THERMOREGULATION AND INDIVIDUAL CHARACTERISTICS DURING COLD AND HEAT STRESS

A Thesis in
Physiology
by
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ABSTRACT

Numerous individual characteristics influence both the physiological responses to cold stress and the ability to predict body core temperature (Tc) during exercise in the heat. This series of studies was designed to 1) determine age-related differences in the defense of Tc during resting, mild cold stress in young and older subjects matched for relevant body composition characteristics, 2) determine the relative influence of individual characteristics on the defense of Tc during resting, mild cold stress in young and older subjects and 3) determine the predictive accuracy of 3 models of human thermoregulation during a unique cross-desert expedition, with reference to differences in individualization allowed by each of the models.

Aging and Cold Stress (Projects 1 and 2)

The purpose of project 1 was to determine the influence of primary human aging on the defense of Tc during a mild cold transient. Thirty-six young (YS; 23±1 years, range 18-30) and 46 older (OS; 71±1 years, range 65-89) subjects underwent a slow transient cold air exposure from a thermoneutral baseline, during which esophageal (Tes) and mean skin temperatures (Tsk), O2 consumption, and skin blood flow (SkBF; laser-Doppler flowmetry) were measured. Cold exposure was terminated at the onset of visible sustained shivering. Net metabolic heat production (Mnet), heat debt, predicted change in mid-region temperature (ΔTmid), tissue insulation (Ii), and cutaneous vascular conductance (laser-Doppler flux/mean arterial pressure, expressed as percent change from baseline (ΔCVC%base)) were calculated. There were no baseline group differences for Tes, but Mnet was lower in older subjects (OS: 38.0±1.1; YS: 41.9±1.1 W·m⁻², p<0.05).
Tes was well maintained in YS but fell progressively in OS (p<0.01 for all timepoints after 35 min). The cutaneous vasoconstrictor response to mild cold stress was attenuated in OS (OS: 42±3 vs. YS: 53±4 ΔCVC%base, p<0.01). There were no group differences for Tsk or Ii, while Mnet remained lower in OS during cooling (p<0.05). The ΔTmid did not account for the drop in Tes in OS. Healthy aged humans, matched with a young subject population for relevant anthropometric characteristics, failed to maintain Tes; however, the mechanisms underlying this response are not clear.

The purpose of the second project was to determine the relative influence of individual characteristics on Te and Ii during mild cold stress. Forty-two young (23±1 years, range 18-30) and 46 older (71±1 years, range 65-89) subjects, varying widely in muscularity, adiposity, and body size, underwent a transient cooling protocol during which Tes was measured continuously and Ii was calculated. Multiple regression analyses were performed to determine predictors of Tes and Ii and standardized regression coefficients were analyzed to determine the relative influence of each predictor. Putative predictors included age, sex, weight, body surface area, body surface area-to-mass ratio, sum of skinfolds, %fat, appendicular skeletal muscle mass (ASMM), and thyroid hormone concentrations ([T3], [T4]). The sum of skinfolds explained 67% (p<0.01) of the Tes variance in young subjects vs. 2% (p=0.30) in older subjects. Conversely, ASMM explained a greater portion of the variance in older subjects for both Tes (older: 28%, p<0.01; young: 8%, p=0.05) and Ii (older: 46%, p<0.01; young: 17%, p<0.01). The residual variance for Tes was considerably larger in older subjects (59-72% vs. 14-42% in young), possibly due to varying rates of physiological aging. The individual
characteristics that explain the variance in $T_c$ and $I_e$, as well as the relative influence of these characteristics, differ between young and older subjects.

**Predicting Core Temperature during Exercise in the Heat (Project 3)**

Models of human thermoregulation have been developed and validated from short duration laboratory data utilizing relatively large sample sizes. However, data collected in field studies may introduce additional sources of variability that may reduce model accuracy. Additionally, the accuracy of existing models is uncertain when applied to individuals or small groups or longer duration exposures. Recently, 3 runners undertook a unique expedition to run across the Sahara Desert where we collected the environmental and physiological data necessary for the prediction of $T_c$ by 3 models of thermoregulation over 2 days at the start of the expedition. The SCENARIO and Initial Capability Decision Aide (ICDA) models allow for input of individual characteristics while Fiala’s model relies solely on environment and exercise intensity. The runners intermittently ran 8.0 km/h over 6 h during NIGHT desert conditions and 7.0 km/h over 7 h 45 min on during DAY desert conditions. The $T_c$ standard deviation (SD) was 0.34 and 0.51 for NIGHT and DAY, respectively. The root mean squared deviation (RMSD) of the $T_c$ prediction was calculated and model accuracy was considered acceptable when RMSD < $T_c$ SD. NIGHT RMSD= 0.45, 0.64, and 0.91 and DAY RMSD= 0.66, 0.70, and 2.09 for SCENARIO, Fiala and ICDA, respectively. Increased RMSD during day was likely due to overestimation of solar radiation effects. The RMSD was smaller when only the first 2 h of the exposure was analyzed. SCENARIO, which offers the user the greatest opportunity for individualization, resulted in the lowest RMSD. When SCENARIO was configured to match the individual characteristics assumed by Fiala, the
RMSD increased from 0.66 to 0.82, illustrating the importance of individualizing the passive system.

