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Review

Using thermal stress to model aspects of disease states

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ABSTRACT

Exposure to acute heat or cold stress elicits numerous physiological responses aimed at maintaining body temperatures. Interestingly, many of the physiological responses, mediated by the cardiovascular and autonomic nervous systems, resemble aspects of, or responses to, certain disease states. The purpose of this Perspective is to highlight some of these areas in order to explore how they may help us better understand the pathophysiology underlying aspects of certain disease states. The benefits of using this human thermal stress approach are that (1) no adjustments for inherent comparative differences in animals are needed, (2) non-medicated healthy humans with no underlying co-morbidities can be studied in place of complex patients, and (3) more mechanistic perturbations can be safely employed without endangering potentially vulnerable populations. Cold stress can be used to induce stable elevations in blood pressure. Cold stress may also be used to model conditions where increases in myocardial oxygen demand are not met by anticipated increases in coronary blood flow, as occurs in older adults. Lower-body negative pressure has the capacity to model aspects of shock, and the further addition of heat stress improves and expands this model because passive-heat exposure lowers systemic vascular resistance at a time when central blood volume and left-ventricular filling pressure are reduced. Heat stress can model aspects of heat syncope and orthostatic intolerance as heat stress decreases cerebral blood flow and alters the Frank–Starling mechanism resulting in larger decreases in stroke volume for a given change in left-ventricular filling pressure. Combined, thermal perturbations may provide *in vivo* paradigms that can be employed to gain insights into pathophysiological aspects of certain disease states.

Contents

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1. Developing analogues for aspects of certain disease states using healthy thermal stressed humans

Thermal stress, whether heat or cold, engages thermoeffector responses in humans to maintain relatively stable internal body temperatures. During cold stress blood flow to the periphery is reduced to minimize heat loss, while heat stress increases cardiac output and blood is shunted to the skin to increase heat loss and maximize evaporative cooling. These important thermoregulatory responses are accompanied by other physiological responses such as increased systemic vascular resistance during cooling and decreased systemic vascular resistance during heating. These and other thermoregulatory responses in the cardiovascular and autonomic nervous systems have the potential to reproduce physiological conditions present in certain diseases and/or to reproduce symptoms in these states. Thus, the purpose of this Perspective is to highlight and discuss the potential use of thermal stress as a model or analogue, which can be exploited by researchers to further our understanding of normal physiology in health, as well as to possibly better understand aspects of certain disease states.

The development of models that may provide insight into particular diseases can be important for identifying mechanisms underlying the development and progression of disease, as well as the testing of countermeasures and treatments that address the signs and symptoms of the disease. The benefit of developing human thermal analogues, as compared to non-human animal models, is that no adjustments for comparative anatomical or physiological differences are needed. Healthy non-medicated human subjects can be studied in place of complex patients who often have numerous co-morbidities, and possible physical limitations. In addition, a healthy human can more safely undergo more mechanistic experimental perturbations. Finally, a human thermal analogue can provide *in vivo* data possessing the interactive richness of the body's internal milieu rather than relying on an *in vitro* model without complex local and systemic control and regulation.

The approach of this Perspective will be to describe: (a) the general human response to thermal stress, (b) the disorder to be modeled, its prevalence, and need for the model, (c) the specific acute responses to thermal stress that pertain to the proposed model, and (d) how well the model fits or deviates from aspects of the actual disease state.

2. Cold stress

In humans exposure to cold ambient temperatures causes cutaneous vasoconstriction in an effort to decrease the delivery of heat to the skin surface and thereby increase the thermal insulation properties of the skin. This variable insulation that depends on the distribution of skin blood flow is added to the fixed insulation (subcutaneous body fat and skeletal muscle) to minimize environmental heat loss. If cooling is of significant enough magnitude, whole body metabolic rate increases via shivering and non-shivering thermogenesis to offset heat lost through the skin. The precise response to a cold stress is highly dependent on the type, duration, severity, and pain involvement during the stress (Burton and Edholm, 1955; Castellani et al., 2010; Frank et al., 1997; Giesbrecht, 2000; Leblanc, 1975; Stocks et al., 2004; Toner and McArdle, 1996; Wilson and Crandall, 2011). A summary of the physiological responses to various cold exposures is provided in Table 1. This Perspective will focus on acute, mild skin-surface cooling because: (a) skin temperature can be easily maintained with a water-perfused suit, and (b) temperature-controlled suits provide no hydrostatic forces, as occur in water immersion. These cool skin temperatures can be maintained for extended durations. Temperatures that are used in this approach do not alter core temperature or engage shivering, which can increase muscle blood flow and decrease systemic vascular resistance (Burton et al., 2009; Hales et al., 1976). Perception is that the stress provides sensation of cold, but not pain. Hence, measured effects are not the result of pain, which can induce pressor responses independent of cooling. Thus, for purposes of modeling aspects of vascular-based elevations in blood pressure and myocardial supply/demand mismatch, the water-perfused suit cooling method appears to provide a suitable approach.

