individuals by perfusing hot water (typically 45–50°C) through a tube-lined suit worn by the subject, or by covering the individual with a tube-lined blanket. With the aid of a pump, the heated water is circulated through the suit at varying rates [typically ~600 mL/min to ~8 L/min; (223)], which elevates and clamps skin temperature to 37 to 40°C and subsequently elevates internal temperature as high as 40°C, although most report increases within the 38 to 39°C range. This uncompensable technique has some of the previously discussed disadvantages of moderately high skin temperature in the areas under the suit. Like lower leg immersion, these suits permit the evaluation of reflex induced cutaneous vasodilation in areas not covered by the heating source. Being that the water within the suit imparts a thermal gradient but does not directly touch the skin, there are no hydrostatic pressures to induce central fluid displacement. Other important advantages to this approach are the ability to access just about every region of the body (assuming the employed suit has openings, zippers, etc. to those regions), as well as the ability to rapidly modulate and clamp skin temperature at various temperatures.

Another approach to passively heat individuals is to simply expose the subject to warm ambient conditions, often via a climate, sauna, or environmental chamber. A unique difference in this approach, relative to the aforementioned approaches, is that subjects inhale warm air throughout the evaluation period and the entire body is exposed to the same

ambient temperatures. An experimental limitation of this approach is the relatively slower rate of heating, because these heat stresses are often more compensable and thus longer durations are required to appreciably increase internal temperature. Moreover, if efferent thermoregulatory responses are sufficient, and depending on the selected climate conditions, it is likely that thermoregulatory stability will be attained (i.e., compensable heat stress). In contrast, studying human health and safety issues often necessitate that participants be exposed to uncompensable heat stresses, which may be more difficult with this mode of heating.

There are a few other whole-body heating methods used primarily in clinical settings. One is the Pomp-Siemens hyperthermia cabin that uses a combination of radiofrequency, hot air, and microwave energy to induce-hyperthermia (202). In these cancer-related treatments, patients internal temperatures are increased and maintained at nearly 42°C for 2 h (64,250). The use of anesthesia and subject comfort issues in this approach has impeded wide research adoption. Other clinical approaches to passively heat individuals, that also do not have wide research adoption, include forced air heating (e.g., Bair Hugger® patient warmer), inhalation heating (e.g., RES-Q-AIR®), and intravascular/extracorporeal heating.

“Classic” Cardiovascular Responses to Passive Heat Stress

A number of excellent reviews on cardiovascular responses to heat stress have previously been published [e.g., (99,211–213,216)], most recently by Johnson and Proppe in 1996 (99) and reissued as an appendix in *Comprehensive Physiology*. Given those comprehensive reviews, the present review will focus primary on findings pertaining to cardiovascular responses to passive heat stress published since 1996; although where appropriate and foundationally necessary we discuss selected studies prior to this 1996 review. Consistent with this premise, Figure 1 illustrates classic cardiovascular responses, as reported by Rowell et al. across multiple studies (54,211,219,221,222), to uncompensable passive heat stress sufficient to elevate skin temperature by up to 5°C and internal temperature (i.e., pulmonary artery blood temperature) often over 2°C. Foremost is the potential for cardiac output to double its resting value, which is discussed in later sections. This increase in cardiac output is necessary to maintain arterial blood pressure, which does not change or slightly decreases by only 5 to 10 mmHg depending on the level of heating, to offset large decreases in systemic vascular resistance. Consistent with a redistribution of blood to the skin, blood flow to renal and splanchnic vascular beds decreases (discussed in detail in a later section). The net effect of these cardiovascular responses is the potential for a 7 to 8 L/min increase in blood flow to the skin (211).

Heat Stress and Cardiac Responses

Cardiac output & function

The increase in cardiac output during heat stress in humans is in contrast to most other mammals (e.g., rat, dog, sheep, and baboon) where cardiac output does not appreciably change during similar thermal perturbations. The primary reason for this species difference is the aforementioned large reliance on high blood flow capacity to nonglabrous skin for human thermoregulation, versus lower blood flow capacity in the oral mucus membrane and

carotid rete (the extensive nasal vasculature network) of panting species. Assuming a typical resting cardiac output of 5 L/min, cardiac output would need to increase roughly 2.5-fold to fully perfuse the skin [assuming a maximal skin blood flow capacity of 7–8 L/min (95) with flow to other vascular beds held constant]. The precise magnitude of the cardiac output increase with passive-heat stress is influenced by the duration, severity, and type of heating perturbation utilized. To better understand how these changes occur, this section will address intrinsic and regulatory factors of heart rate during heat stress, followed by those of stroke volume, and finally those of cardiac work.

Heart rate

Passive-heat stress increases heart rate, which is the primary driver behind the observed increases in cardiac output. The chronotropic effect of temperature has been widely documented in both hypothermic and hyperthermic conditions (3,10,28,73,100,119,121). Nakazawa and colleagues (168,169) observed consistent increases in heart rates when directly heating chick and rat embryos from 37 to either 40 or 42°C, followed by recovery of heart rate to basal levels when heating was discontinued. This research model indicates a direct effect of temperature on heart rate in these species, independent of fully developed feedback or neuroendocrine systems. Using anticholinergics and β-adrenergic antagonism to functionally remove various neural inputs, Jose et al. (100) identified an 7.15 ± 0.19 bpm increase per 1.0°C elevation in internal temperature in humans, while Gorman and Proppe (76) identified an 8.4 ± 0.8 bpm increase per 1.0°C increase in internal temperature in primates. Approximately 40% of heat stress induced increases in heart rate was due to increases in cardiac temperature, while the residual ~60% was attributed to autonomic nervous system activity (76). Thus, for the purposes of control and regulation of heart rate and subsequent ventricular contraction during heat stress, the primary determinants are: 1) direct effects of temperature on cardiac nodal cells (sinoatrial and atrioventricular) and conduction velocity and 2) sympathetic and parasympathetic effects on cardiac nodal cells and impulse propagation through the heart.

Direct heating and the sinus node: The cardiac action potential can be divided into 4–5 distinct phases; Phase IV is the duration after repolarization before the next depolarization. In atrial and ventricular myocytes, Phase IV is isoelectric, while in nodal cells Phase IV is sloped such that over time this increase in membrane potential will eventually trigger a subsequent depolarization. Heat increases the Phase IV slope and shortens action potential duration of both sinoatrial and atrioventricular nodes (246,270) (Fig. 2). This response decreases the time necessary to engage T- and L-type Ca^{2+} channels to initiate depolarization (i.e., Phase 0) in a nodal cell. The precise mechanism behind the Phase IV slope change is unclear but could simply be related to greater conductance through funny channels. Although heat-induced Phase IV effects are confined to nodal cells, other cardiac myocytes (Purkinje, atrial, and ventricular myocytes) also demonstrate a shortening of the cardiac action potential duration during heating (246,270).

In addition to the positive chronotropic effect of heating, elevated temperatures increase the speed of delivering the pacemaker signal to adjacent cardiac myocytes via the effects of temperature on gap junction conduction (26). Gap junction conduction is a primary

determinant of conduction velocity between cardiac myocytes, both within the primary conduction pathway (e.g., arteriovenous node, Bundle of His, bundle branches, and Purkinje fibers) and between the general atrial and ventricular myocytes. Thus, via these mechanisms direct heating also has a positive dromotropic (velocity of conduction) effect.

Heat stress and cardiac sympathetic and parasympathetic activity—Heat stress can be described as a global hyperadrenergic state (217), resulting in increases in both noradrenergic signaling and circulating catecholamines. Gorman and Proppe (76) identified that in the baboon, autonomic-mediated increases in heart rate during heating were due to 25% sympathetic activation and 75% parasympathetic withdrawal. The sympathetic and parasympathetic mechanisms for modulating heart rate are likely due to the cyclic nucleotide modulation of HCN4 (hyperpolerization-activated cyclic nucleotide-gated cation type-4 channels) and L-type Ca^{2+} channels, whereby β-adrenergic stimulation increases cytosolic cAMP and muscarinic receptor stimulation decreases cAMP (57,254). The modulation of HCN4 gating would then increase Phase IV slope of the cardiac action potential and allow for earlier opening of L-type Ca^{2+} channels, causing the sinoatrial node to “fire” more frequently in the presence of epinephrine and norepinephrine and with reductions of acetylcholine. Although this is the most likely mechanism, other pathways could also be involved. For example, β-adrenergic stimulation increases downstream products such as protein kinase A and Ca^{2+}, either of which can independently cause positive chronotropic effects (134).

Sympathetic stimulation also has a positive dromotropic effect on the heart (116), which results in greater speed of delivering the pacemaker signal to adjacent cardiac myocytes. The precise mechanism is unknown but is likely related to the neural effects on increased gap junction conduction. Faster conduction allows for shorter systolic fractions and greater diastolic fractions within a given beat.

Heat stress decreases cardiac parasympathetic effects (20,39,49,271), which increases heart rate. In addition to the above-mentioned cAMP mechanism, there could also be decreases in acetylcholine activated potassium channel activity ($I_{k,}$ ACh) (204,226). An increase in $I_{k,}$ ACh decreases sinoatrial nodal cell firing frequency, while an inhibition of this current increases heart rate because nodal cells do not hyperpolarize to the same extent and thus less of a voltage change is needed to reach threshold. Muscarinic or parasympathetic ganglion stimulation also decreases conduction velocity (228); thus heat-induced decreases in the parasympathetic nervous system also likely cause a positive dromotropic effect as noted above for sympathetic effects.

Stroke volume

Unlike heart rate, the direct and indirect effects of temperature on stroke volume are unclear. Stroke volume generally does not appreciably change during passive heat stress. This is despite increases in cardiac sympathetic outflow, as identified by the associated positive chronotropic effects in response to passive heat stress. Sympathetic stimulation has well-documented effects of increasing contractility (inotropy) of both atrial and ventricular myocytes (103). An increase in inotropy in a static environment (i.e., holding other

physiological variables constant and only changing inotropy) increases stroke volume. Since increases in stroke volume do not occur to a large extent, logic dictates that other factors in the dynamic passive heat stress environment must be counteracting this effect or that heating per se alters the relationship between sympathetic stimulation and inotropy. To address these issues we will discuss: (i) the essential regulatory mechanisms of stroke volume (e.g., cardiac preload, cardiac afterload, inotropy, and diastolic function) associated with a dynamic heat stress environment; (ii) the effects of positive inotrope administration during heat stress; and (iii) how the increases in cardiac contractility work within the limits of the Frank-Starling relation to off-set these passive heat stress-induced physiologic changes.

Cardiac preload

The tension created by the lengthening ventricular myocyte during the end-diastolic phase of the cardiac cycle equates to ventricular preload. The relation between cardiac preload and force production was first described by elegant *in vitro* heart studies of Otto Frank and then Earnest Starling and colleagues (67,181,182). Myocyte length changes produced by ventricular filling are very difficult to quantify, especially *in vivo*. Consequently, *in vivo* experimental measures of preload are surrogates and include: right atrial pressure/central venous pressure, pulmonary capillary wedge pressure, left-ventricular end-diastolic volume, and central blood volume. Each of these measurements has advantages and disadvantages in identifying aspects of and associated changes in left-ventricular preload, as well as safety issues for participants.

Using the water-perfused suit method of whole-body heating discussed above, Rowell et al. (223) identified a decrease in right atrial pressure from 5.4 to 2.2 mmHg at 10 min of heating with skin temperatures clamped to 39 to 41°C and increases in blood temperature of 0.3°C. When a subject-determined subjective heat tolerance point was reached, blood temperature had increased a further 1.9°C and right arterial pressure had been reduced to 0.5 mmHg (223). Subsequent work by other investigators consistently validated the finding that whole-body heating decreases right-sided preload as indexed by right atrial pressure as well as actual and estimated central venous pressure (16,33,38,99,102,106,162,163,190,266).

Right-sided preload is informative, but it is left-sided preload that determines the stretch of left ventricular myocytes and thus systemic stroke volume. Previous work in this area was equivocal, because of varied results, use of anesthesia, and many indirect methods of assessing left-sided preload (99). Using a whole-body heating approach in unanesthetized subjects, Wilson et al. (259) and then Bundgaard-Nielsen et al. (21) observed mean decreases of 2 to 3 mmHg in pulmonary capillary wedge pressure (an index of left ventricular filling pressure) with passive heating. In healthy humans, it appears that right- and left-sided preload changes follow the same relation during passive heat stress (Fig. 3), which is beneficial for investigators to reduce risks associated with invasive studies. Another method to reduce subject risk is by using a noninvasive method of assessing left-sided preload via cardiac imaging of left ventricular volume rather than a pressure catheter approach. Some, but not all, of these cardiac imaging studies report decreases in left-ventricular end-diastolic volume during passive heat stress (38,172–174,243,259). Although the volume of the left ventricle directly relates to the cardiac myocyte length, current

imaging technologies (i.e., echocardiography, magnetic residence imaging, and radionucleotide ventriculography) provide only approximations of left-ventricular end-diastolic volume, as a number of assumptions and calculations are necessary to fully describe the three-dimensional left-ventricular geometry. Thus, gross changes are easily observed but subtler changes are sometimes less clear with some of these technologies.

Assessment of central blood volume is another approach to provide an index of preload; early attempts in this area were completed via x-ray, dye-dilution, and transthoracic impedance (24,46,99,216), while current methodology employs gamma scans of Tc^{99} radiolabeled erythrocytes (37,38). Highlighting this latter methodology, Crandall et al. (38) observed 17 ± 2% decreases in blood volume within the heart and large blood vessels during a passive whole-body heat stress. These data were in contrast to central blood volume work using less precise techniques, where both increases and decreases were observed (99,216). Thus, these new central blood volume measures also validate a decrease in cardiac preload. It should also be noted that these decreases in preload are occurring during a time when there is an increase in cardiac output and presumably venous return. Increases in venous return, however, do not directly indicate increased stretch on cardiac myocytes during end-diastole; in fact, high steady-state venous returns are often associated with lower right atrial pressures (129).