Summary of Findings

Older humans fail to adequately defend $T_c$ during mild cold stress compared to young subjects; different individual characteristics mediate the respective responses in each age group. Greater individualization of model inputs contributes to greater predictive accuracy in models of thermoregulation. Several variables, including solar radiation, fluctuations in exercise intensity and environmental conditions, and minute-by-minute errors in the estimation of the change in $T_c$, likely contributed to decreased model accuracy during prolonged exercise in desert conditions.
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<th>Description</th>
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<tbody>
<tr>
<td>%fat</td>
<td>percent body fat</td>
</tr>
<tr>
<td>$A_d$</td>
<td>Dubois body surface area</td>
</tr>
<tr>
<td>$A_d$/mass</td>
<td>$A_d$: body mass ratio</td>
</tr>
<tr>
<td>ASMM</td>
<td>appendicular skeletal muscle mass</td>
</tr>
<tr>
<td>C</td>
<td>convection</td>
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<tr>
<td>$c_b$</td>
<td>specific heat of the body</td>
</tr>
<tr>
<td>CVC</td>
<td>cutaneous vascular conductance</td>
</tr>
<tr>
<td>DXA</td>
<td>dual-energy x-ray absorptiometry</td>
</tr>
<tr>
<td>E</td>
<td>evaporation</td>
</tr>
<tr>
<td>FBF</td>
<td>forearm blood flow</td>
</tr>
<tr>
<td>FVC</td>
<td>forearm vascular conductance</td>
</tr>
<tr>
<td>$I_t$</td>
<td>tissue insulation</td>
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<tr>
<td>HD</td>
<td>heat debt</td>
</tr>
<tr>
<td>HRR</td>
<td>heart rate ratio</td>
</tr>
<tr>
<td>ICDA</td>
<td>Initial capability decision aide</td>
</tr>
<tr>
<td>K</td>
<td>conduction</td>
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<tr>
<td>LBM</td>
<td>lean body mass</td>
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<td>LDF</td>
<td>laser-Doppler flowmetry</td>
</tr>
<tr>
<td>M</td>
<td>metabolic heat production</td>
</tr>
<tr>
<td>MRT</td>
<td>mean radiant temperature</td>
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<tr>
<td>Abbreviation</td>
<td>Description</td>
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<tr>
<td>NE</td>
<td>norepinephrine</td>
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<tr>
<td>NPY</td>
<td>neuro-peptide Y</td>
</tr>
<tr>
<td>R</td>
<td>radiation</td>
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<tr>
<td>RMSD</td>
<td>root mean squared deviation</td>
</tr>
<tr>
<td>S</td>
<td>storage</td>
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<tr>
<td>SkBF</td>
<td>skin blood flow</td>
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<tr>
<td>[T3]</td>
<td>triiodothyronine concentration</td>
</tr>
<tr>
<td>[T4]</td>
<td>thyroxine concentration</td>
</tr>
<tr>
<td>Tc</td>
<td>body core temperature</td>
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<tr>
<td>Tdb</td>
<td>dry-bulb temperature</td>
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<td>Tes</td>
<td>esophageal temperature</td>
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<td>globe temperature</td>
</tr>
<tr>
<td>Tmid</td>
<td>mid-region temperature</td>
</tr>
<tr>
<td>Tpill</td>
<td>telemetry pill temperature</td>
</tr>
<tr>
<td>Tpred</td>
<td>predicted core temperature</td>
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<tr>
<td>TsK</td>
<td>mean skin temperature</td>
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<tr>
<td>Twb</td>
<td>wet-bulb temperature</td>
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<tr>
<td>VC</td>
<td>vasoconstriction</td>
</tr>
<tr>
<td>VO&lt;sub&gt;2max&lt;/sub&gt;</td>
<td>maximal oxygen consumption</td>
</tr>
<tr>
<td>VOP</td>
<td>venous occlusion plethysmography</td>
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<tr>
<td>WBGT</td>
<td>wet bulb globe temperature</td>
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Background and Significance

The maintenance of body core temperature ($T_c$) within a relatively narrow range is an essential homeostatic function of the human body. However, there are numerous internal and external influences which may alter $T_c$. For example, heat and cold stress may lead to hyper- or hypothermia, respectively. Reflex mechanisms, including cutaneous vasoconstriction and vasodilation, shivering, and sweating function to counteract these environmental stressors to maintain thermal homeostasis. Individual characteristics including age, adiposity, muscle mass, hydration status, acclimation state, and fitness level may influence or directly modify the $T_c$ response to a thermal challenge, depending on the environmental conditions.

Aging and Cold Stress

In older individuals, attenuated reflex cutaneous vasoconstriction during cold stress may result in greater heat loss to the environment and a concomitant decrease in $T_c$. Additionally, body composition characteristics such as percent body fat (%fat) and muscle mass that change with advancing age may effect thermoregulation.
Epidemiological data indicates that the rate of deaths due to hypothermia increases dramatically in those 65 years and older (1). During cold stress, in order to prevent excess heat loss and to defend $T_c$, the cutaneous vasculature constricts, thereby limiting heat transfer to the skin and to the environment. If necessary, metabolic heat production via shivering thermogenesis may occur as well. In the context of human aging, cutaneous vasoconstriction (VC) is attenuated in older individuals (22; 75; 123). In young healthy vasculature VC is mediated by release of norepinephrine (NE) and an unknown non-noradrenergic co-transmitter, putatively neuropeptide Y (NPY) (115) released from sympathetic nerve terminals. Additionally, in vitro evidence suggests that ATP may also play a role in cutaneous VC, acting through P$_{2x}$ purinergic receptors, but in vivo data supporting such a role are lacking. Alterations in the mechanisms mediating impaired VC in aged skin include a reduced responsiveness to NE (122) and a lack of function co-transmitter(s) (123) in older adults. Due to impaired VC in aged skin, skin temperature ($T_{sk}$) may be higher, leading to greater heat loss to the environment via radiation and convection.

When cutaneous vasoconstriction alone is no longer sufficient to maintain $T_c$, metabolic heat production ($M$) is increased via shivering thermogenesis. $M$ may be altered with aging due to age-related body composition changes. In young subjects, increased adiposity is inversely related to a lower metabolic response to cold stress (16) and directly related to $T_c$ (5). The same inverse relation holds true in older subjects (13).

Tissue insulation ($I_t$) from the cold is provided by the static effects of subcutaneous fat and muscle mass, mediated by the dynamic effect of blood flow through those tissues. In addition to actively producing metabolic heat, muscle mass may
contribute up to 80% of total body $I_t$ (106). However, others have shown during cold water immersion that greater lean body mass (LBM), while associated with increased tissue insulation, did not contribute to a higher $T_c$ (130). Aging is often associated with a loss of muscle mass, clinically defined as sarcopenia after a critical threshold is reached. The relation between muscle mass and $T_c$ in young vs. older subjects during cold stress is unclear, although it has been hypothesized that sarcopenia may contribute to a lower $T_c$ through reduced $I_t$ during cold stress (76). Furthermore, the influence of attenuated VC and M on $T_c$ in groups matched for body composition has not been systematically explored.

The maintenance of $T_c$ and therefore heat balance is represented in its simplest form as heat production equaling heat balance. However, there is a discrepancy between the thermometric and calorimetric determinations of heat debt during cold stress, such that determination of changes in body heat content may not be valid using thermometric methods (86; 131). The temperature change of a ‘mid-region’ ($\Delta T_{mid}$), anatomically distinct from the core and skin regions, may help explain this discrepancy (129). The calculation of $\Delta T_{mid}$ has only been conducted using data from young subjects during severe cold stress; calculation using data from older subjects are lacking and may be relevant because attenuated VC may result in redistribution of body heat content, such that $T_c$ decreases but heat is not lost to the environment.

In addition to adiposity and muscle mass, other individual characteristics, such as sex (134), Dubois body surface area ($A_d$; (25)) and $A_d$/mass (80; 90; 105; 128) may be related to the ability to defend $T_c$ during cold stress. A common experimental paradigm is to recruit and compare 2 subject groups matched for all but one relevant individual
characteristic. However, this method may be flawed as many anthropometric variables are interrelated, making it difficult to determine the relative influence of each. An alternative approach is the use of a large, heterogeneous subject population and multiple regression analysis (57-60) to determine the relative contribution of individual predictors to $T_c$.

**Core Temperature and Exercise-Heat Stress**

Upright exercise in the heat presents the greatest challenge to the cardiovascular system (110) and poses a formidable challenge to thermoregulation as well. An average sized individual running at 160 m·min$^{-1}$ (6 mile·h$^{-1}$) produces $\sim 475$ W·m$^{-2}$ of metabolic heat, which if not dissipated to the environment will rapidly lead to hyperthermia. A hot and/or humid environment will add to the thermal stress due to decreased heat transfer capacity between the individual and the environment.