Table 1
Summary of the thermal, cardiovascular, and metabolic responses to common classifications of passive cold stress. Magnitude of change was estimated based on previous studies and reviews (Burton and Edholm, 1955; Castellani et al., 2010; Frank et al., 1997; Giesbrecht, 2000; Leblanc, 1975; Stocks et al., 2004; Toner and McArdle, 1996; Wilson and Crandall, 2011).

Variable	Cold water immersion	Prolonged cold air exposure	Core cooling	Skin-surface cooling
Skin temperature	↓↓↓	↓↓	↔	↓↓
Core temperature	↓	↓ ↔	↓↓	↔
Shivering	↑	↑	↑	↔
Heart Rate	↓↔	↑	↔	↔
Stroke Volume	↑	↑	↑	↔
Cardiac Output	↔	↑	↔	↔
Arterial Blood Pressure	↑	↔	↑↑	↑↑
Central Venous Pressure	↑	↔	↑	↑

3. Cold stress models

For the purpose of cold stress modeling, a custom one- or two-piece high-density tube-lined suit (e.g., Med-Eng Systems, Ottawa, ON, Canada) that covers the entire body except for the head, hands, and feet can be used for skin-surface cooling. Standard tube density suits may not provide enough exposure to maintain a uniform skin temperature. Large zippers and cutouts are also needed in the suit to accommodate measurement devices (e.g., sensors, probes, and cuffs), while not significantly reducing areas exposed to the thermal stimuli. The water temperature perfusing the suit can be easily maintained at 15 °C by adding ice to an external 7-liter water-bath circulator (e.g., E100, Lauda Dr. R. Wobser, Lauda-Konigshofen, Germany) that is located in series with a high-flow pump (e.g., Magnetic drive pump, Iwaki, Tokyo, Japan) that interfaces with the suit through quick connections. In our experience, manually adding ice to the circulator allows for a quieter and more rapid change in circulating water temperature than using a refrigerated circulator. Exposure to a 15 °C water perfusion temperature is well tolerated by most subjects for 20–30 min without inducing a shivering response. If shivering or pre-shivering tonus is observed, the water temperature can be rapidly increased by 0.5–1.0 °C increments (up to as high as 18 °C) and still achieve the desired effects. Using this cooling paradigm, mean skin temperature decreases from 34 to 35 °C during thermoneutral conditions to 29–30 °C during cooling, without altering sublingual, intestinal, and pulmonary artery temperature (Cui et al., 2005; Durand et al., 2004; Keller et al., 2011; Wilson et al., 2007a, 2007b).

4. Thermal analogue of elevated blood pressure

There are an estimated 972 million persons in the world who suffer from hypertension with an estimated 9.4 million deaths per

year being attributed to high blood pressure (WHO, 2013). The incidence rates in the United States are nearing 30% (Hajjar et al., 2006). Human hypertension is defined as a chronic systolic blood pressure (BP) $\geq$ 140 mmHg and/or diastolic BP $\geq$ 90 mmHg and prehypertension as systolic BP 120–139 mmHg and/or diastolic BP 80–89 mmHg (Chobanian et al., 2003). There are numerous rodent models of hypertension (e.g., spontaneously hypertensive and Dahl salt-sensitive rats) that have been developed to mimic various etiologies of hypertension (Dornas and Silva, 2011); nevertheless, rodent models suffer from numerous species and phenotype differences, such as a rat's basal heart rate being 6-fold higher than human heart. The development of chronic models of hypertension in humans is not a viable experimental approach for ethical reasons, but the use of acute models may be applicable if increases in BP are consistent, stable, and reproducible and the pressor perturbation is safe and non-painful. Skin-surface cooling appears to satisfy these criteria and thus may provide a suitable model to study aspects of elevated arterial and venous pressures.

In response to skin-surface cooling, BP increases rapidly (within 2 min) and can be comfortably maintained in excess of 20 min. Previously, we reported that this pressor response was augmented in individuals who possess stiffer (less compliant) central arteries, such as healthy older as compared to healthy younger adults (Hess et al., 2009). This cold-induced pressor effect (20–25 mmHg increase in systolic BP and 6–8 mmHg in diastolic BP in older subjects) can acutely increase a normal BP ($<$120/80 mmHg) to prehypertensive (120–139/80–89 mmHg) or even stage 1 hypertensive levels (140–159/90–99 mmHg) within several min (Fig. 1). The greater pressor response (systolic and mean BP) in older as compared to younger adults is observed within the first measurement and is maintained throughout the cold stress. This response can be comfortably reengaged in the same experimental session in a reproducible fashion (Gao et al., 2012; Hess et al., 2009; Wilson et al., 2010, 2007a).