The reasons for this decrease in cardiac preload (as indexed via central venous pressure, pulmonary capillary wedge pressure, left-ventricular end-diastolic volume, and central blood volume) during heat stress are multifactorial. Heat stress causes thermal-induced increases in sweating which can decrease plasma and interstitial fluid volumes (150,229,230). In addition to this absolute blood volume change, regional blood volume changes in response to heat stress can also contribute to the decrease in central blood volume. For example, large increases in cutaneous vascular volume (53) associated with heat dissipation will, if not counteracted by equivalent decreases in vascular volumes elsewhere, lead to a decrease in central blood volume. Though splanchnic blood volume decreases during heat stress, this change is insufficient to counter such increases in cutaneous vascular volume, resulting in central venous pressure and volume decreasing in this thermal state (38). In addition to these regional volume changes, the increase in heart rate associated with passive heat stress (see above section) would in theory decrease the time available for ventricular filling and stretching of myocytes which can decrease preload on a per beat basis.

The hyperbolic Frank-Starling relation (plotting stroke volume to a preload index such as pulmonary capillary wedge pressure; Fig. 4A) allows for the determination of the effect of preload on stroke volume. Decreases in preload associated with heat stress shifts the operating point off the flatter portion of the curve to a steeper portion (Fig. 4B), assuming no direct heat effects on the curve or additional changes that affect the curve such as heart rate, cardiac afterload, or inotropy. Klabunde et al. (117) tested if direct heating affected the Frank-Starling relation in an isolated heart preparation by inflating a balloon in the left ventricle and measuring the corresponding left-ventricular developed pressure while heating hearts via 1°C increments. They did not identify an effect of heat itself on the Frank-Starling relation. If those findings are consistent with human responses, direct heat, within the ranges of a passive heat stress, does not inherently alter the Frank-Starling relation. Given this

finding, coupled with stroke volume not decreasing with reductions in cardiac preload, strongly indicates that other stroke volume regulatory factors must be counteracting the effects of reduced ventricular preload with heat stress.

Cardiac afterload

Cardiac afterload (hydraulic load the ventricle must overcome to eject blood) is difficult to quantify in vivo during human studies. One way to approximate this hydraulic load is via ventricular wall stress during systole; this wall stress relates ventricular pressure and radius to the ventricular wall thickness. Doppler estimates of this variable identified reductions during passive heat stress (173). In addition, systemic vascular resistance, an index of mean systemic afterload, also decreases with passive heat stress (34,99,213,216,260). Not all physiological factors induced by heat stress indicate a reduction in cardiac afterload. For example, vessel compliance (e.g., Windkessel effect) can also affect afterload, where more compliant vessels decrease and stiffer vessels increase afterload. However, using a pulse-wave velocity approach, Ganio et al. (71) identified that arterial vessel properties such as stiffness are unchanged by heat stress, both centrally and peripherally. The chronotropic effect of passive heat stress may oppose some of the heat-induced reductions in afterload as the linear relationship between pressure at end-systole and end-diastolic volume (an alternate index of afterload) increases with increases in heart rate (25). Combined, these data indicate that heat stress acutely decreases afterload, as evidenced, in part, by a decrease left ventricular wall stress during systole, decrease in systemic vascular resistance, and a left and upward shift in the Frank-Starling relation. These effects likely are manifested as a greater stroke volume for a given tension created by any given filling pressure (Fig. 4B). However, due to multiple factors that could affect cardiac afterload during passive heat stress, further work is necessary to fully understand the relative contributions of afterload vs. other factors that affect the Frank-Starling relation.

Inotropy

As discussed in previous sections, during passive heat stress, stroke volume is maintained when factors (e.g., cardiac preload) would predispose it to decrease. Although reductions in cardiac afterload may be contributing, an increase in inotropy may also be involved, especially since cardiac sympathetic activity increases (76,100). Multiple imaging studies (e.g., radionucleotide multi-gated acquisition and echocardiography derived increases in ejection fraction (38,173,259)), isovolumic acceleration of the septal and lateral mitral annulus (14), and increases in left-ventricular twist rates (173,243) indicate positive inotropic effects of passive heat stress (see Fig. 5 for an example of such data). Pulmonary artery catheter studies also indicate heat-induced increases in inotropy, where volume loading revealed that heat stress shifts the Frank Starling relationship upward and to the left (21) (Fig. 6).

What are the mechanisms for the inotropic effect of heat stress? One possibility is via the increase in heart rate, as increases in heart rate can contribute to increases in the strength of contractions via a Bowditch effect (92), although whether this effect is a major contributor needs to be established. Other possibilities for heat-induced increases in ionotropy include increases in cardiac sympathetic activity working through β-adrenergic-mediated Ca^{2+}-

induced Ca^{2+} release mechanisms to increase cardiac myocyte cross-bridge cycling and/or heating may alter the relation between neurohormone contractility agents and postsynaptic inotropic responses. To identify if direct heating alters agonist to contractility relations, Klabunde et al. (117) administered isoproterenol (β-adrenergic agonist) to isolated hearts heated to 37, 38, 39, and 40°C while measuring left-ventricular developed pressure. They observed no difference in left-ventricular developed pressure responses to isoproterenol until temperature reached 40°C, although a reduction in developed pressure was observed at this highest temperature. Assuming those findings are consistent with human responses, those data indicate that within the range of ≤2°C from normothermia, temperature itself has no direct effect on positive inotropes, but once a 3°C increase in core temperature is reached, some attenuation in contractility can occur.

Diastolic function

Diastolic function comprises both the ventricular relaxation and filling components of the cardiac cycle, encompassing many features other than solely the traditional view of left-ventricular compliance. Expressions of left-ventricular compliance, that is, plotting an index of left-ventricular volume to an index of left-ventricular filling pressure, do not exhibit changes during passive heating (259). When exploring other aspects of left-ventricular diastolic function, it is important to note that most are preload dependent, whereby decreases in preload, as indexed by central venous pressure, pulmonary capillary wedge pressure, left-ventricular end-diastolic volume, and central blood volume cause reductions in indices of left-ventricular diastolic function (187). However, during passive heat stress, despite these measures of preload decreasing, diastolic function is preserved (14,173). These observations suggest that heat stress may be functionally increasing diastolic function, but this response occurs in a background of reduced preload. To test this hypothesis, Brothers et al. (17) returned central venous pressure to normothermic levels in heat stressed individuals via volume infusion. The perturbation increased indices of diastolic function (e.g., early diastolic mitral annular tissue velocity and early diastolic propagation velocity) that were otherwise unchanged between normothermic and heat stressed conditions. This effect has not been observed in all studies, as indices of left-ventricular diastolic function were not changed when preload was increased via head-down tilt (172). One possibility explaining these differences is unique loading patterns between volume infusion and head down tilt.

Nelson et al. (173) proposed that augmented left-ventricular untwisting maintains the forces that drive early filling during passive heat stress. Their findings, along with others (243), suggest that mechanical factors associated with untwisting, such as increased recoil and ventricular suction, could facilitate diastolic filling. Complementing or underlying this mechanism, the rate of relaxation of cardiac myocytes (lusitropy) may also play a role in diastolic function in passive heat stress conditions, as indicated in other studies (14). In a simplistic three-part model of ventricular relaxation (i) rate of pressure fall during isovolumic relaxation, (ii) rate of filling during early diastole, and (iii) slope of the relationship between ventricular volume and pressure during mid-to-late diastole (103)), the first two have the potential to change during acute stress conditions. The third, however, is related to ventricular compliance, which does not change with heat stress (259). Nearly half of the untwisting observed by Nelson et al. (173) occurs prior to the opening of the mitral

valve—that is, isovolumic relaxation phase (164,196), which is also when lusitropy effects are the greatest. Sympathetic stimulation could account for the increases in the rate of relaxation of cardiac myocytes (positive lusitropy effect), which is regulated largely by Ca^{2+} affinity of troponin-C and Ca^{2+} sequestering rate of the sarcoplasmic reticulum following muscle contraction (103). The precise effect of small changes in cardiac temperature and other components of the responses to passive heat stress on these aspects of lusitropy are largely unknown.

Combining the effects of cardiac preload, cardiac afterload, inotropy, and diastolic function in the regulation of stroke volume can be observed, in part, from Frank-Starling curves. Passive heat stress decreases cardiac preload and moves the operating point to a different relative location on a unique curve (see Figs. 4 and 6). The increase in diastolic function is not directly expressed on a Frank-Starling curve but improved diastolic function would improve left-ventricular filling properties in reduced preload conditions associated with passive heat-stress. The heat-induced decreases in afterload and increases in inotropy are grounds for the left and upward shift in the Frank-Starling curve, which allows greater stroke volume at any given ventricular filling pressure.

Cardiac work

The primary determinants of myocardial oxygen consumption are heart rate, inotropy, afterload, and to a lessor extent, preload (116). During passive heat stress, heart rate can more than double while arterial blood pressure is fairly well maintained (see above sections for discussion). This leads to consistent increases in cardiac minute work and rate pressure product (259), both of which are correlates of myocardial oxygen consumption (103). Stroke volume, as discussed above, is also fairly well maintained during passive heat stress, which leads to no overall change in stroke work (21,259). An increased myocardial oxygen consumption should correspond to an increased need for coronary oxygen delivery to match supply with demand, but this has not been directly tested.

Heat Stress and the Splanchnic and Renal Vascular Beds

Combined, the splanchnic (comprising of the gastrointestinal tract, spleen, pancreas, and liver) and renal vascular beds receive approximately 40% to 50% of cardiac output in basal preprandial conditions, and thus the control of blood flow through these regions can be very important in the redistribution of cardiac output from central regions to the skin during heat stress. In humans, assessment of global blood flow through the splanchnic bed is accomplished primarily through the clearance of indocyanine green dye, while renal plasma flow is evaluated primarily via clearance of para-aminohippuric acid (plasma flow is then converted to blood flow by accounting for hematocrit). Recently, Doppler ultrasound has been used to evaluate renal artery blood velocity, as well as blood velocity through major arteries perfusing regions of the splanchnic vascular bed, such as the superior mesenteric artery. However, employing this tool to investigate regional perfusion changes to heat stress has yet to be performed, and thus comparative responses between the aforementioned clearance and Doppler ultrasound techniques in evaluating splanchnic and renal blood flow to heat stress remain unknown.

Numerous studies report that splanchnic blood flow decreases during passive heat stress (see Fig. 1). Rowell et al., and others (162,163,218–222), observed progressive increases in splanchnic vascular resistance that generally parallel the increase in internal temperature, culminating in a range of reductions in splanchnic blood flow from 20% to 60% (averaging ~40% reduction). It is interesting to note that this relatively wide range of the reduction in splanchnic blood flow was from the same protocol and thus reflects high intra-individual differences to comparable levels of heating. Likewise, Minson et al. (162) observed an ~40% reduction in splanchnic blood flow during passive heating to tolerance. Passive heat stress likewise increases renal vascular resistance, resulting in 15% to 30% reductions in mean renal blood flow (162,197,219). Interestingly, the magnitude of reduction in the combined splanchnic and renal blood flows during heat stress was attenuated in older men (162), resulting in the investigators proposing that less blood redistribution from these regions may contribute to attenuated increases in skin blood flow in the older group.

Due to splanchnic and renal vasoconstriction accompanying heat stress, coupled with increases in cutaneous blood volume, one would reason that blood volume in splanchnic and renal regions would likewise decrease. Moreover, venoconstriction (which is difficult to accurately measure in humans) is also a potential mechanism to redistribute blood volume to the skin, with high capacitance splanchnic vasculature containing ~20% and low capacitance renal vascular containing <1% of venous volume (215). With those questions in mind, blood volume changes to heat stress in organs within the splanchnic bed (liver and spleen) were investigated via technetium-99m labeled autologous red blood cells, coupled with gamma camera imaging (37,38). Increasing internal temperature by 1.0 to 1.3°C reduced liver and spleen blood volumes ranging from 16% to 22% and 14% to 27%, respectively. Though renal blood volume changes were not investigated in those projects, reductions in indices of splanchnic blood volume are consistent with the theoretical model proposed by Rowell (213,216) which accounts for blood volume changes associated with heat-induced regional vasoconstriction (Fig. 7).

The mechanism(s) by which splanchnic and renal blood flows (and blood volume for the splanchnic bed) decrease during heat stress is proposed to be due to a combination of a reduction in perfusion pressure, given slight decreases in arterial blood pressure often observed during heat stress (70,221), combined with sympathetically mediated vasoconstriction (99,162,219,222); the latter of which will reduce distending pressure of the highly compliant splanchnic vasculature resulting in a reduction in blood volume in this region, see Figure 7. Baroreceptor unloading is unlikely to appreciably contribute to these responses given that normalization of arterial blood pressures in heat stressed individuals did not change splanchnic blood flow/vascular resistance (222), and that normalizing cardiopulmonary loading status (referenced from central venous pressure) did not change muscle sympathetic nerve activity (MSNA) (33). Thus, the signal responsible for increases in sympathetic activity and corresponding increases in splanchnic and renal blood vascular resistances is unlikely to be baroreflex-dependent. An alternate candidate is an increase in sympathetic activity due directly (i.e., not reflex mediated) to elevated brain temperatures.

Heat Stress and Skeletal Muscle Vascular Bed

Resting skeletal muscle receives approximately 15% to 20% of cardiac output (i.e., 750–1000 mL/min); however, blood flow per unit mass of muscle is relatively small in resting conditions, being 3 to 5 mL/min/100 g muscle. It is notable that muscle has a huge capacity to increase blood flow during elevated metabolic states, such as exercise, resulting in flows approaching 300 mL/min/100 g tissue (1,206,224,227).