Numerous models of human thermoregulation exist to mathematically predict $T_c$ ($T_{pred}$). These models have been developed in order to assess the cumulative physiological strain of environmental and exercise stressors, and to predict water losses in order to determine subsequent fluid replacement guidelines. Furthermore, when coupled with real-time measurement of environmental conditions and estimated metabolic heat production, these models can predict impending heat casualties during athletic, occupational, or military activities.

There are several different types of models; some models are described as rational, or bioengineering; a familiar example is the Stolwijk 25-node model (117; 118).
Rational models consist of a passive controlled system and an active controlling system. The passive system defines the geometry of the body, sub-dividing the body into several tissue compartments, the specific number varying among models, and calculates temperature distributions and heat transfer rates within the tissue compartments and between the body and the environment. The active system defines the physiological control mechanisms, such as sweating, shivering, and cutaneous vasoconstriction and vasodilation that attempt to control the rate of heat transfer within the passive system.

Development and validation of the active system control equations are conducted using existing laboratory data from multiple studies covering a wide range of environmental and exercise intensity conditions; the cumulative sample size is often greater than 30 subjects. Validation studies are usually not more than 2 h in duration, conducted under tightly controlled conditions where $T_c$ can be measured. Rational models function in the time domain, in which incremental changes are algebraically summed over time. Minor errors in the calculation of these incremental changes may not be apparent in relatively short-term exposures but may be revealed in longer simulations, leading to less accurate predictions.

Rational models of thermoregulation differ considerably in the construction of the passive system. At one extreme is the 3 dimensional model constructed by Werner (140), with 63 tissue types and a temperature grid of the body represented by ~400,000 data points, and on the other is the 2 node Pierce model (39), which considers the body as a single cylinder divided into core and shell layers. Other models, such as Stolwijk’s 25 node model (117; 118), Kraning’s SCENARIO model (81-83; 147), or Fiala’s model (33; 34), fall toward the simpler end of these extremes. Some models allow for input of
individual characteristics while others employ standard body dimensions. For example, SCENARIO allows for input of the individual’s height, weight and %fat, and calculates body density, cylinder lengths, radii and areas, and inter-compartmental conductance accordingly while others (33; 34) assume standard dimensions.

In addition to differences in the construction of the passive system, the active system may differ due to individual differences as well. For example, the SCENARIO model incorporates adjustments to the algorithms for skin blood flow and sweat rate based on hydration status and fitness level (83), while heat acclimation reduces baseline $T_c$, if an individual’s actual $T_c$ is not input by the user. Further complication arises through the estimation of metabolic rate, such as with the prediction equations of Berglund (9) and Pandolf (28; 101), which are integrated into models of thermoregulation. With one exception (147), there are a lack of data validating models of human thermoregulation during longer duration field exposures and few data comparing the $T_{pred}$ by different models (49; 54; 82).

The three projects that comprise this dissertation were carried out in order to 1) examine the role of primary aging, on the defense of $T_c$ during resting cold stress 2) determine the relative importance of individual characteristics on the $T_c$ response to cold stress and 3) using 3 existing models of human thermoregulation during a unique cross-desert expedition, determine the accuracy of $T_{pred}$ during longer duration exposure and assess the importance of individualization on the prediction of the heat stress response.
Specific Aims and Hypotheses

Specific aim 1: The purpose of the study “Impaired defense of core temperature in aged humans during mild cold stress” was to determine the influence of primary human aging in the absence of overt pathology, in a relatively large subject population, on the defense of $T_c$ during a mild cold transient.

Hypothesis 1a: Older subjects, with similar group anthropometric characteristics compared to young subjects, would have an impaired defense of $T_c$ due to impaired cutaneous vasoconstriction and/or a lower metabolic rate.

Hypothesis 1b: Calculated $T_{mid}$ will explain any discrepancy between $T_c$ and heat debt calculated via partitional calorimetry.

Specific aim 2: The purpose of the study “Responses to mild cold stress are predicted by different individual characteristics in young and older subjects” was to determine the individual characteristics that influence the responses to cold stress, as assessed by esophageal temperature ($T_{es}$) and $I_t$, in heterogeneous young and older subject groups and to determine the relative contributions of the predictors to the responses.

Hypothesis 2: The individual predictors of $T_{es}$ and $I_t$ would differ between age groups, as would the relative contributions of predictors to the explained variance.
Specific aim 3a: The purpose of the study “Modeling human core temperature during a unique cross-desert expedition” was to validate three rational models of thermoregulation, including two which were recently developed and that have not as yet been subjected to extensive validation, during long duration exercise performed by 3 ultra-endurance athletes.

Hypothesis 3a: Due to the variability inherent to field studies, the root mean squared deviation (RMSD; a statistic describing the mean difference between $T_{pred}$ and $T_c$) would be greater than during laboratory studies, though still within acceptable limits, even for 3 individuals.

Hypothesis 3b: Different estimates of metabolic rate would yield similar $T_{pred}$ when input into the same model.

Hypothesis 3c: The RMSD of each the models would be smaller during the first 2 h of the run than during the entire run.
Chapter 2

REVIEW OF THE LITERATURE

The control of body core temperature ($T_c$) within a relatively narrow range is one of the essential homeostatic functions of the human body. The maintenance of a stable $T_c$ and heat balance is represented in its simplest form as heat production equaling heat loss. Heat is produced due to metabolism (M) and lost via evaporation (E) of sweat, while external work (W), radiation (R), conduction (K), and convection (C) can be avenues of either heat loss or gain depending on the environmental conditions. In mathematical terms, these are represented in the heat balance equation, which forms the basis for describing heat exchange between an individual and the environment:

$$\text{Storage (S)} = M \pm W - E \pm C \pm K \pm R$$

In most cases, W can be ignored, except when external movement up or downhill is performed. Likewise, K, or heat transfer between solid objects is usually ignored. R and C are often together referred to as dry heat exchange, in contrast to heat loss due to evaporation of sweat.

Numerous individual characteristics may influence or modify variables in the heat balance equation and individual responses to cold or heat stress, such as age, sex, anthropometric characteristics, hydration status, acclimation state, and fitness level. The first section of this review concerns aging and the defense of $T_c$ during cold stress, with an emphasis on individual characteristics. The remainder of the review is concerned with
the prediction of $T_c$ during exercise in the heat, with particular reference to the limitations of existing models of human thermoregulation and the individualization, or lack of individualization, in these models.