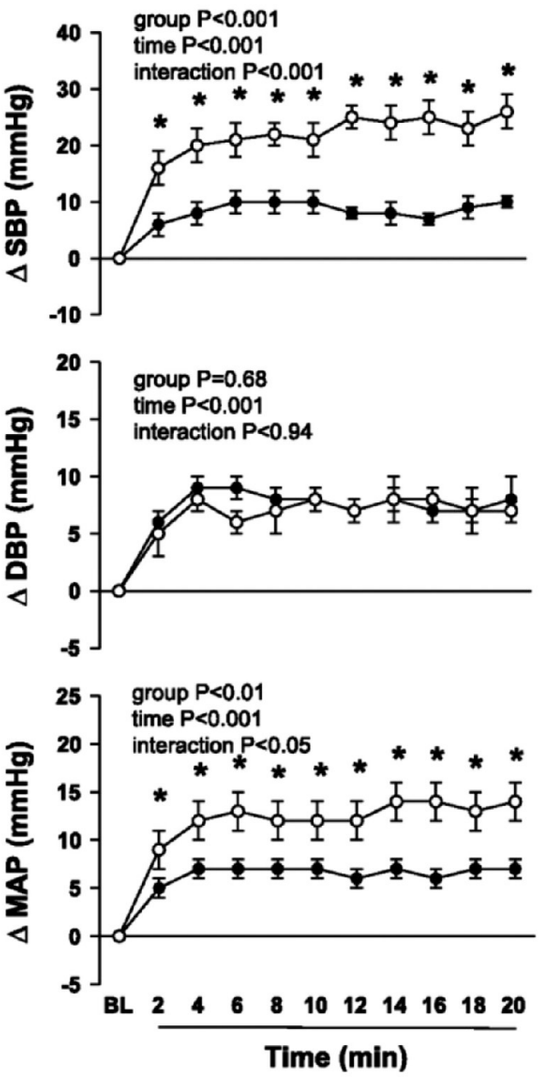

Fig. 1. Skin surface cooling-induced changes in systolic, diastolic, and mean arterial pressure (SBP, DBP, and MAP, respectively) in 12 younger (filled circles) and 12 older (open circles) adults. BL=normothermic baseline. Values are means $\pm$ SE. $^{*}P < 0.05$ vs. younger at the same time point. Adapted from Hess et al. (2009).

Pressor responses to skin-surface cooling appear to be of vascular origin because cardiac output measured by echocardiography (Wilson et al., 2010, 2007a), acetylene rebreathing (Cui et al., 2005; Durand et al., 2004), or thermodilution (Wilson et al., 2007b) is unchanged during skin surface cooling. Both ejection fraction and tissue Doppler indices of contractility (i.e., myocardial acceleration during isovolumic contraction and peak systolic mitral annulus velocity) do not change with skin-surface cooling (Wilson et al., 2010). Additionally, in studies that expose subjects to cold air, cardioinhibitory agents (β-adrenergic or calcium channel antagonists) do not blunt the cold-induced pressor responses (Komulainen et al., 2004, 2000; Tahtinen et al., 1999), providing further evidence that pressor responses are of vascular origin.

Skin-surface cooling increases some indices of preload such as central venous pressure (Cui et al., 2005; Wilson et al., 2007b), pulmonary capillary wedge pressures (Wilson et al., 2007b), and transthoracic impedance (Cai et al., 2000b) but has little effect on left-ventricular end-diastolic volume (LVEDV) in younger persons (Wilson et al., 2009, 2010). In older persons, LVEDV and left-ventricular internal diameter during diastole increase during cooling (Wilson et al., 2010). These data indicate a small increase in central volume load. However, manipulating blood volume via sodium loading does not alter the pressor response to cooling (Arjamaa et al., 2001a, 2001b). Combined, these data indicate that cardiac mechanisms (contractility and preload) are not the primary mechanisms responsible for the cold-induced increase in arterial BP.

Vascular mechanisms for the cold induced pressor response appear to be quantitatively more important than cardiac responses and they coincide with thermoregulatory effector responses to increase tissue insulation. Skin-surface cooling engages thermoregulatory reflexes, causing decreases in whole-limb blood flow, as well as blood flow in both glabrous and non-glabrous skin (Wilson et al., 2007a). Decreases in skin blood flow during skin-surface cooling can approach 100%, but the stimulus does not appear to be severe enough to cause cold-induced vasodilation of glabrous skin of the hands (Cheung and Daanen, 2012). The observed decreases in whole-limb blood flow are likely confined to the skin because directly recorded efferent sympathetic nerve activity directed to skin (Cui et al., 2007; Strom et al., 2011) but not muscle (Cui et al., 2006) increases during skin-surface cooling. However, the vasoconstrictor response to skin-surface cooling is not isolated to the skin, as indices of vascular resistance in the celiac, superior mesenteric, and renal arteries all increase during skin-surface cooling (Wilson et al., 2007a). These latter effects may be sympathetically mediated, as plasma norepinephrine levels increase during skin-surface cooling (Durand et al., 2004). Increased vascular resistance changes lead to the well-documented increase in BP associated with the initial stages of cooling (Aoki et al., 2003; Cui et al., 2007; Durand et al., 2004; Hess et al., 2009; Raven et al., 1981, 1980; Wilson et al., 2002b, 2007a; Yamazaki and Sone, 2000, 2001).