From the 1940s through as recent as 2011, investigators sought to identify the effects of heat stress on muscle blood flow. Technologically, measures of muscle blood flow can be difficult to obtain given that thermal stimulation can cause large changes in blood flow in tissues superficial to muscle (e.g., skin). Thus, to address this question techniques were developed that isolated muscle blood flow from skin blood flow. One clever approach was to constrict the cutaneous vasculature of a limb (typically a forearm) through iontophoretic administration of epinephrine, with the assumption that the drug delivery was primarily confined to the skin so that any subsequent changes in limb blood flow (assessed via venous occlusion plethysmography) would reflect changes in muscle blood flow more than skin blood flow. Using this approach, some studies concluded that limb muscle blood flow was unaffected by heating (54,62), while other studies proposed large increases in muscle blood flow (6). The primary difference between these studies may have been related to the dosing of epinephrine, and specifically whether the cutaneous vasculature remained in a maximally constricted state throughout the duration of the heating stimulus. An alternate research approach is to evaluate the rate of clearance of a radio-labeled substance (such as antipyrine or xenon) injected directly into the muscle, where the rate of disappearance of that substance is proportional to blood flow in that region (i.e., the muscle). Using this tracer methodology (4-iodoantipyrine-^{125}I) Detry et al. (54) reported that forearm muscle blood did not change during whole-body heating, while Johnson et al. (96) found an absence of an increase forearm muscle blood flow during direct local heating. The latter finding is in contrast to Keller et al. (108) who observed that locally heating the leg increased the rate of disappearance of ^{133}Xenon injected into the gastrocnemius muscle, indicative of increased gastrocnemius muscle blood flow. Although the observed increase was relatively small, ~1 mL/min/100 g tissue, if that increase occurred in all skeletal muscle (which is unlikely given Johnson et al.’s findings), it is possible that no more than an ~350 mL/min increase in muscle blood flow occurs during such a heat stress for a person with an average muscle mass of 35 kg. The third commonly used approach evaluates oxygen saturation from blood withdrawn from a deep vein (proposed to drain primarily from muscle) and a superficial vein (proposed to drain primary from skin). The basis of this approach is that muscle metabolism would remain effectively stable during the heating stimulus, and thus changes in oxygen saturation from the deep vein would reflect differences in flow through the muscle vasculature. Using this approach some investigators did not observe a change in oxygen saturation from a deep vein (208), whereas others found increases of saturation (i.e., increases in blood flow) (54,185). However, upon comparing results from multiple techniques evaluated in the same lab, and in some cases in the same subjects, Detry et al. (54) proposed that increases in deep vein oxygen saturation during heating was “caused by

its contamination with cutaneous venous blood" and thus did not reflect real changes in muscle blood flow.

The rationale for the aforementioned diverging responses is not readily clear, possibilities include differences in responses between limbs and/or the approach used to heat the muscle; that is, heating both the assessed limb and the body (combination of direct heating and reflex-induced changes in perfusion), heating the body but not the assessed limb (only reflex-induced changes in perfusion), or only heating the assessed limb (only direct heating induced changes in perfusion). To address these possible methodological inconsistencies, Heinonen et al. (81) employed a unique approach in which perfusion in the gastrocnemius muscle was assessed via positron emission tomography under all three of these conditions. One leg was initially covered with a water perfused suit, while the other leg remained uncovered. Heating the covered leg increased muscle temperature of that leg from 33.4 ± 1.0 to 37.3 ± 0.5°C, which was accompanied with an increase in muscle blood flow of ~1 mL/min/100 g tissue (Fig. 8). In contrast, blood flow through the muscle not directly heated did not change. Subsequently, subjects donned a water perfused suit that covered their entire body, with the exception of the leg that was uncovered in the first part of the study. The subjects underwent a whole-body heat stress sufficient to increase intestinal temperature ~1°C, after which perfusion through both legs were re-evaluated. Muscle blood flow through the leg that was covered by the suit remained elevated, whereas muscle blood flow in the leg that was not covered by the suit did not change (see Fig. 8). These investigators concluded that direct heating (i.e., heating sufficient to cause ~4°C increase in muscle temperature), but not indirect heating (i.e., increasing core temperature by ~1°C but not directly heating the muscle), results in significant but relatively small increases in muscle blood flow. It should be emphasized that a 1 mL/min/100 g tissue increase in muscle blood flow under a heating source remains quite small, maybe ~350 mL/min for the entire body (see above), compared to ~8 L/min increase in skin blood flow by such a heat stress (95,211).

The mechanism(s) by which heating has the capability to slightly increase muscle blood flow is not clear but may be related to a direct effect of heat on the muscle vasculature (4,30), heat-induced release of vasodilator substances such as ATP (185) and nitric oxide (80), and/or heat induced increases in metabolism (i.e., a Q_{10} effect) that could result in reductions in regional vascular resistance (81).

Whole-body heat stress is a profound sympathoexcitatory stimulus (217), which is particularly evident by two to three fold increases in MSNA (42–46,104,135,175). Within the context of either no change or an increase in muscle blood flow during whole-body heat stress, such increases in MSNA are perplexing particularly since heat stress does not impair vasoconstrictor responsiveness to intravascular administration of adrenergic agents (108), although that conclusion has recently been challenged from in vitro studies of human feed arteries (90,91). It is important to note that direct local heating itself does not increase MSNA (201), and internal temperature must be elevated at least ~0.3 to 0.6°C before increases in MSNA begin to occur (135,175). Given these observations, it may be that differences in muscle vasodilator responses between a directly heated limb, and a nonheated limb during a whole-body heat stress may be due to a balance between heat induced muscle vasodilation and sympathetically mediated vasoconstriction. For example, in Heinonen et

al.'s (81) study increasing muscle temperature ~4°C increased blood flow in that region; however, core temperature did not change to that local heating stimulus and thus it is unlikely that MSNA increased. Conversely, during whole-body heating in which a limb is not in direct contact with the heating source, the muscle of that limb would still be exposed to warmer blood secondary to the heat stress. Increases in muscle blood flow associated with this "indirect" heating may be countered by sympathetically mediated vasoconstriction, with the net result being no change in muscle blood flow in the limb that was not directly heated. Finally, the effects of substances released during the heating stimulus (e.g., nitric oxide and ATP) in causing a sympatholytic effect that opposes heat-induced increases in sympathetic activity has been proposed (81,90,185).

Heat Stress and the Cerebral Circulation

Passive heat stress generally decreases cerebral perfusion, as measured primarily from cerebral artery blood velocities using transcranial Doppler (19,65,68,139–141,174,210,264,265). A limitation of this technique is the assumption that the diameter of the insonated artery does not change by the perturbation (i.e., heat stress), which has not been confirmed. That said, recent studies evaluating volumetric flow of the internal carotid and vertebral arteries via ultrasonography, a technique that accounts for changes (if any) in the diameter of these arteries, during heat stress report comparable relative reductions in cerebral perfusion versus simultaneously obtained values from transcranial Doppler (5,180). Such findings validate the utility of evaluating relative changes in cerebral perfusion via transcranial Doppler during heat stress conditions.

Although whole-body passive heat stress clearly decreases cerebral blood velocity, the magnitude of that reduction varies greatly both among subjects (Fig. 9) and investigations. Regarding the former, in an evaluation of 25 heat stress trials, some subjects show relatively little change in cerebral perfusion, whereas others showed up to a 30% reduction (264). Assessing repeated trials in some of these subjects, cerebrovascular responses had a low coefficient of variation of method error (9%) and a high interclass correlation coefficient (r = 0.87). The severity of the heat stress, indexed primarily by the elevation in both skin and internal temperatures relative to normothermia, likely influences the extent of the reduction in cerebral perfusion. For example, during a heat stress that increases internal temperature 0.5 to ~1.2°C, mean cerebral perfusion either does not change, or only modestly decreases (137,141,264,265). In contrast, up to 20% to 30% reductions in mean cerebral perfusion are observed when internal temperature is elevated 1.5°C or more (65,68,127,174,210). Based upon these observations, the magnitude of the reduction in cerebral perfusion seems to be related, in a graded manner, to the extent of the heat stress; though the specifics of this response, such as the threshold, "gain," and saturation points remain uninvestigated. Moreover, the relative contribution of skin versus internal temperatures in mediating cerebrovascular response during heat stress has not been thoroughly investigated.

The mechanism(s) by which heat stress reduces cerebral perfusion are not readily apparent, although a number hypotheses have been proposed, which are addressed herein.

Perfusion pressure—Severe passive heat stress generally reduces arterial blood pressure, although this is not consistently observed. In a classic study, Rowell et al. (221) likewise observed divergent responses with some subjects showing clear reductions in mean aortic pressure, while others did not. Reductions in arterial pressure were likewise reported from the radial artery by Ganio et al. (70) during ~1.5°C increase in internal temperature via passive heat stress. To account for such a reduction in perfusion pressure during heat stress on cerebral blood flow, an index of cerebral vascular conductance often, but not always, indicates increases in cerebral vascular tone (i.e., decreases in cerebral vascular conductance or increases in cerebral vascular resistance) (5,18,19,65,127,138,141,142,174,180,210,264). Of course, any influence of cerebrovascular autoregulation in buffering the effects of decreases in perfusion pressure on cerebral perfusion (discussed below) is not addressed through this simple calculation of cerebral vascular conductance/resistance. Nevertheless, in a number of studies the reduction in perfusion pressure accompanying passive heat stress does not consistently account for the observed reduction in cerebral perfusion.

Arterial carbon dioxide tensions ($PaCO_2$)—Heat stress induced hyperventilation decreases $PaCO_2$ and end-tidal CO_2 ($PetCO_2$) tensions (5,15,23,65,68,69,174,191,210,221,248,258). Although clearly individualized, the internal temperature threshold at which hyperventilation occurs and $PaCO_2$ begins to decrease is often between ~1 and 1.5°C above normothermic baseline (258), with that threshold being modulated by skin temperature (139). As heat stress continues to progress beyond this threshold, further hyperventilation occurs along with further reductions in $PaCO_2$ (65,68,191,258), sometimes culminating in the subjects complaining of numbness in the extremities and lips as well as lightheadedness. The cerebral vasculature is very sensitive to changes in $PaCO_2$, resulting in an ~2% to 4% reduction in cerebral perfusion for each 1 mmHg reduction in $PaCO_2$ (207). Importantly, Low et al. (138) confirmed that this $PaCO_2$/cerebral perfusion relationship was unaltered by heat stress. Given findings of up to 10 mmHg reductions in $PaCO_2$ or $PetCO_2$ during severe passive heat stress, coupled with the aforementioned $PaCO_2$/cerebral perfusion relationship, reductions in cerebral perfusion of up to 30% in some individuals are to be expected. Due in part to these observations, investigators sought to identify the contribution of reductions in $PaCO_2$ in mediating heat stress induced reductions in cerebral perfusion. This question was addressed by returning $PaCO_2$ to normothermic levels while individuals were profoundly heated. Brothers et al. (18) used a computer controlled end-tidal gas targeting system to return $PetCO_2$ to normothermic levels in heat stressed subjects and found that ~50% of the decrease in cerebral perfusion is $PaCO_2$ dependent; a finding confirmed by others (68,210). However, this observation is not universal as some laboratories, using related approaches, report complete normalization of cerebral perfusion when returning PetCO2 or $PaCO_2$ to normothermic levels (5,174). When taken together, a large percentage, or perhaps the entire reduction in cerebral perfusion during passive heat stress is mediated by hyperventilation induced reductions in $PaCO_2$. That said, the source of these apparently diverging responses is not readily apparent; possibilities include the level of heating, the approach used to return $PaCO_2$ to normothermic levels, and perhaps the body position of the subjects.

Sympathetic stimulation—Brothers et al. (18) hypothesized that increases in cerebral sympathetic stimulation may be a mechanism by which cerebral perfusion remains reduced after taking into account the influence of reductions in $PaCO_2$. Sympathetic neural activity to muscle can more than double during progressive passive heat stress (42,44–46,49,135,175), plasma norepinephrine concentrations can likewise double (159), while blood flow to the renal and splanchnic vascular beds decreases presumably due to increases in sympathetic activity in these regions (99,162,211,216,222). Such responses have resulted in passive heat stress being termed a “hyperadrenergic” state (217). Although controversial, evidence suggests the cerebral vasculature may be under sympathetic control (89,170,171,179,194,244,249,251,255,281), and thus it is reasonable to hypothesize that a component of the reduction in cerebral perfusion during heat stress may be sympathetically mediated. Further investigation is needed to definitively confirm or refute this hypothesis.

Cerebrovascular autoregulation—Although recently challenged (144), cerebral perfusion is generally thought to be maintained over a relatively wide range of perfusion pressures (e.g., from ~60 to ~150 mmHg), secondary to intrinsic changes in cerebral vascular resistance upon changes in perfusion pressure (82,183). Likewise, Zhang et al. (280) showed that oscillatory changes in arterial blood pressure were buffered within the cerebral vasculature, particularly at lower frequencies. These responses, termed cerebrovascular autoregulation, protect cerebral perfusion against both hypo- and hypertensive challenges. Should heat stress impair cerebrovascular autoregulation, decreases in arterial blood pressure often accompanying heat stress may result in larger decreases in cerebral perfusion relative to when the individuals were normothermic. Doering et al. (59) pursued this question in mildly heat stressed subjects (~0.4°C increase in internal temperature), concluding that heat stress improves cerebrovascular autoregulation. Given the relatively low level of heating in that study, others (19,65,137) further investigated this question but in subjects whose internal temperature was elevated greater than 1.0°C. Using different experimental approaches, these studies concluded that heat stress either does not alter or perhaps improves cerebrovascular autoregulation, depending on the assessed frequency of blood pressure oscillations. Therefore, it is unlikely that heat stress-induced alterations in autoregulatory control of the cerebrovascular vasculature contribute to the accompanying reductions in cerebral perfusion while in this thermal condition.

Heat Stress and Human Baroreflex Responsiveness

A tremendous amount of research has been performed to investigate the effects of exercise on baroreflex responsiveness, much of which is presented in the cited review papers (101,125,145,178,192,198–200). However most, if not all, of these studies do not consider the potential for elevated internal temperature that accompanies exercise to contribute to the modification of the baroreflex. It is particularly noteworthy that the central components governing thermoregulation are located in the hypothalamus (245), and stimulation of the hypothalamus has the capability to modify the baroreceptor reflex (74,203). Thus it is reasonable to hypothesize that heat stress can modify baroreflex responsiveness.