**Aging and Cold Stress**

**Cutaneous Vasoconstrictor Function**

Thermoregulatory responses are adversely affected by the aging process. In response to cold stress, the cutaneous vascular constricts and skin blood flow (SkBF) is reduced, limiting convective transfer of heat from the body core to the periphery and minimizing dry heat loss to the environment. Cutaneous vasoconstriction (VC) in the cold is attenuated in older humans (22; 134; 135). Moreover, cutaneous VC is slower to develop in older compared to young subjects. However, a common difficulty in interpreting cold stress studies is distinguishing chronological age effects from other relevant changes, such as increased adiposity, decreased muscle mass, and decreased physical fitness. For example, Budd et al (13) showed that greater adiposity in older subjects offset age effects on whole body heat loss. In order to clarify the effect of chronological age on the VC response to cooling, Kenney and Armstrong (75) tested young and older subjects closely matched for relevant anthropometric characteristics such as body surface area ($A_d$), %fat, sum of skinfolds, and fitness. During whole body cooling, cutaneous VC was measured using venous occlusion plethysmography (VOP) as
an index of forearm blood flow, and forearm vascular conductance (FVC; FBF/mean arterial pressure) was calculated. Additionally, forearm skin temperature ($T_{sk}$) was clamped at 37.0°C, such that any observed VC would be reflex in nature due to reduced mean $T_{sk}$ over the remainder of the body, rather than local, non-reflex-mediated effects. Over 2 hours of whole body cold stress, FVC fell more rapidly and was significantly lower in young subjects during the final 30 min of the exposure. An assumption for the use of VOP during cooling is that vasoconstriction is limited to the skin. With the development of laser- Doppler flowmetry (LDF), SkBF could now be directly measured. Several investigators (37; 78; 108) utilized LDF as an index of SkBF during reflex cooling and verified attenuated VC in aged skin, using this skin-specific technique in a variety of experimental protocols. In spite of these methodological differences, and the continued presence of possible non-age-related confounding variables, attenuated VC is consistently reported in aged subjects.

The development of the intradermal microdialysis technique, coupled with selective pharmacological agents, has enabled researchers to examine the mechanism(s) underlying VC in young (114; 115) and older adults (121-123). Selectively utilizing the sympathetic adrenergic pre-synaptic inhibitor bretylium tosylate and the post-synaptic adrenergic antagonists yohimbine ($\alpha_1$ and $\alpha_2$) and propranolol ($\beta_2$) to post-synaptically antagonist either or receptor adrenergic receptor sub-types, Stephens (114) concluded that ~60% of reflex VC is due to norepinephrine (NE) and the balance is due to an unknown non-noradrenergic co-transmitter. Neuropeptide Y (NPY) is co-stored and co-released with NE in perivascular sympathetic nerve endings in several vascular beds. These investigators utilized the Y1 receptor antagonist BIBP-3226 to block the action of NPY
during whole body cooling and concluded that NPY is a likely co-transmitter (115). However, ~10% of VC was not blocked with yohimbine + propranolol + BIBP-3226, suggesting the potential for another co-transmitter. *In vitro* studies suggest adenosine triphosphate (ATP), though *in vivo* studies examining a possible role for ATP are lacking.

There are a number of possible explanations for attenuated VC function in older adults, including reduced NE and/or co-transmitter release and/or decreased post-synaptic responsiveness. Thompson and Kenney (123) confirmed similar contributions of NE and co-transmitter(s) in young subjects, however, in older subjects VC was attenuated, due to a lack of functional co-transmitter function and a decreased NE contribution. The NE contribution to VC was less in older subjects, which suggests the possibility that in addition to a lack of functional co-transmitters, post-synaptic responsiveness to NE is attenuated as well. Later, Thompson et al demonstrated an age-related attenuation in VC during graded localized NE infusion (122).

Due to methodological considerations, in many studies $T_{sk}$ is usually clamped at a thermoneutral temperature or controlled via a water-perfused suit, which precludes calculation of dry heat loss during cold stress. Greater heat conductance from the core to the skin has been suggested (135) in older subjects, but increased dry heat loss as a result of attenuated VC has not been empirically demonstrated.

**Metabolic Heat Production and Body Composition**

In addition to limiting dry heat loss via vasoconstriction during cold stress, body heat balance is maintained by increasing metabolic heat production, though the
magnitude of the metabolic response to cold stress may be mediated by body composition. Separate investigators (53; 56) have calculated the in vitro insulation of adipose tissue as 0.048 °C·m²·W⁻¹·cm⁻¹ while an identical in vivo value has been calculated as well(132). In contrast, the insulation provided by muscle tissue is ~half that of adipose (56) per unit thickness and assuming equal perfusion. During whole body cooling in men encompassing a wide range of adiposity, Baker and Daniels (5) found that local skin temperature was inversely related to skinfold thickness. Considering that dry heat loss is estimated in part by the T_{sk}-dry-bulb temperature (T_{db}) gradient (40; 42), a lower skin temperature due to greater subcutaneous adiposity should reduce dry heat loss. These authors also reported a positive relationship between %fat and T_c after 2 h of cooling (5). Furthermore, others (16) have reported that the metabolic response to 2 h of cooling at 10°C was inversely related to %fat, such that the leanest subjects had the greatest increase in heat production, yet obese subjects tended to maintain T_c better than lean subjects. Similar findings were reported by Budd et al (13) in a group of men aged 26-52 years, representing a range of fitness and adiposity levels.

The insulation provided by muscle is less than adipose tissue; yet muscle mass is critical for thermoregulation in the cold due to its contribution to tissue insulation (I_t). Early studies I_t (18; 107) reported that the intercept of the regression line for subcutaneous fat vs. I_t was positive, suggesting that other tissues besides adipose must be contributing. It has been estimated that muscle contributes 92% to the total I_t in the human forearm during cold water immersion (26). However, total body superficial shell insulation, i.e. skin + subcutaneous fat, accounted for 26-30% of total body I_t (62; 132); the balance must to due to lean tissue. The smaller adipose insulation calculated by in the
forearm (26) was likely due to proportionately less forearm subcutaneous fat (~3.0 mm) compared to mean total body subcutaneous fat thicknesses of ~5.6 mm and ~5.2 mm in (132) and (62), respectively.

A role for $A_d$/mass has been suggested in human thermoregulation, in which an individual with a smaller $A_d$/mass would lose less heat in a cold environment (80; 105). In order to directly test this hypothesis, Toner et al (130) immersed 2 groups of men matched for %fat, sum of skinfolds and $A_d$, but differing in body mass and $A_d$/mass in 26°C water. Due to similar adiposity and greater body mass, the small $A_d$/mass group also had significantly greater LBM. The large $A_d$/mass group had significantly lower $I_t$ likely due to smaller muscle mass, but there were no differences in $M$, $T_\text{es}$ or $T_\text{re}$. A criticism of this study was that the difference in $A_d$/mass between groups may have been too small (0.22 m²·kg⁻¹) to detect a difference in responses. In order to address this issue, Glickman-Weiss et al (47) utilized a similar protocol in subjects groups with a greater difference in $A_d$/mass (0.35 m²·kg⁻¹) and a greater cold stress. Similar to the previous study (130), there were no group differences for $T_\text{re}$ or oxygen consumption, however there was also no difference for $I_t$, which the authors attributed to the greater cold stress and therefore greater VC in the large $A_d$/mass group.

Studies examining sex differences in thermoregulatory responses support the relation between muscle mass and the increase in $M$ during cold stress. Several studies have reported a greater $M$ during cold stress in men, presumably due to a larger LBM (50; 51; 90; 116). When matched for adiposity, $T_c$ drops more in women (90), likely due to a relatively larger $A_d$ (80); when normalized for lean body mass (LBM), metabolic rate does not differ between men and women (128).
A decline in LBM is a common characteristic of aging, often attributed to changes in physical activity patterns, dietary habits, and/or hormonal influences. In severe cases, this loss of lean body mass is called ‘sarcopenia’, a term coined by Rosenberg (109) which loosely translated means ‘deficiency of flesh’. The most common clinical definition of sarcopenia is LBM, referenced to the individual’s height\(^2\) to remove the correlation between height and muscle mass, greater than 2 standard deviations below the mean of a young, sex-matched population (6). Cross-sectional studies indicate that the prevalence of sarcopenia ranges from 4 to >50% (6; 19; 68); moreover the prevalence increases with advancing age. Limited longitudinal data suggests that the loss of limb muscle mass is \(-0.2\) kg per year, which is masked by a similar increase in adiposity (43).