Based upon the preceding discussion it appears that skin-surface cooling is a promising model that may be used to gain

insight into the physiology of acute elevations in blood pressure and possibly aspects of hypertension. However, this model possesses several limitations that need to be considered: (1) the hypertension stimulus is only acute during skin-surface cooling and therefore chronic aspects of hypertension are not modeled, (2) responses to only moderate increases in BP are normally obtained and thus insight into more severe hypertension may not be obtained, and (3) the cooling stimulus needs to be below the shivering threshold to obtain the correct cardiovascular responses. In summary, cold stress increases BP via sympathetic activation and increased vascular tone. This allows for a model of acute hypertensive responses before vascular remodeling and cardiorenal changes have occurred.

5. Thermal analogue of myocardial supply/demand mismatch

Coronary artery disease accounts for an estimated 7.3 million deaths per year worldwide (WHO, 2013). The incidence rates in the United States are age dependent, with prevalence rates being 19.8% among persons older than 65 years and 7.1% for those between 45 and 64 years (CDC, 2011). When myocardial oxygen supply fails to meet myocardial oxygen demand, ischemia can occur. Myocardial ischemia is exacerbated by coronary artery disease that restricts blood flow to the myocardium. Ischemia can cause angina, altered electrical conduction, arrhythmias, and mechanical dysfunction; severe ischemia can lead to infarction. Angina, myocardial infarction, and mortality occur more frequently in cold conditions and during winter months (Danet et al., 1999; Juneau et al., 1989; Sheth et al., 1999; Wolf et al., 2009). The development of chronic models of myocardial ischemia in humans is unethical, but the use of acute models may be applicable if there is a safe and moderate alteration of myocardial oxygen supply and demand, such as an increase in cardiac work without a corresponding increase in coronary blood flow.

Skin surface cooling appears to satisfy these criteria in older healthy adults. Skin-surface cooling increases cardiac preload and afterload (Section 4). As a result, the rate pressure product, cardiac minute work, and left ventricular wall stress all increase during skin surface cooling (Gao et al., 2012; Hess et al., 2009; Wilson et al., 2010, 2007a). In young healthy adults, increases in myocardial oxygen demand results in decreased coronary vascular resistance in the myocardium supplied by the left-anterior descending artery (Fig. 2). However, these decreases in coronary vascular resistance during skin surface cooling are blunted in older adults (see Fig. 2) at a time when indices of myocardial oxygen demand are increased at least as much in older as compared to young adults (Gao et al., 2012). In a related cold stress study where participants immersed one hand into ice water (cold pressor test) for 2 min, investigators identified that the blunted coronary vascular resistance during the cold stress was likely due to an adrenergic mechanism, as younger individuals' responses matched those of older subjects during combined α- and β-adrenergic blockade (Monahan et al., 2013). These data may indicate a myocardial supply/demand mismatch in older individuals. Importantly for the safety of the model, the mismatch is not to the extent that it causes angina or electrocardiography alterations. A myocardial supply/demand mismatch in adults may also be able to be induced by combining cold stress with other stressors, such as cold air inhalation during physical stress (Muller et al., 2012).

The mechanisms underlying altered coronary vascular responses to cold stress are not clear. Coronary vasospasm can be induced by a cold pressor test and is associated with a temporary decrease in coronary blood flow and potential angina (Raizner et al., 1980; Rasmussen et al., 1984). Another possibility is that cold exposure is associated with platelet aggregation, neutrophil adhesion to the endothelial wall, and thrombus formation, which could also lead to ischemia and angina (Bokenes et al., 2000, 2004; Woodhouse et al., 1994; Zhang et al., 2004). Because of rapid onset and because skin surface cooling does not change blood temperature, it may be that cold stress causes a slight vasospasm that maintains coronary vascular resistance during a time when coronary vasodilation should occur. An alternate mechanism could be impaired flow-induced dilation via endothelial dysfunction, as studies suggest that vitamin C can preserve nitric oxide vasodilator mechanisms in older diseased coronary arteries during cold pain tests (Jeserich et al., 1999; Schindler et al., 2000).