A baroreflex “arc” is comprised of afferent receptors and associated afferent neural signal, central integration of that signal, efferent neural outflow, and an end-organ response. In

humans, research into the effects of heat stress on the baroreflex has focused primarily on the efferent neural outflow (i.e., sympathetic nerve activity to muscle and skin) as well as the end-organ response (e.g., changes in heart rate as well as systemic and regional vascular resistances). This section will review the effects of passive heat stress on responses secondary to perturbations of the carotid baroreceptors, perturbations of the integrative baroreflex (i.e., all baroreceptors perturbed), and postsynaptic responsiveness.

Heat stress and the carotid-cardiac/vascular baroreflex—Carotid baroreceptors can be directionally perturbed by applying suction and pressure specifically over the carotid sinus region (61,146,195). Carotid-cardiac (heart rate) and carotid-vascular (arterial blood pressure) responses are then evaluated relative to the applied pressures, typically via nonlinear regression modeling. From this modeling, an estimate of the maximal gain, or responsiveness, of the baroreflex is obtained. Yamazaki et al. (274) was the first to evaluate the effects of heat stress on carotid-cardiac baroreflex responsiveness. They concluded that despite ~30 bpm increase in heart rate to heat stress alone, heat stress did not change the maximum gain of the carotid-cardiac response; a finding that was subsequently confirmed in follow-up studies by that group and others (32,275). Interestingly, given the hyperbolic relationship between heart rate and R-R interval, when the carotid-cardiac baroreflex was evaluated using the inverse of heart rate, R-R interval, the maximum gain of the reflex was reduced by ~50% while heat stressed (32). Thus, heat stress either does not change or attenuates carotid-cardiac baroreflex responsiveness. A key limitation in the interpretation of these data is that cardiac output, not heart rate, is a primary component governing blood pressure during baroreceptor loading/unloading. Without knowing the effects of baroreceptor perturbations on stroke volume, and more specifically cardiac output, the aforementioned heart rate responses are incomplete.

Passive heat stress decreases the maximal gain of the carotid-vascular baroreflex by ~35% (Fig. 10), thereby demonstrating that for a given change in carotid transmural pressure, the corresponding change in arterial blood pressure is attenuated when the individuals were heat stressed (32). Reduced carotid-vascular responses may be related to findings suggesting the carotid baroreflex does not have an efferent limb governing skin blood flow (35,257), coupled with a large fraction of cardiac output going to the skin during heat stress (162,219,221). That said, recent findings challenge this hypothesis (105).

Heat stress and integrated baroreflex responses—Integrated baroreflexes encompass high-pressure inputs from the carotid arteries and the aortic arch, as well as low-pressure inputs from the heart and large pulmonary vessels. Integrated baroreflexes are often more generalizable to clinical conditions such as hemorrhage relative to the aforementioned carotid baroreflexes. Heat stress results in an intriguing integrated baroreceptor-mediated blood pressure response during the Valsalva maneuver (Fig. 11), characterized by a very low hypotensive response coupled with an attenuated recovery during phase IIb of that maneuver (50,277); responses remarkably similar to that which occurs during complete autonomic blockade (279). These observations raise the possibility that integrated baroreflex responsiveness may be impaired by heat stress. A number of other techniques have been

used to evaluate integrated baroreflex responsiveness (44–46,48,272,275–277), including pharmacological manipulations of blood pressure (e.g., modified oxford technique), hypotensive challenges induced by simulated hemorrhage (e.g., LBNP and head-up tilt), and mathematical evaluations of heart rate and neural responses to spontaneous changes blood pressure (i.e., both the transfer function gain analysis and the sequencing technique). Results from these differing techniques sometimes contradict each other which complicate interpretation, though an alternate interpretation is that each of these different techniques may highlight different aspects of the reflex arc.

Recordings of MSNA provide a reasonable and quantifiable measure of efferent sympathetic activity that is often used to evaluate efferent neural responses to baroreceptor perturbations. Conversely, recordings of multiunit skin sympathetic activity are not responsive to baroreflex perturbations (47,261,263), even though single-unit recordings present with a degree of autorhythmicity (148). A common approach to evaluate baroreflex function is to pharmacologically induce hypotensive and hypertensive challenges while measuring MSNA and heart rate responses. This is the approach that Cui et al. (45) used to identify the effects of heat stress on integrative baroreflex responsiveness. Under both normothermic and heat stressed conditions, arterial blood pressure was first decreased with bolus intravascular administration of the endothelial-independent vasodilator sodium nitroprusside and then increased with bolus administration of the alpha-adrenergic agonist phenylephrine. They found that heat stress did not alter the slope of the relationship between changes in MSNA and diastolic blood pressure or changes in heart rate and systolic blood pressure, relative to when subjects were normothermic; concluding that heat stress does not alter baroreflex modulation of MSNA or heart rate. Rather, they observed that this thermal perturbation shifted the baroreflex curves to the prevailing elevated heart rate and MSNA. A related study demonstrated an absence of a difference in baroreflex regulation of MSNA and heart rate to sustained (i.e., 20 min) increases in arterial blood pressure between normothermic and heat stressed conditions (48). Thus, regardless of whether changes in blood pressure were acute or sustained, heat stress did not alter integrated baroreflex control of MSNA or heart rate.

Although, mechanistically, pharmacological evaluation of baroreflex function is beneficial, evaluation of baroreflex responsiveness to a hypotensive challenge evoked by a perturbation that simulates the upright posture or hemorrhage (such as LBNP) can also be insightful. Cui et al. (46) identified that the magnitude of the increase in MSNA during LBNP was greater when individuals were heat stressed, owing to the greater reduction in arterial blood pressure (and thus baroreceptor unloading) to a given level of LBNP while in this thermal condition. To address this potential limitation, MSNA responses were re-evaluated after normalizing for the reduction in an index of central blood volume during LBNP between thermal conditions. Interestingly, the slope of the relationship between the increase in MSNA relative to the reduction in central blood volume was greater when individuals were heat stressed. This finding is consistent with the hypothesis that heat stress increases the sensitivity of a “gating” mechanism governing frequency of sympathetic neural firing (104). These studies suggest that baroreflex modulation of MSNA may actually be elevated by whole-body heat stress.

A number of investigators have assessed the effects of heat stress on baroreflex control of heart rate via an approach that has been termed the sequence technique (88,128,272,275,276). This method evaluates the slope between spontaneous changes in arterial blood pressure and corresponding changes in heart rate or R-R interval. Similar to that observed with carotid-cardiac baroreflex responsiveness, the outcome of this assessment depends on whether the evaluated variable was heart rate or R-R interval. When heart rate was analyzed, heat stress did not change baroreflex responsiveness (128,275), however when R-R interval was analyzed, heat stress decreased baroreflex responsiveness (128,272,276). A primary limitation of the sequencing technique is that the range of changes in arterial blood pressure can be relatively small, which can affect the calculation of baroreflex responsiveness and the range to which these results can be applied. That said, heat stress did not change baroreceptor control of heart rate when greater changes in blood pressure were imposed pharmacologically (45).

Heat stress and postjunctional adrenergic vasoconstrictor responses—The end organ response to a neural signal is a critical component of any reflex arc, such as the arterial baroreflex. For example, even if a perturbation (e.g., heat stress) does not change baroreflex modulation of the efferent neural limb (e.g., MSNA), but the postjunctional responses are attenuated by that perturbation, then the overall baroreflex response will be attenuated. A number of investigations have sought to identify the effects of heating, in either whole-body or isolated vessel preparations, on postjunctional vasoconstrictor responses (30,90,91,93,118,124,152–154,165,193,253).

In a rat model, the elevation in arterial blood pressure to an infusion of norepinephrine was attenuated during heat stress (124). Cui et al. (48) sought to translate that work in humans by carefully monitoring arterial blood pressure during administration of varying doses of the α_1-adrenergic agonist phenylephrine in both normothermic and heat stressed conditions. Though this approach is not without its limitations, they identified that heat stress attenuates the increase in both mean arterial blood pressure and systemic vascular resistance (Fig. 12). These data suggest that α_1-mediated elevations in arterial blood pressure are attenuated in the heat stressed human. Using a non-pharmacological approach, Cui et al. (43) evaluated MSNA and arterial blood pressure responses to immersion of a hand in an ice water slurry (e.g., cold pressor test) while individuals were normothermic and heat stressed. Despite similar increases in MSNA to the cold pressor test between these thermal conditions, the elevation in arterial blood pressure was reduced by ~50% when individuals were heat stressed. Although in both of these studies the mechanism(s) by which heat stress attenuates the increase in arterial blood pressure was not the primary aim, a viable hypothesis is that heat stress attenuates cutaneous vasoconstrictor responsiveness to both exogenous (i.e., phenylephrine) and endogenous vasoconstrictor agonists.

As previously discussed, whole-body heat stress has the capability of increasing human skin blood flow from ~300 to 7,500 mL/min, resulting in more than 50% of cardiac output being directed to the skin and up to 50% of systemic vascular conductance attributed to the skin (216,221). Under such thermal conditions the skin has the capacity to significantly increase arterial blood pressure through reducing cutaneous vascular conductance (i.e., vasoconstriction or reduced vasodilation). Thus, attenuated cutaneous vasoconstriction in a

heat-stressed state could, theoretically, attenuate the increase in arterial blood pressure upon administration of exogenous, or release of neuronally derived, vasoconstricting agents. Consistent with this hypothesis, cutaneous vasoconstrictor responsiveness to exogenous and endogenous vasoconstrictor stimuli are attenuated during both whole-body and local heating (186,262). These findings are consistent with the effects of local and whole-body heating on constrictor responses in isolated hand veins (282). Subsequent studies revealed that substances released during heat stress, such as nitric oxide and/or vasoactive peptide(s), may directly attenuate cutaneous adrenergic vasoconstrictor responsiveness for a given neural signal (136,239–241).

Studies focusing exclusively on the skin left unanswered whether attenuated systemic vasoconstrictor responses to such stimuli were exclusively a result of attenuated cutaneous vasoconstriction, or whether heating also impairs vasoconstrictor responses in other vascular beds such as the splanchnic, renal, and muscle beds. Addressing that limitation, Minson et al. (163) observed that the increase in both splanchnic and renal vascular resistances to head-up tilt were comparable between when subjects were normothermic and heat stressed, arguing against the hypothesis that heat stress attenuates vasoconstrictor responses in those beds. However, those data must be interpreted with the understanding that heat stress conditions were relatively mild (~0.5°C increase in esophageal temperature) and thus the effects of a more substantial heat stress on vasoconstrictor responsiveness to adrenergic stimuli on these vascular beds remain unknown. Keller et al. (108) sought to identify the effects of elevated tissue temperature on vasoconstrictor responses in the muscle vasculature. Using ^{133}Xenon clearance techniques, an index of muscle vascular conductance was evaluated during intra-arterial infusion of phenylephrine (α_1-selective agonist) and BHT-933 (alpha$_2$-selective agonist) while the muscle was normothermic and after muscle temperature was elevated by ~4°C via local heating. Regardless of the adrenergic subtype tested, the reduction in local muscle vascular conductance to those agents was not attenuated by locally heating. In contrast to those findings, heating isolated human skeletal muscle feed arteries attenuates vasoconstrictor responsiveness (91). This attenuated response was rescued with nitric oxide synthase inhibition (90), suggesting that nitric oxide-related mechanisms are responsible for heat-induced attenuated vasoconstrictor responses in that vascular bed; a response similar to that observed in human skin (136,239–241). Currently, it is difficult to reconcile differences between the absence of heat-induced attenuation in skeletal muscle and whole-limb vasoconstrictor responses (108), relative to attenuated responses observed in the skin and human feed arteries. It is possible that the extent and mode of heating, isolated versus a more “intact” preparation, and the regions from which the responses were assessed could be factors in interpreting the above data.

Combining data from a number of the above studies indicate that heat stress attenuates postjunctional cutaneous vasoconstrictor responsiveness to adrenergic agonists, while local muscle vasoconstrictor responsiveness is apparently preserved, despite attenuated responses in isolated muscle feed arteries (91). The effects of profound heat stress on postjunctional vasoconstrictor responsiveness to adrenergic agonists in other organs/structures, such as the renal and splanchnic vascular beds in humans, remains to be determined.

Heat Stress and Tolerance to a Hypotensive Challenge

While heat stressed, individuals' tolerance to challenges that induce central hypovolemia and accompanying hypotension—such as head-up tilt, simulated hemorrhage via LBNP (31,267), and during footward gravitational acceleration (i.e., +Gz acceleration)—is greatly attenuated relative to when these individuals are normothermic (87,106,133,177,242,264,273). This point is particularly emphasized by Keller et al. (273) in which ~85% of subjects could not complete 40 mmHg LBNP while heat stressed, despite ~70% of subjects tolerating 70 mmHg or more LBNP when normothermic (Fig. 13). The consequences of heat induced reductions in such tolerances range from a relatively minor inconvenience of light-headedness upon standing after a hot bath, to an inability to adequately maintain blood pressure sufficient to perfuse organs, including the brain, in a heat stressed soldier, firefighter, miner, foundry or construction worker, who experience a hemorrhage injury.

The mechanisms by which heat stress compromises tolerance to these challenges are likely multifactorial and are yet to be fully elucidated. It is interesting to note that well-recognized responses to passive heat stress per se (as addressed in previous sections) may contribute to this occurrence. Notable candidates include reduced central blood volume, arterial blood pressure, and cerebral perfusion. These factors, coupled with a limited reserve to recruit other physiological responses beneficial in protecting arterial blood pressure and central hypovolemia during heat stress, compound this problem. As an example, during a hypotensive event baroreflex-mediated responses lead to increases in heart rate and cardiac contractility, as well as mobilization of venous blood volumes from high capacitance beds and decreases in renal and splanchnic vascular conductance. However, since heat stress elevates each of those responses prior to the hypotensive challenge, the reserve by which these factors can further be engaged may be limited. This scenario assumes that maximum cardiac and vascular responses are engaged during a hypotensive event in heat stressed individuals, which may or may not be the case. Nonetheless, a variety other mechanisms have been proposed to contribute to heat stress-induced attenuation in tolerance to central hypovolemia, which will be discussed herein.