There is a growing body of data linking sarcopenia and functional impairment. For example, sarcopenia is associated with poorer balance (95; 119), reduced grip strength (91), difficulty performing activities of daily living (72; 73), and impaired lower extremity performance assessed by walking speed and stair climbing ability (73; 95). Because of the contribution of muscle in total body tissue insulation, it has been hypothesized that sarcopenia may predispose an individual to hypothermia (76). However, evidence to support a role for sarcopenia in impaired thermoregulation during cold stress is lacking.

Taken together, these studies demonstrate the importance of controlling for body composition differences when studying age-related differences in \(T_c\) or \(M\). Several studies have reported a lower metabolic response to cold stress in older subjects (37; 64), though this is not a universal finding (134; 135). Horvath et al (64) exposed 8 older men to 10°C air to the limits of their thermal tolerance. Oxygen consumption increased 59%
in young subjects and only ~7% in the older men. However, the authors noted that all of the young men were exposed until profound gross shivering was observed, but only 1 older man shivered; the higher oxygen consumption may have been due to shivering thermogenesis rather than an age effect. Wagner et al (135) concluded that older men were ‘much less responsive metabolically’ than young men, but this was not supported by their data showing a non-significant difference in metabolic rate at baseline and after 30 min of cooling. Also, the older group in this study ranged from 46-67 years (mean not provided), an age range that would not typically be considered old. Wagner and Horvath (134) exposed young and older men and women to vary degrees of cold stress and found that the percent increase in M was similar across groups; all but the older women demonstrated a significant drop in Tc, likely due to the older women having greater adiposity than the other groups. Similarly, Frank et al (37) showed a smaller increase in oxygen consumption in response to cold saline infusion in older men, resulting in a greater Tc drop, even though adiposity was higher in this group. In light of the established roles for adiposity (5; 16; 126) and muscle mass (18; 26; 47; 107; 130) in thermoregulation during cold stress, the presence of body composition differences between groups (37; 134) or failure to provide body composition data for the subject groups (64; 135), interpretation of age-related differences are difficult. To date, data are lacking comparing young and older subjects matched for relevant body composition characteristics during cold stress.

A decline in maximal oxygen consumption (VO2max) is well documented with advancing age. A high VO2max is associated with enhanced heat dissipation in older subjects (120) during exercise in the heat, though there does not appear to be a role for
VO_{2\text{max}} during cold stress (13; 30). Bittel et al (10) examined the role of varying fitness levels in young men and concluded that fitter subjects thermoregulated more effectively, based on greater heat production during cold air exposures at several different temperatures. However, this effect was offset by lower %fat, higher T_{sk} and increased skin conductance, so that there was no association between T_{c} and VO_{2\text{max}}. Budd et al (13) used regression analyses in a group of 12 men varying in age, fitness and adiposity to examine the separate and combined effects of these variables on the responses to exposure to 10°C air for 2 h. VO_{2\text{max}} did not have any effect on heat production, heat loss, or I_{c}. These findings were confirmed in a study using 3 groups of subjects matched for relevant body composition characteristics, but differing in age and fitness level (30). The young subjects were matched with a group of older subjects for VO_{2\text{max}}, and there was a second, untrained, older group having a lower VO_{2\text{max}}. The rate of decrease of T_{c} was greater in the older subjects, regardless of VO_{2\text{max}}, indicating that a high level of aerobic fitness does not confer a protective effect during cold stress.

**Core temperature and body heat balance**

The calculation of heat debt or storage (S in the heat balance equation) is performed with either partitional calorimetry or thermometric methods. Partitional calorimetry refers to solving the heat balance equation on a minute by minute basis, while the thermometric determination of storage is based on the following equation (40):

\[ S = \frac{\Delta T_b}{\Delta t} \cdot c_b \cdot m/A_d \]
Where $\Delta T_b$ is the change in mean body temperature, $\Delta t$ is the change in time, $c_b$ is the specific heat of the body, and $m$ is body mass. Mean body temperature is the weighted average of $T_c$ and $T_{sk}$. However, during cold stress difficulties arise in assigning the proper weighting coefficients. Livingstone (86) and others (113; 131; 137) concluded that weighting coefficients can vary not only between individuals (likely due to body composition differences) but also by time for a given individual, and that the calorimetric determination of storage is not valid during non-steady state changes in body temperatures. Together, these studies suggest that the stabilization of core temperature occurs after heat balance is reached during cold stress.

In an effort to resolve this issue, Tikuisis (129) proposed a third, ‘mid’ region, anatomically distinct from the core and skin regions. Rather than attempting to adjust the core and shell weighting coefficients on an individual and/or time-dependant basis, the relative masses of the core, shell and mid-regions are fixed at 16, 6 and 78% of non-fat mass, respectively. This 3 region thermometric determination may eliminate the discrepancy between heat balance and core temperature. Theoretically, if $T_c$ is lower in one group compared to another yet there is no difference in dry or evaporative heat loss, a possible explanation may be provided by the mid-region temperature ($T_{mid}$), in which $T_{mid}$ should be higher in the group with lower $T_c$. To date, the mid-region paradigm has not been applied to examine age-related differences or during mild cold stress.
Individual characteristics, aging, and cold stress

Individual characteristics including sex (16; 80; 90; 128; 134), adiposity (5; 16; 47; 126), LBM (Glickman-Weiss 93, Toner 86, Carlson 58, Rennie 62, Haywood 81, Ducharme 91), and $A_d/mass$ (47; 80; 105; 128; 130) may have an effect on thermoregulation during cold stress. However, these variables are inter-related, making interpretation of which variable(s) has the greatest influence on $T_c$ during cold stress difficult. Several of the studies have used the paradigm of recruiting 2 subject groups, matched for all but one anthropometric characteristic (47; 130). While sound in theory, in practice this is difficult, due to inter-relationships between these variables.