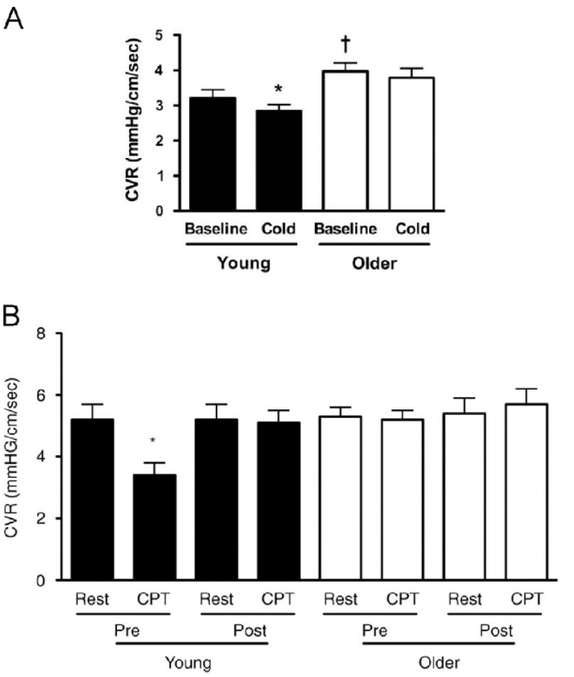

Fig. 2. Coronary vascular resistance (CVR; diastolic blood pressure/peak coronary blood velocity) responses to cold stress. Panel A, CVR before (baseline) and during cooling (cold) in young ($n=10$) and older ($n=11$) adults. Note that CVR, which was increased at rest (before cooling) in older adults, was significantly decreased during cold stress in only young adults. Values are means ± SE. $^{*}P<0.05$ vs. baseline; $^{\dagger}P<0.05$ vs. young adults under the same conditions (baseline or during cooling). Adapted from Gao et al., Am. J. Physiol. Heart Circ. Physiol., 302:H312-H31, 2012. Panel B, CVR data were obtained before (Rest) and at peak responses during the cold pressor test (CPT). CVR at rest was similar in young and older men at all time points. CPT decreased CVR, indicating coronary vasodilation occurred in the young during pre-adrenergic blockade (Pre), but not post-adrenergic blockade (Post). In contrast CVR was unchanged by the CPT in older men both Pre and Post. CPT-induced decreases in CVR were greater in young compared to older men (Pre). $^{*}P<0.05$ compared to rest (same condition; Pre or Post). Adapted from Monahan et al. (2013).

Thus, there is evidence to support the use of skin-surface cooling as a potential model for studying the some aspects of the balance between myocardial supply/demand. However, there are several limitations of this model that deserve mention. First, the model may only be valid in older adults or young adults dosed with adrenergic antagonists. Second, coronary oxygen supply is not known because only coronary blood velocity is measured with transthoracic Doppler echocardiography. Lastly, coronary dynamics can only be measured from a few epicardial coronary arteries using current Doppler technology. In this regard, the left anterior descending artery results in the greatest imaging success.

In summary, cold stress increases both cardiac preload and afterload, with no change in contractility. These effects are associated with increases in myocardial oxygen demand and a blunted increase in myocardial blood supply in older as compared to young adults. This appears to provide an acceptable approach to

study some aspects of mild myocardial supply/demand mismatch. This model could allow for acute experimentation of the early stages of supply/demand mismatch development before vascular remodeling and cardiac changes occur.

6. Heat stress

When temperature of air or water surrounding the body is increased, a number of physiological responses ensue. There is an increase in vascular conductance in the skin (Johnson et al., 1986; Kellogg, 2006) to offload heat, and sweat glands are engaged to provide a hypotonic solution to the skin's surface for evaporation (Sato et al., 1989; Shibasaki et al., 2006). Thermal-induced increases in sweating can decrease plasma and interstitial fluid volumes (Greenleaf, 1992; Kenefick and Sawka, 2007; Mack and Nadel, 1996; Sawka, 1988). To increase skin perfusion, heart rate and cardiac output increase (Johnson and Proppe, 1996; Sawka et al., 1996) and conductance to renal and splanchnic vascular beds decreases (Minson et al., 1998; Rowell et al., 1968, 1971). Besides increases in cutaneous vascular conductance, there are increases in cutaneous venous flow and volume (Deschamps and Magder, 1990, 1994), which allow for greater duration of thermal exchange of heat with the ambient environment. However, these cardiovascular and fluid changes also decrease effective circulatory volume, which decreases pulmonary capillary wedge pressure (Bundgaard-Nielsen et al., 2010; Wilson et al., 2007b) and central blood volume (Cai et al., 2000b; Crandall et al., 2012, 2008). The precise cardiovascular and autonomic response to heat stress is highly dependent on the type (passive or active), duration, and severity of the stress (Gonzalez-Alonso, 2012; Johnson and Proppe, 1996; Journeay et al., 2006; Nadel, 1988; Peters et al., 2000; Sawka et al., 1996; Wilson and Crandall, 2011). The predominant findings associated with mild passive-heat stress, severe passive-heat stress, and exercise-induced heat stress are summarized in Table 2. This Perspective will focus on passive, whole body heat stress induced by a water-perfused suit. This approach permits: (a) skin temperature to be precisely regulated, (b) a greater surface area to be heated which allows for a more rapid heating process, and (c) recording of physiological responses that are independent of what occur during exercise. Exercise results in many additional physiological responses necessary to perfuse and oxygenate contracting skeletal muscle (Laughlin and Armstrong, 1985; Mitchell, 1990). These particular heat stress conditions may allow for the *in vivo* modeling of some aspects of hemorrhage and orthostatic intolerance.