Heat stress, central hypovolemia tolerance, and central cardiovascular responses—The maintenance of arterial blood pressure is predicated upon the product of heart rate, stroke volume, and systemic vascular resistance. If heat stress affects any one, or a combination, of these responses, without compensation from the other variables, tolerance to the hypotensive challenge will be compromised. Schlader et al. (233) sought to identify whether heat stress attenuates the increase in heart rate during a simulated hemorrhagic challenge evoked by progressive LBNP. In this retrospective study, 60 pairs (normothermic and whole-body heating) of response to presyncopal LBNP were identified and directly compared. As expected, heat stress increased heart rate such that just prior to LBNP heart rate was 101 ± 16 bpm, while the same point in normothermia heart rate was 61 ± 9 bpm. The peak heart rate achieved during LBNP prior to any bradycardia was greater during heat stress (133 ± 23 bpm) relative to normothermia (115 ± 23 bpm), and thus there was no

evidence that heat stress attenuates absolute heart rate responses to a profound hypotensive challenge. However, it should be noted that the elevation in heart rate from just prior to LBNP through the peak heart rate response during LBNP (i.e., delta) was attenuated while subjects were heat stress, likely because of elevated baseline heart rates to heat stress itself. Similarly, in a related study, those subjects with the highest increase in MSNA to upright tilt were the ones who had the greatest tolerance to this orthostatic challenge (44). Thus, although heat stress does not attenuate the absolute heart rate achieved during a profound hypotensive challenge, the magnitude of increase in heart rate, and sympathetic activity, achieved during such a challenge can influence the capacity to withstand that challenge.

As discussed above, indices of ventricular preload (i.e., central venous pressure, pulmonary capillary wedge pressure, left-ventricular end-diastolic volume, and central blood volume) decrease during passive heat stress, but what are the interactions between these decreases and tolerance to a hypotensive challenge? Keller et al. (106) tested this question by measuring central venous pressure and tolerance to a hypotensive event (presyncope limited LBNP) with subjects in three conditions: (i) normothermia, (ii) heat stress, and (iii) heat stress plus the restoration of central venous pressure to normothermic conditions. They observed that profound reductions in LBNP tolerance by heat stress were restored to normothermic levels with volume loading, indicating that maintaining preload may be an underlying mechanism of tolerance (see Fig. 13). Consistent with those observations, Brothers et al. (17) showed that the reduction in left-ventricular end-diastolic volume during LBNP was attenuated following volume loading in heat stressed subjects. Other studies have not identified a relationship between the reduction in central venous pressure during heat stress and the ability to tolerate a hypotensive challenge (16), but that does not negate the benefit of elevating central blood volume prior to a subsequent hypovolemic challenge. One caveat, though, is that central venous pressure does not always reflect central blood volume (236).

Using nuclear medicine techniques to evaluate central blood volume changes, Crandall et al. (37) tested the hypothesis that the magnitude of the reduction in an index of central blood volume during moderate LBNP would be greater when individuals were heat stressed. Consistent with that hypothesis, while subjects were normothermic, 30 mmHg LBNP reduced torso blood volume (as an index of central blood volume) by 22 ± 8%; however, while heat stressed the magnitude of this reduction to the same LBNP was approximately threefold greater being 73 ± 2% (Fig. 14). Such a finding is not surprising given changes in venous properties (i.e., increased capacitance and decreased responsiveness to adrenergic agents) with elevated tissue temperature (83,84,214,253,282).

Appropriate decreases in systemic vascular conductance are critical for the maintenance of arterial blood pressure during a central hypovolemic challenge, such as LBNP or upright tilt. Whole-body heat stress causes profound increases in systemic vascular conductance, primarily due to increases in cutaneous vascular conductance. Likewise, during a hypotensive challenge while heat stressed, reductions in vascular conductance are critical to maintaining the vascular pressures that are necessary to perfuse the brain and other vital organs. Yet, the effects of heat stress on systemic vascular conductance leading up to and at presyncope were previously unclear. To investigate this question, Ganio et al. (72) evaluated

cardiac output, arterial blood pressure, and systemic vascular resistance responses leading up to and at presyncope in heat stressed subjects (Fig. 15). To obtain the required temporal measures of cardiac output to evaluate this response at the point of presyncope, thermodilution-derived measures of cardiac output were obtained in heat stressed subjects throughout LBNP. Consistent with prior findings previously discussed, heat stress itself increased cardiac output by ~5 L/min but did not change stroke volume, while systemic vascular resistance was approximately halved. Progressive LBNP decreased both stroke volume and cardiac output, but systemic vascular resistance was unchanged throughout the hypotensive challenge to presyncope, resulting in the reduction in arterial blood pressure that paralleled the reduction in cardiac output. It is noteworthy that this lack of an increase in systemic vascular resistance during profound baroreceptor unloading leading up to presyncope is accompanied by large increases in sympathetic neural activity (44,46), again suggesting that heat stress has a sympatholytic-type response resulting in little to no changes in vascular tone despite such large increases in sympathetic activity. Mechanism(s) responsible for such an effect remain unknown, although possibilities are discussed in the subsequent sections. It is interesting to note that typically individuals became pre-syncopal about the point when cardiac output had returned to a normothermic level (i.e., ~7 L/min; see Fig. 15). In these conditions, it appears that an adequate cardiac output to maintain arterial blood pressure while normothermic is no longer sufficient to maintain blood pressure while heat stressed due to profound cutaneous vasodilation, coupled with inadequate vasoconstrictor responses despite increases in sympathetic activity. Finally, the interpretation of the aforementioned findings should be constrained to the level of heat stress imposed. Given relatively maintained arterial blood pressure that is often observed during low levels of LBNP under less severe heated conditions (46,139,235), it may be that under such conditions increases in systemic vascular resistance contributes to the maintenance of arterial blood pressure. Alternatively, it may be that under such conditions the reduction in stoke volume is offset by increases in heart rate, thereby minimizing LBNP-induced reductions in cardiac output and supporting arterial blood pressure.

Heat stress, central hypovolemia tolerance and cutaneous vascular responses—The absence of a decrease in systemic vascular conductance in heat stressed individuals during a profound hypotensive challenge is perplexing. As stated above, during severe whole-body heat stress up to 50% of cardiac output perfuses the skin. Under such conditions the cutaneous vascular bed contains the largest fraction of systemic vascular conductance, while vascular conductance in most noncutaneous beds is greatly reduced. Thus, during heat stress combined with progressive reductions in cardiac output, reducing cutaneous vascular conductance would have the greatest capacity to protect arterial blood pressure. A number of studies have investigated the effect of a mild to moderate central hypovolemic challenge (primarily via LBNP) on cutaneous vascular conductance (7,35,40,96,97,109,151,225,247), although only one study was specifically designed to evaluate these responses leading up to and at the point of presyncope (36). In that study, when arterial blood pressure was reduced to 57 ± 9 mmHg during progressive LBNP in heat stressed subjects, cutaneous vascular conductance had decreased by only ~15 ± 21% (Fig. 16). Thus, at a point of profound hypotension and accompanying bradycardia, indicative of cardiovascular decompensation, only very small decreases in cutaneous vascular

conductance occurred despite this vascular bed receiving such a large fraction of cardiac output. This observation is consistent with studies showing relatively small decreases in cutaneous vascular conductance in heat stressed individuals during mild to moderate LBNP challenges (35,109,149).

Minimal reductions in cutaneous vascular conductance during profound hypotension while heat stressed may be related to little to no increases in sympathetic adrenergic nerve activity innervating the cutaneous vasculature during such maneuvers (47,52,256,261,263). Consistent with that hypothesis, electrical stimulation of the carotid sinus nerve, which simulates arterial hypertension, had no effect on skin sympathetic nerve activity despite causing appropriate changes in MSNA (257). Given a few divergent findings relative to those discussed above (58,105), perhaps the baroreflexes either do not have, or have only a minimal vasomotor component, governing skin blood flow. It should be noted, however, that integrated multiunit skin sympathetic nerve activity measured in the aforementioned studies can contain signals responsible for cutaneous vasoconstriction, sudomotor activation, piloerection, and perhaps cutaneous vasodilation.

It may be that minimal reductions in cutaneous vascular conductance during profound hypotension during heat stress is due to “sympatholytic-like” substances released around cutaneous blood vessels that limit the extent to which these vessels can vasoconstrict to an adrenergic stimulus. In support of this hypothesis, Wilson, et al. (262) found that the magnitude of cutaneous vasoconstriction to exogenous norepinephrine was attenuated when subjects were heat stressed. Further work revealed that substances specifically released from sympathetic cholinergic nerves, the nerves responsible for cutaneous vasodilation during heat stress (110), or downstream products from neurotransmitters released from those nerves attenuate the magnitude of cutaneous vasoconstriction to a hypotensive challenge while heat stressed (239,240). Nitric oxide may contribute to this response given enhanced cutaneous vasoconstriction to both endogenous and exogenous stimuli upon blocking nitric oxide synthase (60,240,241). Finally, elevated tissue temperature itself may alter the capacity of the cutaneous vascular bed to appropriately respond to vasoconstricting stimuli, as shown in other vascular beds (90,91,118), also perhaps through nitric oxide-related mechanisms (90).

Heat stress, central hypovolemia tolerance and the cerebral vasculature— Adequate blood flow, and correspondingly oxygen delivery, to cerebral tissue are critical for the maintenance of consciousness during central hypovolemia and accompanying hypotension (106,157,252). Thus, heat stress-induced factors that alter either cerebral perfusion itself, or its control, could contribute to reduced capability to withstand a hypotensive challenge in this thermal condition. That said, as previously addressed, cerebrovascular autoregulation and responsiveness to hypo/hypercapnic challenges are generally unaffected by heat stress. One such factor may simply be the aforementioned reductions in cerebral perfusion caused by passive heat stress (5,18,65,174,264). Regardless of the mechanism, a reduction in cerebral perfusion by up to 30% by heat stress alone would decrease the range (i.e., reserve) by which cerebral perfusion could further decrease during a hypotensive challenge without signs and symptoms of ensuing syncope. Consistent with this thought, cerebral perfusion and cerebral vascular conductance are lower during upright tilt

and at almost every stage of LBNP, prior to pre-syncope, when individuals are heat stressed (141,143,184,264).

Lucas et al. (143) sought to identify the effects of fluid loss associated with sweating during heat stress on cerebral vascular responses to presyncopal limited LBNP. Subjects were exposed to LBNP to presyncope during normothermia, heat stress, and heat stress with intravascular volume infusion throughout the heating period sufficient to match fluid loss due to sweating. They observed that the reduction in cerebral perfusion at any stage of LBNP prior to presyncope was greater in both heat stress conditions compared to normothermia, but steady state volume infusion attenuated the reduction in cerebral perfusion compared to heat stress alone during LBNP. In a related protocol, Schlader et al. (234) found that rapid bolus volume loading likewise attenuated the reduction in cerebral perfusion during LBNP relative to a comparable level of heat stress without volume loading. Thus, changes in fluid status, either associated with sweat-induced dehydration or reductions in central blood volume associated with cutaneous vasodilation, appear to contribute to cerebral perfusion regulation during central hypovolemia and accompanying hypotension.

As previously addressed, 50% or more of the reduction in cerebral perfusion during heat stress is due to hyperventilation induced reductions in $PaCO_2$. Given these observations, if a reduction in baseline cerebral perfusion by heat stress itself contributes to compromised tolerance to central hypovolemia, then augmenting cerebral perfusion should return this tolerance to normothermic levels. To test this question, Lucas et al. (142) had heat stressed subjects breathe a gas mixture containing 5% carbon dioxide to elevate $P_{ET}CO_2$. Upon achieving an elevated cerebral perfusion via this hypercapnic challenge, and while continuing to receive this gas mixture, individuals were exposed to presyncopal limited LBNP. Counter to that hypothesis, hypercapnia-induced increases in cerebral perfusion did not alter the capacity to tolerate an LBNP challenge relative to the heat stress alone trial. It is noteworthy that at presyncope during the hypercapnic trial, middle cerebral artery blood velocity was identical to that observed *prior to the onset* of LBNP (Fig. 17). These data, coupled with comparably depressed arterial blood pressures between heat stress trials, suggest that syncopal symptoms in heat stressed individuals are not necessarily due solely to reduced cerebral perfusion within the area of the insonated vessels, but that other mechanisms likely contribute, or be responsible for, reduced capability to tolerate central hypovolemia and accompanying hypotension.

Heat stress, central hypovolemia tolerance—protective strategies—It is our contention that the displacement of blood from the central reservoirs to the skin, coupled with insufficient redistribution of blood back from the skin to those reservoirs during a hypovolemic challenge (e.g., hemorrhage), is the primary mechanism for heat-induced reductions in tolerance to central hypovolemia. Given this contention, effective strategies to protect against heat-induced reductions in tolerance to central hypovolemia would either prevent skin blood flow/volume from increasing during a thermal challenge or facilitate the return of blood from the skin to central reservoirs. The former is not a practical solution given adverse consequences for thermoregulation, whereas the latter could be accomplished through skin cooling. Wilson et al. (265) and Lucas et al. (139) reported elevations in arterial pressure, vascular resistance, cerebral perfusion, and/or tolerance during upright tilt or

LBNP in heat stress individuals when those stressors were combined with rapid skin cooling. It is interesting to note that despite these responses, a soldier who is experiencing a hemorrhagic injury is often warmed regardless of their thermal status; an approach that has recently been challenged (29).

As discussed a number of times in this review, fluid resuscitation can improve tolerance to central hypovolemia in a heat stressed individual (106). As illustrated in Figure 13, Keller et al. observed a complete restoration of LBNP tolerance in heat stressed individuals following volume loading sufficient to return central venous pressure to preheat stress levels. Moreover, Lucas et al. (143) recently reported that replacing the fluid lost to sweating during passive heat stress partially normalized tolerance to central hypovolemia. Thus, fluid resuscitation remains a viable treatment option for those experiencing actual or simulated blood loss while heat stressed. Moreover, the prevention or attenuation of central hypovolemia induced by heat stress, via adequate fluid replacement, may also prove to be an effective strategy in improving tolerance to central hypovolemia.