An alternative approach is to recruit a large heterogeneous subject population that varies simultaneously in several anthropometric characteristics and use multiple regression analysis to determine which variables have the greatest influence on $T_c$ (57-60). The purpose of multiple regression analysis in this application is not to globally predict $T_c$ during cold stress, as there are several models designed to do so (117; 118; 125; 127; 144), but it is to determine the relative influence of a given characteristic on the final $T_c$. Havenith and colleagues have used this technique to examine the relative influence of individual characteristics during exercise in the heat (57; 59; 60) and to determine the role of age on cardiovascular and thermoregulatory responses (58). This analytical approach to determining the relative influence of individual characteristics has not been employed during resting cold stress.
Predicting Core Temperature during Exercise in the Heat

The accurate prediction of $T_c$ during a wide range of thermal environments is of interest to a variety of organizations. Athletic governing bodies, such as the National Collegiate Athletic Association (NCAA), are concerned about heat illness during practice and competition, an interest shared by military organizations of numerous countries. The International Organization for Standardization (ISO) has also developed guidelines for assessing heat stress in industrial settings and to set work:rest cycles for employee safety (69-71). A benefit of accurate models of thermoregulation is the ability to evaluate the strain of a given environment without conducting an experiment, thereby saving time and expense. For this reason, the National Aeronautics and Space Administration (NASA) contracted with Jan Stolwijk of the John B. Pierce Foundation and Laboratory to create a mathematical model of thermoregulation, so that simulations between man and the life support system developed for the Apollo space program could be conducted. The model of thermoregulation that resulted (117; 118), forms the theoretical basis of several other models, such as the Pierce 2-node model (39), from which other models (61; 87; 146) were derived. Earlier rational models where either open-loop with no controls or regulation (15; 88) or had only a primitive control scheme (23).

Model validation is performed by conducting a simulation with a given model and comparing the model output with the laboratory data used for the simulation. Earlier models were only qualitatively compared; graphs of actual $T_c$ and predicted $T_c$ ($T_{\text{pred}}$) were compared and conclusions were drawn. However, others suggested that a model will yield ‘useful results’ if $T_c$ and $T_{\text{pred}}$ are within $\pm0.5^\circ C$ (142). A more precise method
of model validation, a statistic called the root mean squared deviation (RMSD), was first proposed by Haslam and Parsons (55) for comparing the results of a model’s prediction vs. observed data. The statistic is calculated as follows:

$$\text{RMSD} = \sqrt{\frac{1}{n} \sum_{i=1}^{n} d_i^2}$$

Where $d_i$ is the difference between measured and predicted temperature at each time point and $n$ is the number of time points. This statistic enables comparison of predicted vs. observed data in the units of the variable of interest. The interpretation of this statistic is that a model’s goodness of fit is acceptable when the RMSD is less than the standard deviation (SD) of the measured data. This statistic is almost universally applied in studies over the last 20 years comparing model predictions with measured data.

Models of human thermoregulation can be grouped into 3 categories (27; 103): 1) direct indices, which are based on measurements of environmental variables, 2) empirical indices based on laboratory data used to ‘fit’ a theoretical model, and 3) rational indices using calculations based on the heat balance equation. Direct indices attempt to provide a single value that provides an estimate of the environmental strain. Examples include the wet-bulb temperature (52), effective temperature (66), predicted 4 hour sweat rate (89), the heat stress index (8) and the wet bulb globe temperature (WBGT) (145). More than 40 different heat stress indices have been developed over the last 100 years; this list is likely incomplete (27). Due to the complexity involved in developing a single index to assess heat strain from several variables, a universal system for rating heat stress does not, and will not, exist (7; 41), though this has not deterred recent attempts to formulate such an index (93; 136). However, direct indices have their advantages because they are
simple and easy to use, especially for ‘non-expert’ users, and they only require measurement of simple environmental parameters using off the shelf commercially available devices. For this reason, the WBGT and other direct indices are integral components of numerous heat injury prevention programs (2; 69).

While direct indices only require measurement of environmental variables, empirical and rational models incorporate environmental and physiological data. Empirical indices formulate a theoretical framework to quantify the effects of the environment, activity level, and clothing factors and then use laboratory data to ‘fit’ the theoretical equation to observed data under a variety of experimental conditions. The best known empirical model is Givoni and Goldman’s (44; 102), developed at the US Army Research Institute of Environmental Medicine (USARIEM) and in its present form known as the heat stress decision aide (HSDA). A critical assumption for this model is that for any combination of environmental conditions, activity level and clothing worn, there exists an equilibrium $T_c$, though this value may lie outside physiological limits. The general form of the model is as follows:

$$T_{cf} = 36.75 + a(M_{net}) + b(R+C) + c \exp (d(E_{req}-E_{max}))$$

Where $T_{cf}$ is the final (equilibrium) core temperature, 36.75 is baseline $T_c$ (adjustable in future versions), $M_{net}$ is net metabolic rate, $R+C$ is dry heat exchange, $E_{req}$ is the required rate of sweat evaporation and $E_{max}$ is the maximal rate of sweat evaporation allowed by the environmental conditions. The terms $a$, $b$, $c$, and $d$ are the coefficients used to fit the model to observed data. This model predicts the final equilibrium $T_c$ and intermediate values are calculated using separate curve-fitting functions for rest, at the onset of exercise, and during recovery from exercise. The HSDA has been updated over time as
more data has been added to the historical data set at USARIEM, including modifications for heat acclimation (45), protective clothing ensembles (49), and fine-tuning of the curve fitting function to correct a non-physiological rise in $T_c$ from rest to exercise (17). Validation of this model has consistently indicated that it over-predicts the measured $T_c$ in a variety of environmental conditions (17; 54). The consistent over-prediction of $T_c$ of this model is viewed as a safety feature (17) from the US Army’s perspective as this is preferable to under-predicting $T_c$ when the objective is heat injury prevention.

Stolwijk’s model developed for NASA (117; 118) is perhaps the best known example of a rational model. Rational models are based on the heat balance equation for quantifying heat exchange between the individual and the environment, and consist of a passive controlled system and an active controlling system. The passive system defines the geometry of the body, sub-dividing the body into several tissue compartments, the specific number varying among models, and calculates temperature distributions and heat transfer rates within the tissue compartments and between the body and the environment. The active system defines the physiological control mechanisms, such as sweating, shivering, and cutaneous vasoconstriction and vasodilation that attempt to control the rate of heat transfer within the passive system. Unlike the HSDA and other empirical models, in which intermediate $T_c$ values are estimated by a curve-fitting function, rational models operate in the time domain, in which incremental changes in regional heat content are algebraically summed over time, and knowing (or assuming) the mass and specific heat of a region, the temperature change of the region is calculated.

Rational models differ substantially in the number of nodes and the tissue types specified in the passive system. The structure of a given model is based on the intended
use by whoever developed the model and which characteristics or conditions were considered important (118). For example, cold exposure models require greater detail in the temperature distribution of the passive system due to larger internal temperature gradients compared to heat exposure (142). Regarding the number of nodes, or compartments, at one extreme is the Pierce 2-node model (39), which simply divides the body into core and shell segments of a single cylinder. Wissler’s model calculated 225 temperatures in 15 elements, and appears to be the only model validated for hyperbaric exposures (142). This model is an order of magnitude larger than Stolwijk’s 25 node model, yet pales in comparison to Werner’s model, which calculates the temperatures of a 3 dimensional grid of 1.0 cm resolution for the trunk and 0.5 cm resolution for all other parts, resulting in 400,000 data points per unit time (140). However, the need for a model providing this level of detail has been questioned (142), especially considered that the computer memory requirements for the program would not allow for simulation of dynamic changes and only steady-state simulations were possible (140).