7. Heat stress models

To produce experimental heat stress in a human subject, similar to cold stress (see Section 3), a tube-lined suit with a perfusion system can be utilized. Initially, water perfusing the suit is maintained at 45–49 °C (possibly higher depending on the amount of heat loss in the system prior to reaching the skin). To achieve a steady-state hyperthermic state and not continually drive up internal temperature, the water temperature is often decreased to 40–44 °C prior to heat stress measurements. Perfusate water temperature increases skin temperature from approximately 34 °C to 39–40 °C and also increases sublingual, intestinal, rectal, and pulmonary artery temperatures. The duration of heating can be altered to induce mild (0.8–1.0 °C) or moderate (1.5 °C) increases in internal temperature during heat stresses.

8. Thermal analogues of shock-like conditions

Trauma is the leading cause of death for young persons in the US, and hemorrhagic shock accounts for ~40% of these trauma deaths (Sauaia et al., 1995). Sepsis, which can lead to septic shock, occurs in ~2% of all hospitalizations in developed countries (Martin, 2012). These two types of shock initially present differently, but shock – whether hemorrhagic or septic – in its final stages is a condition of abnormally low BP associated with poor blood flow to organs such as the liver, kidney, intestines, and brain. This causes cellular damage, loss of function, and, ultimately, death. Initially in the shock process, the body attempts to counteract the reduced pressure and perfusion deficits by constricting blood vessels in selective vascular beds and increasing heart rate and inotropy.

Cooke et al. (2004), have made a compelling case for the use of lower-body negative pressure (LBNP) as an *in vivo* model of hemorrhage in humans. LBNP causes a reduction in effective blood volume, via inferior translocation of central blood volume. These reductions in central blood volume mimic conditions present in the initial stages of hypovolemic shock (e.g., reduced cardiac preload). In their LBNP model, 10 to 20 mmHg of negative pressure applied to the lower body corresponds to mild (400–550 ml fluid displaced), 20 to 40 mmHg to moderate (550–1000 ml), and >40 mmHg to severe (>1000 ml) hypovolemic shock. Displaced fluid is fluid that is physically removed with hemorrhage or out of the effective circulatory volume via LBNP. As an example, assuming the upright posture from a supine position displaces 700–800 ml of fluid into the inactive venous circulation of the legs and pelvis (Blomqvist and Stone, 1983).

Our proposed model of shock builds on that of Cooke et al. (2004) by the addition of heat stress during LBNP. Heat stress decreases central blood volume (Cai et al., 2000b; Crandall et al., 2012, 2008) and pulmonary capillary wedge pressure (Bundgaard-Nielsen et al., 2010; Wilson et al., 2009, 2007b) prior to LBNP and beyond that observed during normothermic LBNP (Ahmad et al., 1977; Cai et al., 2000a; Firstenberg et al., 2000). The net result of combined heat and orthostatic stress is lower preload and

Table 2
Summary of the thermal, cardiovascular, and metabolic responses to common classifications of heat stress perturbations to increase internal temperature. Magnitude of change, if known, was estimated based on previous studies and reviews (Gonzalez-Alonso, 2012; Johnson and Proppe, 1996; Journeay et al., 2006; Nadel, 1988; Peters et al., 2000; Sawka et al., 1996; Wilson and Crandall, 2011).

Variable	Exercise-heat stress	Leg heating	Acute whole-body heating	Prolonged whole-body heating
Skin temperature	↔	↑	↑↑↑	↑↑↑
Core temperature	↑↑↑	↑	↑	↑↑
Heart rate	↑↑↑	↑	↑	↑↑
Stroke volume	↑↑	↑	↔	↔
Cardiac output	↑↑↑	↑	↑	↑↑
Arterial blood pressure	↑	↔	↔	↓
Central venous pressure	↔	↔	↓	↓↓
Cerebral blood flow	↑	?	↓	↓