Taken together, the primary strategy to protect against heat induced reductions in tolerance to central hypovolemia is to normalize central blood volume through approaches such as adequate hydration, fluid resuscitation, and/or rapid skin cooling. There are a number of challenges in executing the latter two options in non-hospital settings where individuals may be heat stressed and are at a greater risk for a hemorrhagic injury (e.g., the battlefield, construction sites, etc.). Clearly more research is needed in this area, especially as extreme weather incidence rates continue to climb.

Summary

In summary, passive heat stress causes a myriad of physiological responses, many of which are directed towards heat dissipation to maintain thermal homeostasis. These thermally beneficial responses generally come at the expense of blood pressure regulatory capacity, resulting in a reduced ability to tolerate central hypovolemia that accompanies simple orthostatic changes or a hemorrhagic insult. By understanding the consequences of passive heat stress across multiple physiological systems, this information could prove beneficial towards understanding the mechanisms, and ultimately the prevention, of elevated morbidity and mortality in hyperthermic environmental conditions. These issues would be compounded, and likely become more important, in vulnerable or susceptible individuals (e.g., diseased, younger or older, hypohydrated, fatigued, or wounded). Moreover, studies in these areas are expected to lead towards improved treatment of individuals experiencing a hemorrhagic injury, such as soldiers and firefighters who are also hyperthermic.

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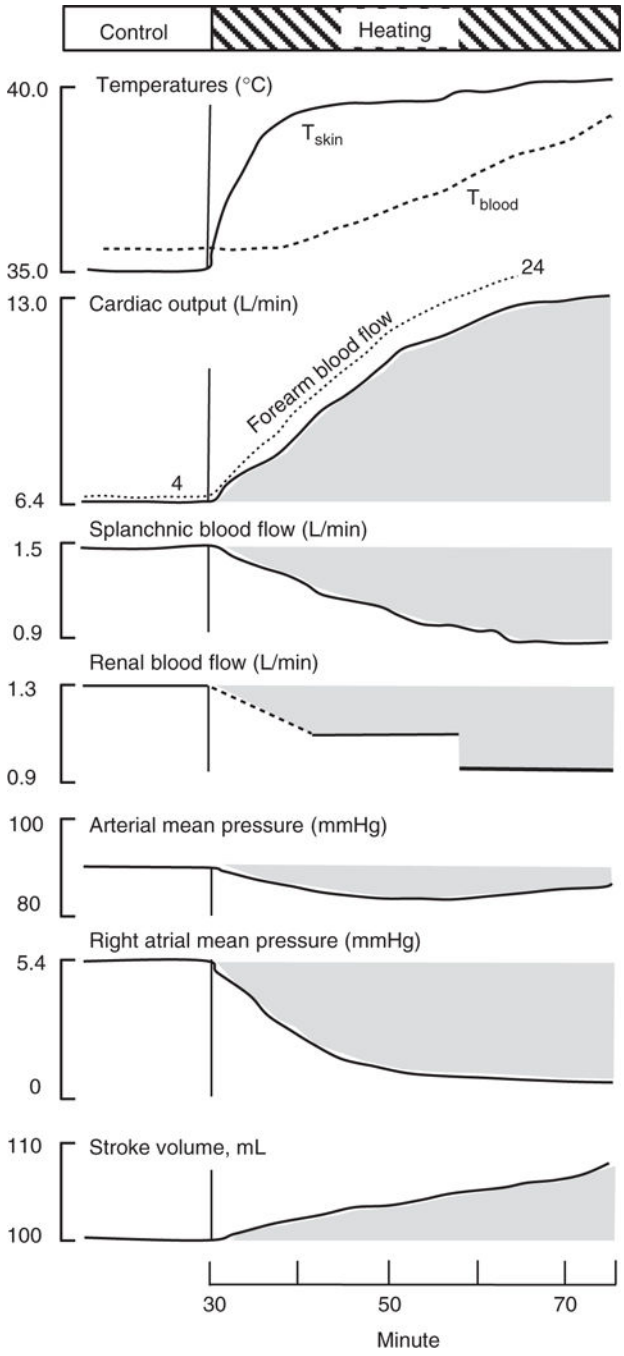

Figure 1.

Typical cardiovascular responses to whole-body passive heat stress in humans. Figure modified, with permission, from Rowell (211).

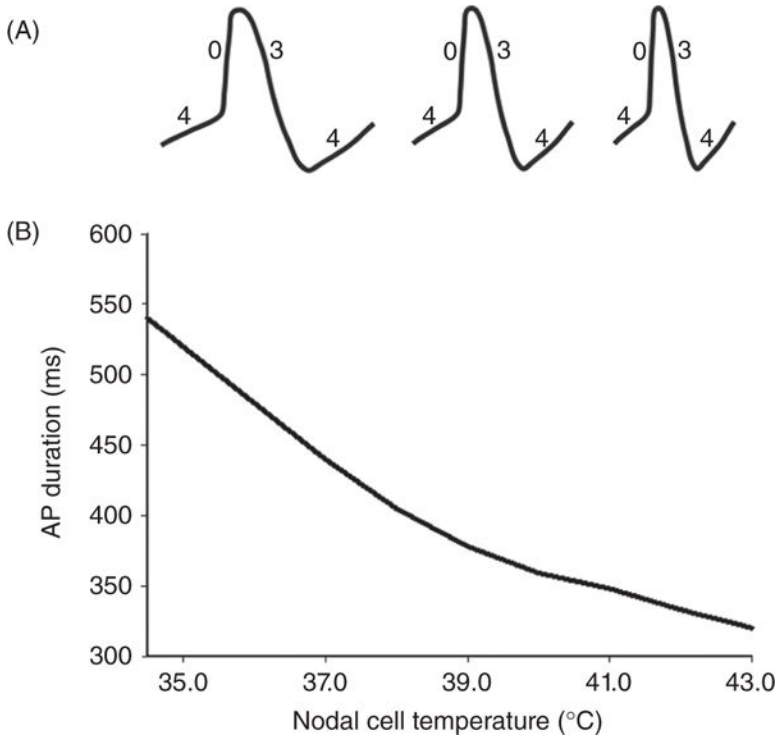

Figure 2.

Panel A denotes hypothetical cardiac nodal action potential changes as nodal cell temperatures increases. Note the narrower duration of the action potential waveform and the steeper Phase 4. Panel B depicts redrawn data from rabbit sinus arterial nodal cell action potential durations as a function of nodal cell temperature. Modified, with permission, from Yamagishi & Sano (270).

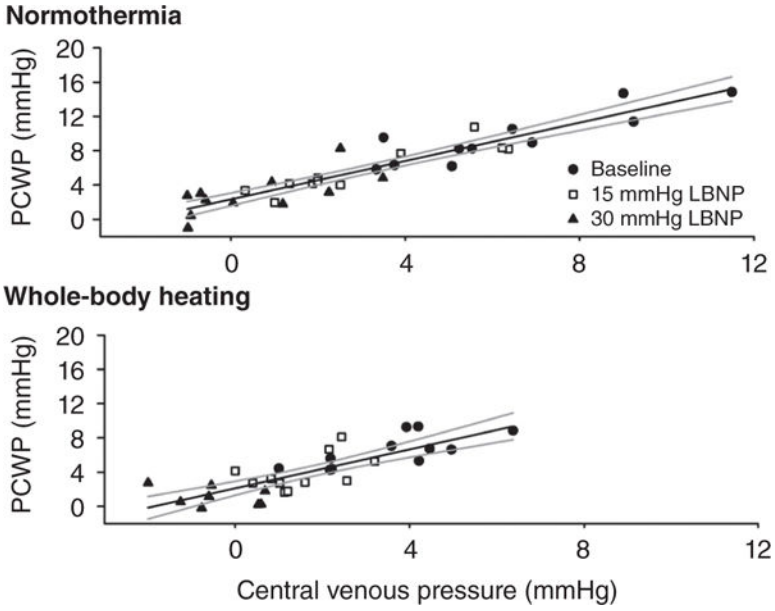

Figure 3.

Regression analysis between central venous pressure (CVP) and pulmonary capillary wedge pressure (PCWP) at baseline and two lower body negative pressures (LBNP; 15 and 30 mmHg). The strength of relationships and regression equations were $r = 0.93$, $P < 0.001$, PCWP = 1.1 × CVP + 2.3 for normothermia and $r = 0.81$, $P < 0.001$, PCWP = 1.1 × CVP + 2.1 for whole-body heating. The black line refers to the line of identity and the grey lines refer to 95% confidence interval. Modified, with permission, from Wilson et al. (266).

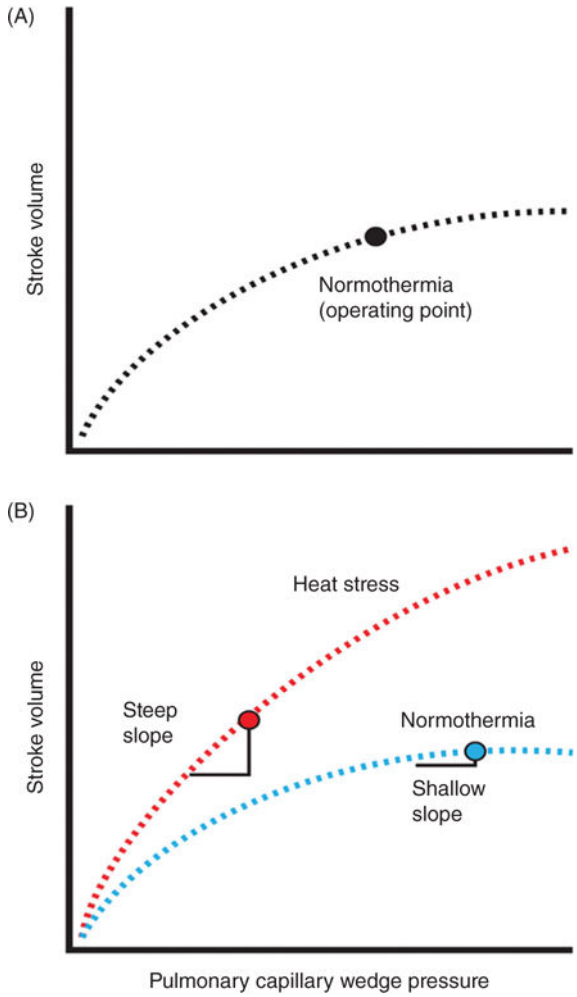

Figure 4.

Schematic of the effect of thermal stress on the Frank-Starling relations. (A) Normothermia Frank-Starling relation with the labeled point being the operating point in the supine position. (B) Heat stress induced changes in the Frank-Starling relations, as well as the location of the supine operating points on those curves. This figure also highlights slope changes where a similar decrease in pulmonary capillary wedge pressure would cause a relatively large decrease in stroke volume during heat stress compared to normothermia. Figure modified, with permission, from Wilson & Crandall (260).

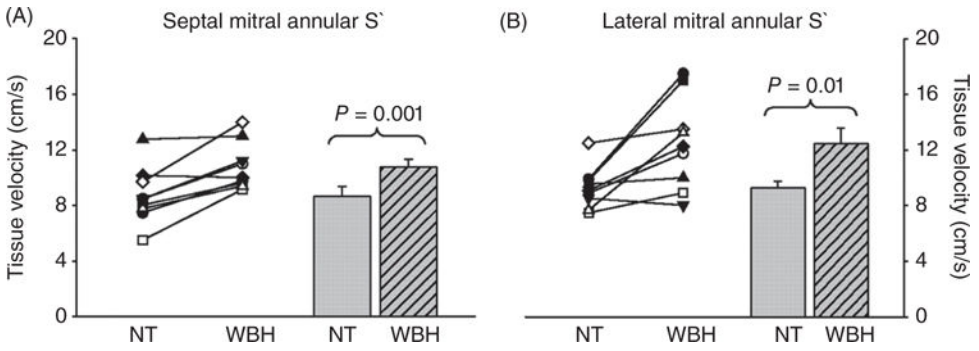

Figure 5.

Peak septal and lateral mitral annular systolic velocities (S′). Individual (left) and group averaged (*right*) echocardiographic measurements of peak septal mitral annular systolic velocity (A) and peak lateral mitral annular systolic velocity (B) during normothermia (NT) and whole-body heating (WBH) conditions. Septal annular and lateral annular systolic velocities were increased during heat stress relative to normothermia, indicative of an increase in cardiac systolic function. Group data are means ± SD. Figure, with permission, from Brothers et al. (14).

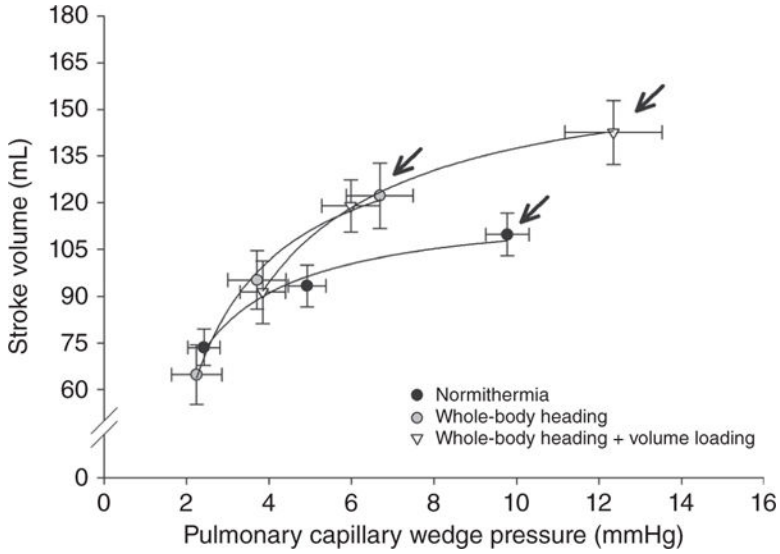

Figure 6.

Effects of heat-stress on Frank-Starling curves by expressing the relation between pulmonary capillary wedge pressure and stroke volume during normothermia, heat stress, and heat stress plus volume loading. Data were obtained prior to lower-body negative pressure (LBNP) and subsequent 15 and 30 mmHg LBNP for each of the indicated conditions. The arrows indicate pre-LBNP responses (i.e., operating point) for each thermal condition. The operating point is the prevailing pulmonary capillary wedge pressure and stroke volume prior to the onset of LBNP. Lines represent fitted approximations. Figure modified, with permission, from Bundgaard-Nielsen et al. (21).

