Journal of Thermal Biology 43 (2014) 24–32

Contents lists available at ScienceDirect

Journal of Thermal Biology

journal homepage: www.elsevier.com/locate/jtherbio

Review

Using thermal stress to model aspects of disease states

Thad E. Wilson [a,b,*], Richard E. Klabunde [a], Kevin D. Monahan [c]

[a] Marian University College of Osteopathic Medicine, Indianapolis, IN, USA
[b] Ohio Musculoskeletal and Neurologic Institute & Department of Biomedical Sciences, Ohio University Heritage College of Osteopathic Medicine, Athens, OH, USA
[c] Penn State Hershey Heart and Vascular Institute, Pennsylvania State University College of Medicine, Hershey, PA, USA

ARTICLE INFO

Article history:
Received 7 February 2013
Received in revised form
14 March 2014
Accepted 21 March 2014
Available online 19 April 2014

Keywords:
Heat stress
Cold stress
Hypertension
Myocardial ischemia
Shock
Orthostatic intolerance

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

* Corresponding author at: Marian University College of Osteopathic Medicine, Michael A. Evans Center for Health Sciences, 3200 Cold Spring Road, Indianapolis, IN 46222, USA. Tel.: +317 955 6256.
E-mail address: twilson@marian.edu (T.E. Wilson).

http://dx.doi.org/10.1016/j.jtherbio.2014.03.003
0306-4565/

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