The active controlling system of a rational model can be conceptualized as 3 components 1) the thermoreceptors that detect the thermal state of the passive system 2) a central controller, which receives data from the thermoreceptors, integrates the information and initiates the appropriate effector output and 3) effector organs, which receives commands for the central controller. The 4 effector outputs are sweating, shivering, vasoconstriction, and vasodilation, which are regulated by controller equations. All of the controller equations consist of control coefficients from the error signal, plus core and skin temperature signals. As it is not possible to describe all possible
experimental results with a single set of control coefficients, the coefficients employed in
the model are valid for the conditions which they were developed under (118).

The models utilized in this dissertation are SCENARIO, developed by Ken
Kraning at USARIEM (81-83; 147), the Initial Capability Decision Aide (ICDA), also
developed at USARIEM (146), and Dusan Fiala’s model of human thermoregulation (33;
34). Each of these are rational models of thermoregulation but have unique
characteristics specific to each model.

The SCENARIO model considers the body as a single upright cylinder consisting
of 5 concentric compartments- core, muscle, fat, vascular skin, avascular skin and a 6th
interconnecting blood compartment. Heat conductance between the vascular and
avascular skin compartments is controlled by the active system. Conduction between all
other compartments is constant and only varies with the anthropometric characteristics of
a given individual. The size of each compartment is calculated based on an individuals
height, weight and %fat; the relative mass distribution among compartments is fixed
according to predetermined proportions.

The SCENARIO model offers the user the greatest opportunity for
individualization. In addition to height, weight, and %fat, the subjects hydration status
(normal, mild hypohydration, or severe hypohydration), acclimation status (full, partial,
or none), and initial T_c can be specified. Metabolic rate is calculated by an integrated
algorithm, based on the subjects weight, load carried, fractional grade and a terrain factor
(28; 101), or can be input directly in Watt units if determined by another method. Mild
and severe hypohydration refer to 2 and 4% body weight loss (BWL), respectively.
Hypohydration alters the skin blood flow algorithm by increasing the T_c threshold toward
a higher $T_c$ for increasing SkBF via active vasodilation by 0.06°C·%BWL$^{-1}$ and decreasing the slope 0.13 L·min$^{-1}$·1.0°C$^{-1}$·%BWL$^{-1}$. The sweat rate algorithm is also altered by hypohydration, whereby the $T_c$ threshold for sweating increases 0.06°C·%BWL$^{-1}$ and the slope decreases 0.6g·min$^{-1}$·1.0°C$^{-1}$·%BWL$^{-1}$. The default baseline $T_c$ is 39.96°C; this value is reduced by 0.25°C or 0.50°C when partial or full acclimation, respectively, is input. This function is over-ridden if the subject’s actual baseline $T_c$ is known. While heat acclimation is known to decrease the $T_c$ threshold for sweating, and increase the slope and plateau (143), an examination of the SCENARIO model literature (81-83; 147) gives no indication that these effects of heat acclimation are incorporated into the model.

In earlier versions of SCENARIO, the algorithm for sweat rate was modified to account for an individual’s fitness level (83; 84) by adding a multiplicative term that proportionately increased or decreased sweat rate for an individual whose $VO_2$ was above or below 3.65 L·min$^{-1}$. For unknown reasons, this modification is not present in the most recent version (v1.0b3, 2003) of the model. Validation data for the changes to the model incorporating fitness level and hypohydration are not contrasted with data from previous versions of the model; whether these modifications improved the models $T_c$ prediction is unknown.

The ICDA model utilizes the 2 node passive system defined by the Pierce model (39) and active system components from the SCENARIO model (81). The goal in developing this model was to predict physiological responses from a minimum of non-invasive inputs. The only individual data required to execute the model are an individual’s height, weight, resting and exercising heart rates, baseline $T_c$, and baseline
T_{sk}. If any or all of these values are unknown, default population average values are used. The key feature of this model is the estimation of metabolic rate, in MET units, from T_{db} and the ratio of exercising HR to resting HR (9):

$$\text{METS} = 0.68 + 4.69 \times (\text{HRR}-1) - 0.052 \times (\text{HRR}-1) \times T_{db}$$

where HRR is the heart rate ratio. This equation was originally validated for T_{db} 20-40°C and HRR 1.2-2.0; fit individuals with a low resting heart rate exercising at a relatively high intensity may exceed the HRR limits of this equation.

The model developed by Fiala (33; 34) is unique in the construction of the passive system, which is represented by 15 spherical or cylindrical elements: head, face, neck, shoulders, arms, hands, thorax, abdomen, legs and feet. Each segment is then divided into layers based on the tissue types present in a particular segment (brain, lung, bone, muscle, viscera, fat and skin), resulting in 43 tissue segments. In order to account for asymmetric removal of body heat due to inhomogeneous ambient conditions, solar radiation, clothing differences, etc, each segment is then subdivided into a variable number of sectors per tissue segment, totaling 132 for the entire passive system. Heat exchange within the passive system and between the individual and the environment is calculated using equations similar to other rational models.

The Fiala model does not include any method for estimation metabolic heat production; rather it is input in METS, determined by a method of the users choosing. Unlike SCENARIO and ICDA, the model assumes standard height, weight and body surface area; input of individual anthropometric characteristics is not an option.

These and other models of thermoregulation have been validated using data from multiple studies not used in the development of the model, covering a wide range of
environmental and exercise intensity conditions. Validation studies are usually not more than 2 h in duration, conducted under tightly controlled conditions were \( T_c \) can be measured. Because rational models function in the time domain, in which incremental changes are algebraically summed over time, minor errors in the calculation of these incremental changes may not be apparent in relatively short-term exposures but may be revealed in longer simulations, leading to less accurate predictions. None of the models utilized in this dissertation have been validated during resting exposures longer than 4 h or exercising exposures longer than 2 h. Data collected under field conditions will likely differ from laboratory data in several respects. Due to time of day effects dry-bulb (\( T_{db} \)), wet-bulb (\( T_{wb} \)) and mean radiant temperatures (MRT) and relative humidity will fluctuate. Unless the field study is conducted under strictly controlled conditions, terrain conditions, grade, and movement speed, and therefore metabolic heat production, may vary as well.

SCENARIO is the only rational model for which a series of papers are available documenting the continuing evolution of the model (81-83; 147). However, with each modification of the model, data comparing output from the new and old versions of the model are not provided; new version output is only compared to measure \( T_c \) data, making evaluation of the model improvements difficult.

The only paper which provides data comparing new vs. old versions of a model is Havenith’s individualized version (61) of the Pierce 2-node model (39). This model allows for the input of body mass, mean skinfold thickness, \( A_d \), \( VO_{2\text{max}} \), and acclimation status. These variables are used to modify the calculations for sweat rate, maximal sweat production, specific heat of the body, core-to-skin conductance, the threshold and slope
for sweat rate and for maximal skin blood flow. Data from previous studies in the authors lab (57-60), during which subjects exercised for 60 min at similar relative or absolute intensity in either hot-dry, warm-humid, or cool conditions, were used for simulations with the new and old models.