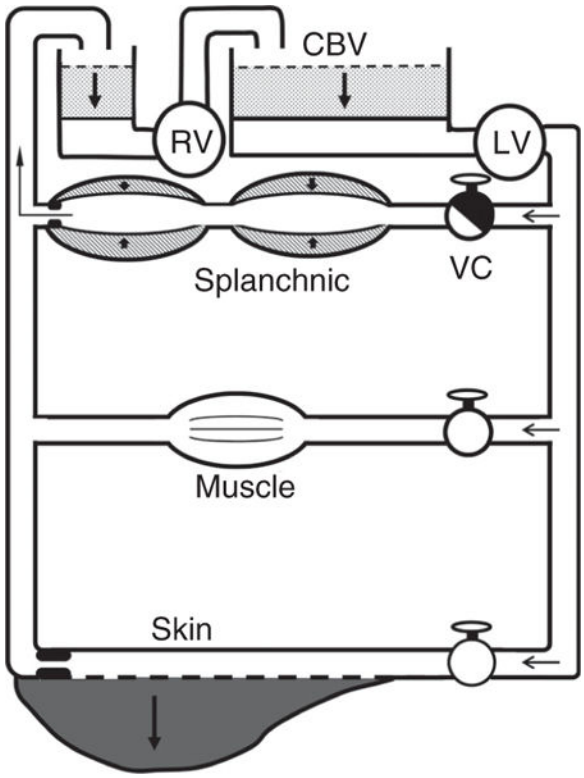

Figure 7.

Hypothetical model of blood volume distribution as a result of heat stress. Increases in cutaneous blood volume associated with heat stress are partially offset by reductions in splanchnic and renal (not shown) blood volumes secondary to vasoconstriction within these beds. However, the net effect is a reduction in central blood volume (CBV). RV: Right ventricle, LV: Left ventricle, VC: Vasoconstriction. Figure modified, with permission, from Rowell (212).

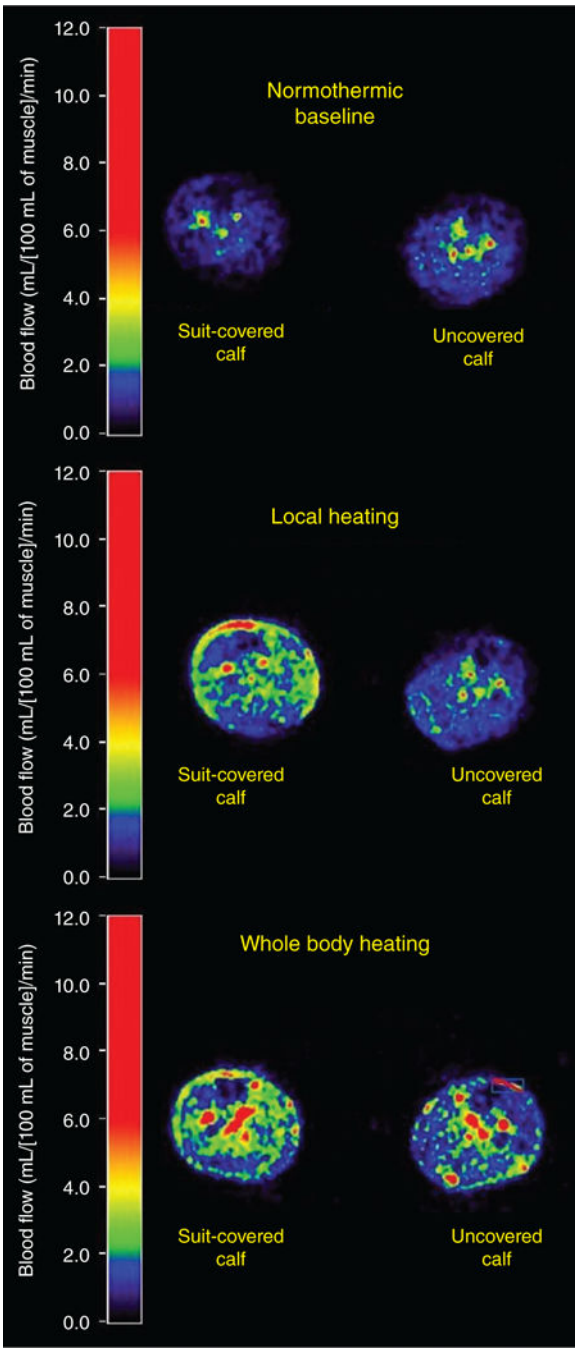

Figure 8.

Representative cross-sectional Positive Emission Tomography images from mid-calf during normothermic baseline, local heating, during whole body heating. Note that the water-perfused suit used to heat the subjects was exposed to only one leg (suit covered calf), and thus the direct and the indirect effects of the applied heat stress were evaluated. Increases in muscle blood flow were only identified from the leg which was covered by the water perfused suit during both the local heating and whole body heating protocols. Figure, with permission, from Heinonen et al. (81).

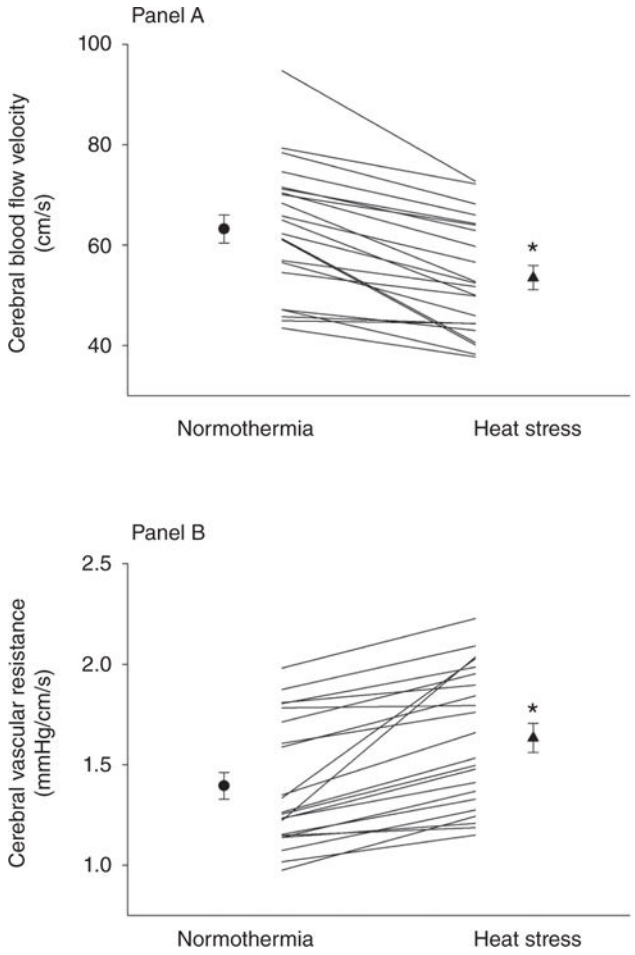

Figure 9.

Effects of whole body heat stress on blood velocity from the middle cerebral artery. Notice the degree of heterogeneity of the response amongst these 25 observations. *Significantly different from normothermia. Figure adapted, with permission, from Wilson et al. (264).

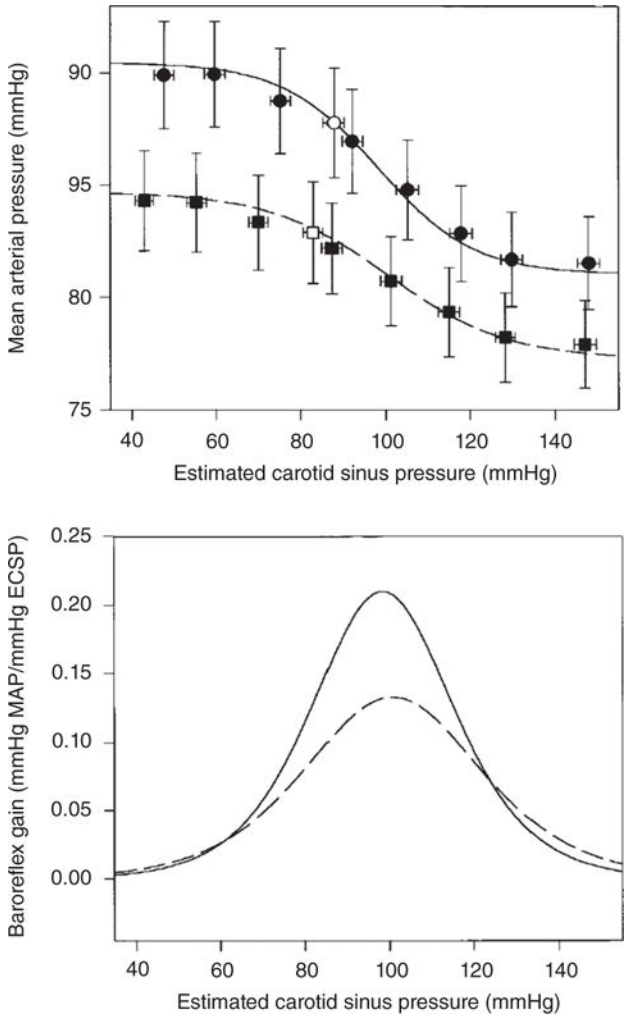

Figure 10.

Carotid-vascular baroreflex responses in normothermia (solid line and circles) and heat stress (dashed lines and squares). The upper panel depicts the averaged baroreflex curves while the lower panel shows the gain of the respective curves in both thermal conditions. Heat stress significantly reduced the gain of the carotid-vascular baroreflex. Figure adapted, with permission, from Crandall (32).

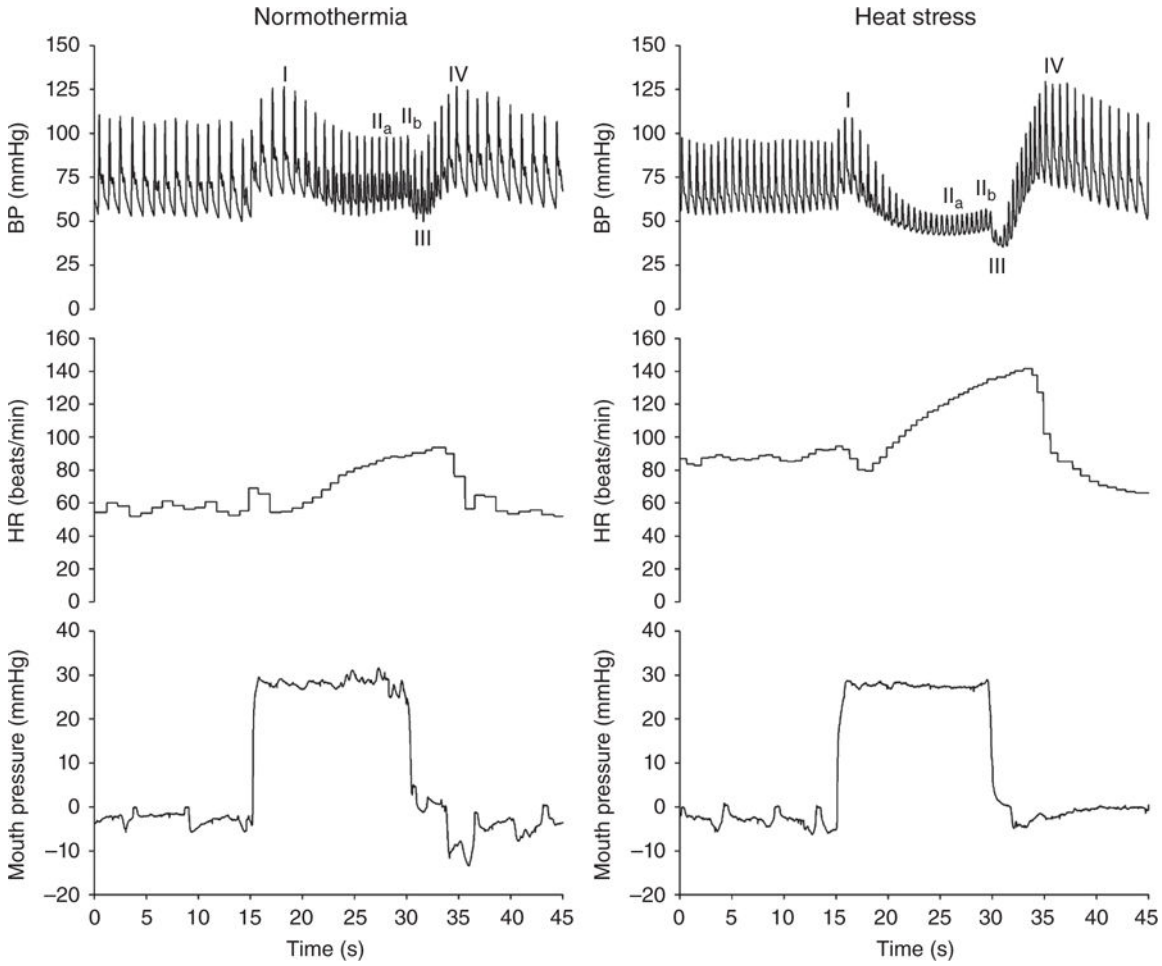

Figure 11.

Blood pressure (BP), heart rate (HR), and mouth pressure responses to a Valsalva maneuver while in normothermic and heat stressed conditions from one subject. The phases of the Valsalva are indicated. Notice the distinctly lower phases IIa and IIb while subjects are heat stressed. Figure adapted, with permission, from Davis et al. (50).