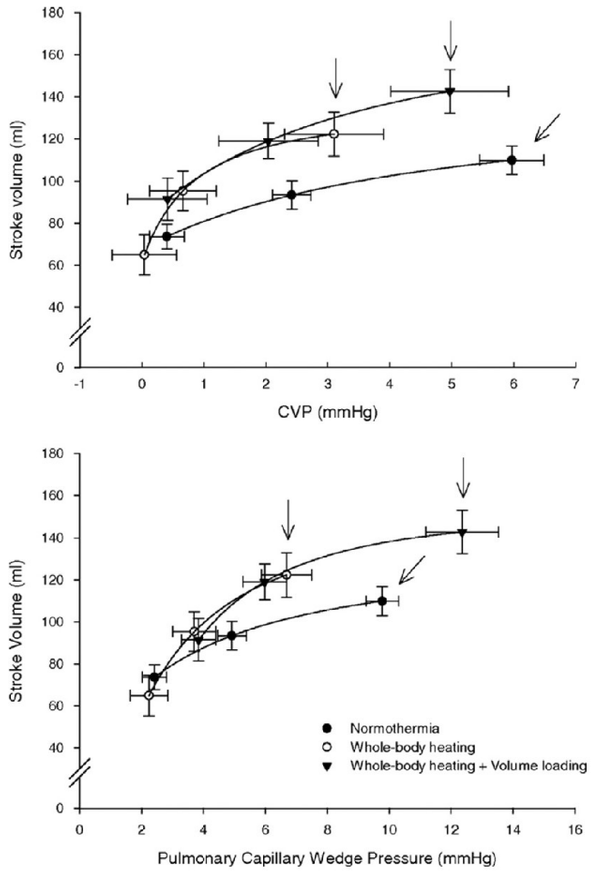

Fig. 3. Effects of heat-stress on Frank–Starling curves by expressing the relation between CVP (upper panel) and PCWP (lower panel) to SV during normothermia, heat stress, and heat stress plus volume infusion. Data were obtained prior to LBNP and subsequent 15 and 30 mmHg LBNP for each of the indicated conditions. The arrows indicate pre-LBNP responses (i.e., operating point) for each thermal condition. The operating point is shifted to a new curve during heat stress, where volume loading moves the operating point to the flatter portion of the curve. Lines represent fitted approximations; note the steeper slopes in these curves when subjects were heat stressed. Adapted from Bundgaard-Nielsen et al. (2010).

effective circulatory volume than each of the stresses individually. The initial decrease in preload induced by heat pushes the operating point of the Frank–Starling relation to the steeper part of the curve prior to LBNP (Fig. 3). Subsequently, LBNP, which further decreases preload, causes linear and large decreases in stroke volume (Bundgaard-Nielsen et al., 2010; Wilson et al., 2009) compared to the more curvilinear responses when beginning LBNP while on the flatter portion of the Frank–Starling relation, as occurs in normothermia (see Fig. 3). The model can be further manipulated via hypohydration and colloid or crystalloid volume infusion (Jans et al., 2008; Mack and Nadel, 1996; Perhonen et al., 2001); these volume changes allow for additional movement of the operating point of the Frank–Starling relation either downward (simulating greater hypovolemia) or upward (simulating recovery or compensation) (Truijen et al., 2010).

Data support the use of LBNP combined with whole-body heating as a model for shock-like conditions that occur in hemorrhagic and early stages of septic shock with a few limitations. First, heat stress increases internal temperature, which is often observed in septic but not hemorrhagic shock. Second, redistribution of blood out of the effective circulatory volume is similar, but not identical to, actual removal of blood from the body. Third, patterns of sympathetic activation and organ blood flow redistribution are different from hemorrhage. For example, muscle blood flow decreases initially during hemorrhage, but in heat stress there is an increase in muscle sympathetic nerve activity (Low et al., 2011; Niimi et al., 1997) but little change in absolute flow (Detry et al., 1972; Heinonen et al., 2011).

In summary, heat stress decreases systemic vascular resistance, central blood volume, and ventricular filling pressures. This also causes an inotropic shift in the Frank–Starling relation as well as moving the operating point to a steeper portion of the curve. The combined LBNP-induced central hypovolemia and heat stress may provide a more severe and robust model than the LBNP hemorrhagic shock model (Cooke et al., 2004).

9. Thermal analoge of heat syncope and orthostatic intolerance

Approximately 1% of all emergency department visits are related to syncope, pre-syncopal symptoms, or falls (van Lieshout et al., 2003), and it is estimated that 500,000 Americans suffer from chronic issues of orthostatic intolerance (Robertson, 1999). Orthostatic intolerance is the body's inability to appropriately respond to a gravitational stress (G_z) that causes hypotension (decrease in systolic and diastolic BP >20 mmHg and 10 mmHg, respectively) and a decrease in cerebral perfusion and oxygenation (Freeman et al., 2011; Hainsworth, 1999; Madsen and Secher, 1999; van Lieshout et al., 2003). Orthostatic intolerance and syncope occur more frequently in heat stress (Wilson and Crandall, 2011) and less frequently during cold stress conditions (Durand et al., 2004; Keller et al., 2011; Lucas et al., 2010; Wilson et al., 2002b). Heat-induced physiological changes increase susceptibility to syncope and might be exploited as an orthostatic intolerance model, of which there are few because of the dramatically different effects of G_z forces experienced by quadruped animals compared to bipeds. In this model, healthy subjects could be made more prone to syncope in studies of orthostatic intolerance.