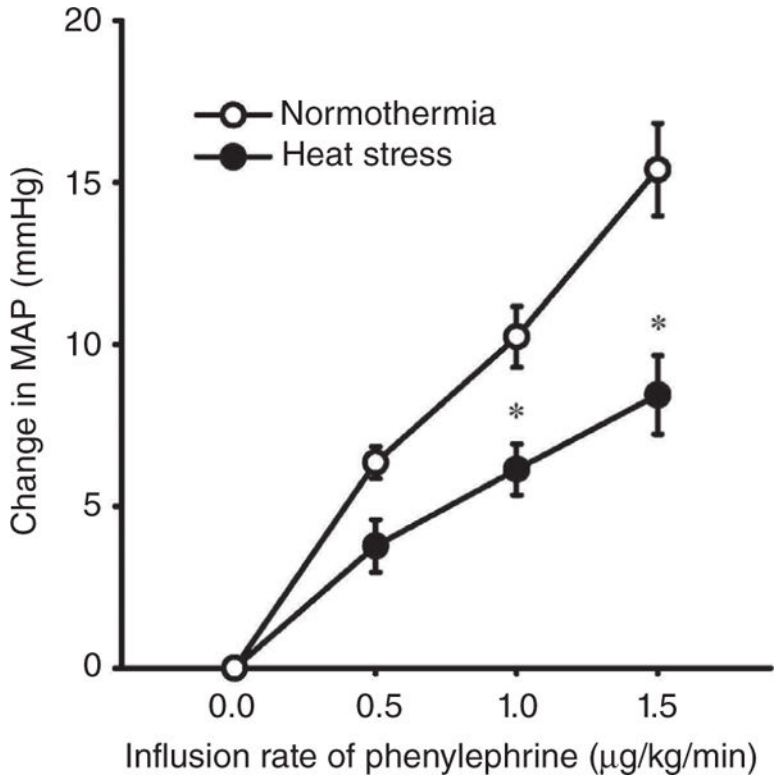

Figure 12.

Effects of whole-body heat stress on changes in mean arterial pressure (MAP) during steady-state infusions of the α_1 agonist phenylephrine. Values are reported relative to a pre-drug baseline MAP. The magnitude of the elevation in MAP to systemic phenylephrine infusion as attenuated by heat stress. Figure adapted, with permission, from Cui et al. (48).

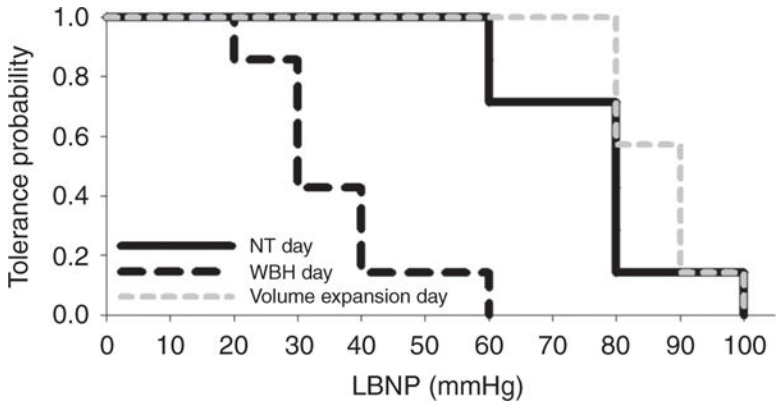

Figure 13.

Tolerance probability curves for lower-body negative pressure (LBNP) trials while subjects were normothermic (NT day—solid line), whole-body heat stressed (WBH day—black dashed line), and heat stress with accompanying volume infusion (gray dashed line). Heat stress significantly attenuated the capability to withstand LBNP challenge, whereas this response was preserved when subjects were heat stressed with accompanying rapid volume expansion. Figure adapted, with permission, from Keller et al. (106).

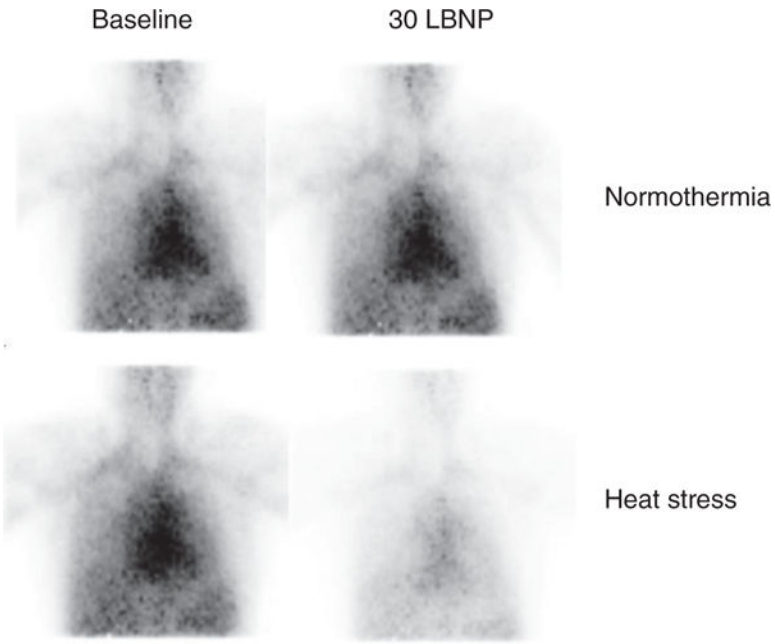

Figure 14.

Scintigraphic images from a subject during normothermia, with and without 30 mmHg lower-body negative pressure (LBNP), and heat stressed, with and without 30 mmHg LBNP. Changes in blood volume to the respective challenges are depicted by changes in the density of the images within particular regions (e.g., the heart), after accounting for isotope decay, attenuation correction, and hematocrit changes associated with the imposed conditions. The magnitude of the reduction in this index of central blood volume to 30 mmHg LBNP was appreciably greater when subjects were heat stressed, relative to normothermic. Figure adapted, with permission, from Crandall et al. (37).

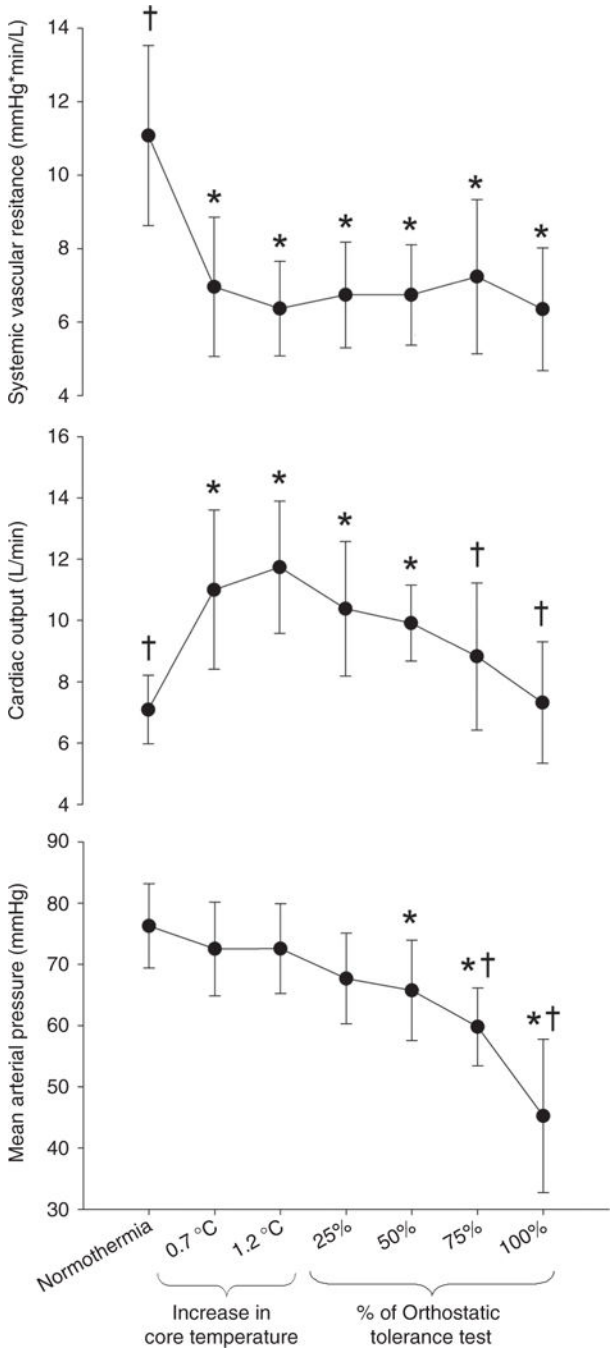

Figure 15.

Systemic vascular resistance, cardiac output, and mean arterial pressure responses at normothermia, after internal temperature increased ~0.7 and 1.2°C via whole-body heating, an during simulated hemorrhage (via LBNP) to presyncope. Notice the relative absence of a change in systemic vascular resistance during simulated hemorrhage despite profound reductions in arterial blood pressure. Also notice that a cardiac output to maintain arterial blood pressure while normothermic (~7 L/min) is no longer sufficient when individuals are heat stressed. †Significantly different from heat stress (i.e., 1.2°C elevation in internal

temperature); *significantly different from normothermia. Figure is adapted, with permission, from Ganio et al. (72).

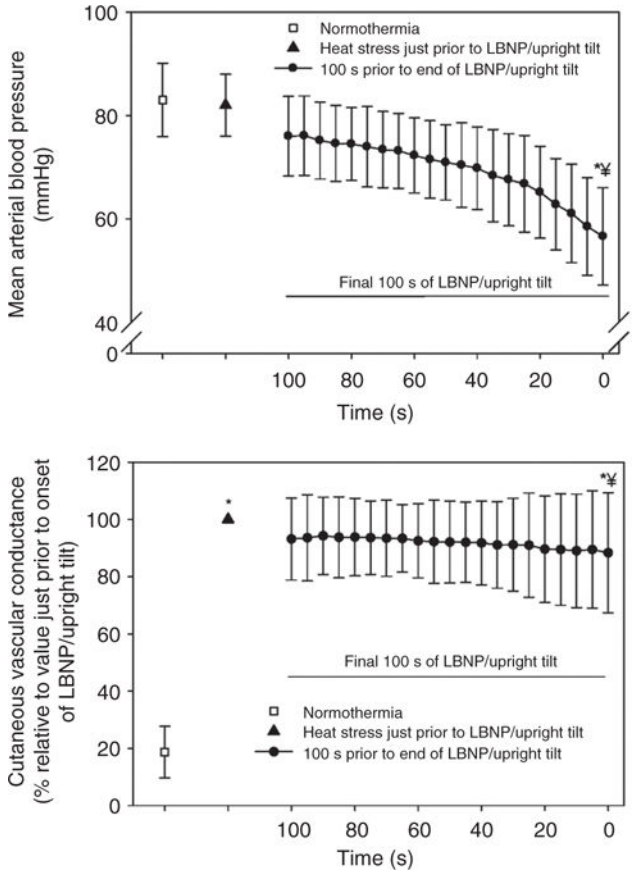

Figure 16.

Upper panel: Mean arterial blood pressure during normothermia, heat stress just prior to the onset of lower-body negative pressure (LBNP) or upright tilt, and the final 100 sec of LBNP or upright tilt due to syncopal signs and/or symptoms. Lower Panel: Cutaneous vascular conductance at the same time points as arterial blood pressure. Note that despite profound hypotension leading up to and at presyncope, very little reductions in cutaneous vascular conductance occurred. *Significantly different from normothermia. ¥Significantly different from heat stress just prior to LBNP/upright tilt. Data adapted, with permission, from Crandall et al. (36).

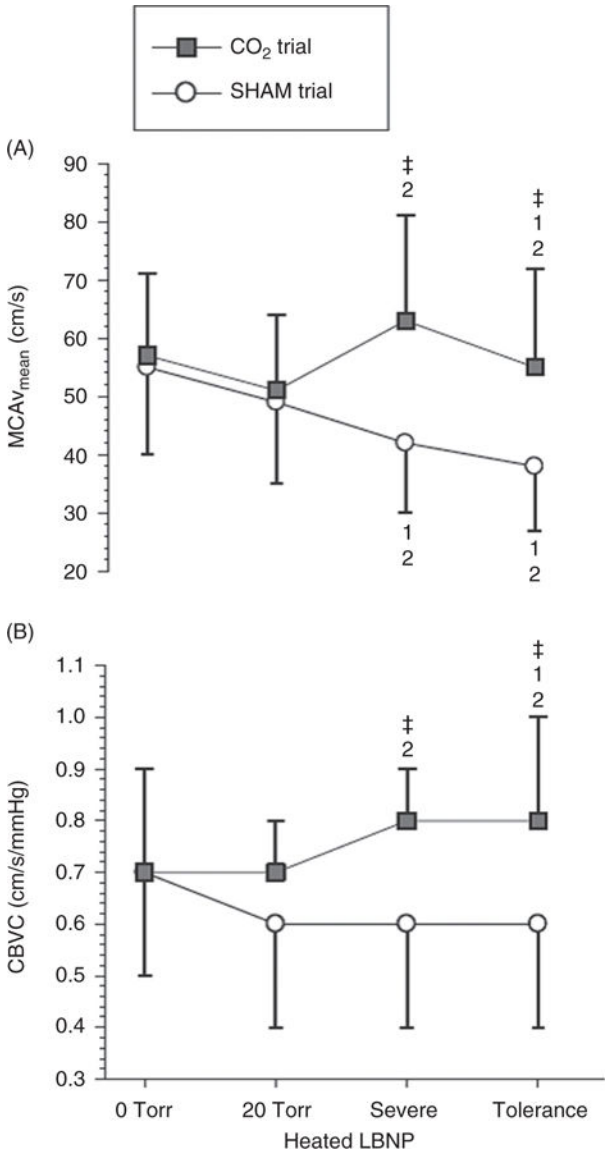

Figure 17.

Cerebral blood velocity from the middle cerebral artery ($MCAv_{mean}$) and calculated cerebrovascular conductance (CBVC) during heat stress and lower-body negative pressure (LBNP) where subjects inhaled either a hypercapnic gas mixture (solid squares) or room air (open circles—Sham). Notice that at tolerance, both $MCAv_{mean}$ and CBVC were significantly elevated with during the hypercapnic trial relative to the Sham trial. ‡Significantly different from Sham trial; [1]Significantly different from 0 mmHg LBNP; [2]Significantly different from 20 mmHg LBNP. Figure adapted, with permission, from Lucas et al. (142).