Heat syncope is significant enough to warrant identification by the National Institute of Occupational Health and Safety for hazards and exposures for workers exposed to heat stresses (CDC, 2012). In tilt table studies, approximately 44% of persons could not stand for 10 min without developing presyncopal symptoms after a 1 °C degree increase in core body temperature to 38.0 ± 0.1 °C while none of these subjects experienced symptoms in the normothermic state (Wilson et al., 2002b). The mechanisms underlying this decrease in orthostatic tolerance during heat stress are multifactorial; likely candidates include: altered cerebral blood flow and autoregulation, decreases in cardiac preload, and a less responsive vasculature. Wilson et al. (2006) identified robust decreases in cerebral blood velocity

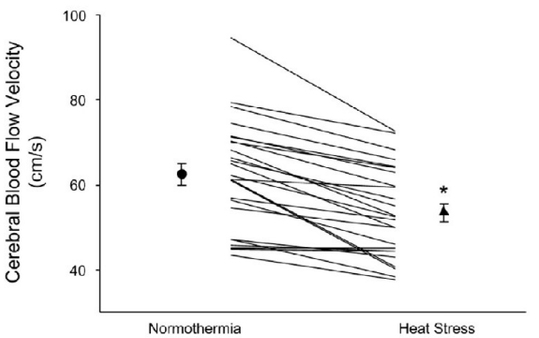

Fig. 4. Effects of whole body heating on cerebral blood flow velocity from the middle cerebral artery in 15 subjects. The symbols with error bars denote mean responses, while lines denote individual responses. *$P<0.001$ compared to normothermia. Adapted from Wilson et al. (2006).

during whole-body heating, although there is a fair amount of individual variation as to the magnitude of decrease observed (Fig. 4). These heat-induced decreases in cerebral blood velocity are well documented (Brothers et al., 2009a; Fan et al., 2008; Low et al., 2008; Lucas et al., 2008; Nelson et al., 2011; Wilson et al., 2006) and also occur during orthostatic stress (Immink et al., 2006; Jorgensen et al., 1993; Levine et al., 1994; Zhang et al., 1998). During heat stress there may also be larger decreases in cerebral blood velocity per level of orthostatic stress (Wilson et al., 2006), but dynamic cerebral autoregulation remains intact (Brothers et al., 2009b; Low et al., 2009). Changes in cerebral blood velocity during heating are exacerbated by hypohydration (Carter et al., 2006). There are also alterations in the Frank–Starling relations and ventricular filling pressure and volume, as noted above (Section 8), which could cause inadequate stroke volumes under heat and orthostatic stress conditions. Based on isolated heart experiments, these changes in the Frank–Starling relation appear to be related to increased sympathetic outflow rather than direct effects of heating per se (Klabunde et al., 2013). There also appear to be decreases in adrenergic responsiveness systemically (Cui et al., 2002) as well as in the cutaneous vasculature (Wilson et al., 2002a; Wingo et al., 2009). Thus, it can be argued that the cutaneous vasculature is less responsive at a time when skin blood flows and volumes are very high. This inability to shunt blood elsewhere and move volume back to the central vasculature to maintain cardiac output could contribute to reductions in orthostatic tolerance (Crandall et al., 2010). Data support the potential use of whole-body heating as a model for orthostatic intolerance; however, the pattern of autonomic reflexes and associated changes in blood flow distribution are different than those observed during orthostatic stress alone.

In summary, heat stress increases cutaneous vascular conductance and volume, alters Frank–Starling relations, and decreases cerebral blood velocity, in addition to reducing orthostatic tolerance. Heat stress and hypohydration do not appear to alter postural balance (Ely et al., 2012) or vestibular reflexes (Wilson and Ray, 2004). Thus, heat stress may provide a model that specifically studies orthostatic intolerance and syncope due to autonomic and cardiovascular mechanisms and serves as an analog of heat syncope.

10. Conclusions

In this Perspective we have made the case for incorporating acute thermal stress in modeling some aspects of elevated blood pressure, myocardial supply/demand mismatch, shock-like conditions, as well as heat syncope and orthostatic intolerance in humans. Although there are many factors related to etiology, adaptation, and genetics that acute stresses cannot account for, it still may be more beneficial to not induce comparative differences of animal models when addressing certain aspects of these disease states. Although developing exact analogues of chronic diseases cannot be performed outside of testing people with these conditions, acute thermal stress appears to be an alternative or adjunct to study mechanisms of cardiovascular responses that may not be otherwise possible in a patient population.

There are many potential applications of these thermal-induced disease state analogues. Skin surface cooling, with its ability to increase both afterload and preload as well as cause myocardial supply and demand mismatch in older healthy adults, can be used to study acute interventions that target afterload, preload, or both while simultaneously measuring coronary artery perfusion during increased cardiac work when ischemia or infarct is most likely. Whole-body heating is one of the few interventions that causes central hypovolemia and an increase in cardiac output, where causing greater central hypovolemia can set up a scenario in which more vascular beds are dilated than can be perfused. Whole-body heating, with its elevated body temperatures, vasodilated vasculature, and increase in cardiac output, can provide a physiological analogue of septic shock without the pathogen infestation. Thus, treatments such as volume loading to counteract physiological effects of this type of shock can be directly tested.

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