Based on the mean error and the mean squared error for Tc (predicted-actual) at the end of the exercise bout, the model modifications implemented by Havenith (61) improved performance in 4 out of 5 conditions tested. Additionally, using both Pearson correlation coefficients and the Spearman rank-order correlation test, the individualized model resulted in correlation coefficients significantly greater in 3 out of 5 conditions studies, suggesting that improvements are due to individualization and not just a reduction in systematic error alone. Acclimation was set to 0 and therefore is not part of this validation; it appears that no model has been validated using modification of active system control equations based on acclimation state. Considering the well known relationships between fitness level (99; 100) and acclimation status (138) on tolerance to exercise in the heat, incorporating the effects of these individual characteristics into future models or revisions of current models of human thermoregulation should be considered.
Chapter 3

IMPAIRED DEFENSE OF CORE TEMPERATURE IN AGED HUMANS DURING MILD COLD STRESS

Introduction

Upon exposure to cold stress, the cutaneous vasculature constricts to reduce heat loss, metabolic heat production increases and shivering begins, in an effort to maintain core temperature ($T_c$). However, with advancing age, these defense mechanisms may be impaired (30; 37; 64; 75; 78; 134). Epidemiological evidence indicates that ~60% of hypothermia deaths in the United States occur in those aged >65 years (1), and it is generally recognized that older adults fail to maintain $T_c$ during severe cold air stress (30; 37; 64) (133). Older adults may have a lower resting metabolic rate (M) (30) due to both decreased skeletal muscle mass (104) and an impaired metabolic response to cold stress (64; 135), although contrary reports exist (98; 134). Furthermore, an attenuated vasoconstrictor response has been well documented in older subjects (22; 75; 78; 123) possibly leading to greater heat loss. However, with few exceptions (37; 133-135), there is a paucity of studies examining both heat production and heat conservation mechanisms during cold exposure in young and older subjects and those that have been published suffer from one or more deficiencies.

Much of the aging and cold-stress literature has used fairly severe cold stimuli, with cold air exposures ranging from 5-10°C dry-bulb temperature ($T_{db}$) (13; 30; 64; 75;
conditions under which individuals, regardless of age, would normally employ behavioral thermoregulation, such as adjusting the temperature or donning more clothing, which they were restricted from doing during these studies. While these studies have been valuable in examining various thermoregulatory reflexes and differences due to aging, sex, and body composition, they have limited application to the environmental stresses normally experienced by most adults in daily living. Moreover, these studies are limited by small sample sizes, as low as 8 subjects (37; 64), the potential interaction between gender and body composition (133; 134), and the frequent use of an ‘older’ subject sample that does not meet commonly accepted age criteria of ‘old’ or ‘elderly’ (i.e. age >65 years) (13; 30; 133; 134). The relationship between body fat content and the metabolic response to cold is well known (16) and may explain age- and gender-associated differences reported by others (134). Additionally, the use of an abrupt transition to a severe cold stimulus in these studies excludes the possibility of determining if a less severe cold stress, which could reasonably be encountered in daily life, would elicit an impaired defense of Tc in older subjects.

The maintenance of Tc and therefore heat balance is represented in its simplest form as heat production equaling heat loss. Data from young subjects indicates that the thermometric determination of changes in body heat content may not be valid compared to estimation by partitional calorimetry (86; 131). It has been proposed that the temperature change of a ‘mid-region’ (tmid), distinct from the core and skin regions, may account for the discrepancy between thermometric and calorimetric determinations of heat debt (129). Calculation of predicted Tmid has not been conducted in older subjects or during mild cold stress.
Thus, the purpose of the present investigation was to determine the influence of primary human aging in the absence of overt pathology, in a relatively large subject population, on the defense of $T_c$ during a mild cold transient. We hypothesized that older subjects, with similar group anthropometric characteristics compared to young subjects, would have an impaired defense of $T_c$ due to impaired cutaneous vasoconstriction and/or a lower metabolic rate. An additional purpose was to determine the applicability of the mid-region concept in young and older subjects undergoing mild cold stress.

Materials and methods

Subjects

Thirty-six young (YS, 18-30 yr; 16 men, 20 women) and 46 older (OS, 65-89 yr; 24 men, 22 women) subjects participated in this study. All subjects were normotensive, non-smokers, and not taking any medications that might alter the cardiovascular or thermoregulatory responses to cooling. Young women were eumenorrheic, not taking oral contraceptives, and were tested in the early follicular phase of the menstrual cycle. All older women were post-menopausal and not taking hormone replacement therapy. All subjects abstained from alcohol and caffeine for 12 h before reporting to the laboratory on the day of the experiment. Verbal and written informed consent was
obtained from each subject prior to participation, and the protocol was approved in advance by The Pennsylvania State University Institutional Review Board.

Preliminary testing: Subjects underwent a standardized medical screening, including a resting electrocardiogram, blood chemistry analysis (CHEM-24, complete blood count, and thyroid hormone analysis, Quest Diagnostics), and a physical exam. Body composition (%fat) was determined via dual-energy X-ray absorptiometry (DXA; model QDR 4500W, Hologic, Waltham, MA). Appendicular skeletal muscle mass (ASMM) was taken as the sum of the arm and leg lean masses determined via DXA and expressed relative to height in meters$^2$ (kg·m$^{-2}$) as proposed by Baumgartner (6). Skinfold thickness was measured at the chest, mid-axillary, tricep, subscapular, abdominal, supra-iliac and mid-thigh sites by the same investigator as an estimate of subcutaneous adiposity. Body surface area ($A_d$) was estimated according to Dubois and Dubois (25) and the surface area-to-mass ratio ($A_d$·mass$^{-1}$) was calculated.

Instrumentation and measurements: Subjects arrived at the laboratory between 0800 and 0900. A copper-constantan thermocouple sealed in a pediatric feeding tube was inserted through the naris a distance equal to $\frac{1}{4}$ of the subjects standing height for measurement of esophageal temperature ($T_{es}$) (139). The subject then entered the environmental chamber (dry-bulb temperature ($T_{db}$) = 26.5°C) and was positioned in a semi-recumbent position, dressed only in shorts (men) or shorts and a sports bra (women). Skin temperatures were measured using copper-constantan thermocouples affixed to the skin at 8 sites. Mean skin temperature ($T_{sk}$) was calculated as follows:

$$0.07T_{head} + 0.175T_{chest} + 0.175T_{back} + 0.07T_{upper\;arm} + 0.07T_{forearm} + 0.05T_{hand} + 0.19T_{thigh} + 0.20T_{lower\;leg}$$

(40; 96).
Skin blood flow (SkBF) was measured via integrated laser-Doppler flowmetry (LDF; DRT4, Moor Instruments, Devon, England). LDF probes were placed on the ventral surface of the right forearm, taking care to avoid any surface blood vessels, and data were recorded continuously throughout the experiment. Arterial blood pressure was measured every 10 minutes via brachial auscultation and mean arterial pressure (MAP) was calculated as $1/3$(pulse pressure) + diastolic blood pressure. Cutaneous vascular conductance (CVC) was calculated as laser-Doppler flux/MAP and expressed as percent change from baseline values ($\Delta$CVC$_{\text{base}}$). Forearm blood flow (FBF) was measured by venous occlusion plethysmography (Hokanson EC4, Bellevue, WA) using a mercury-in-silastic strain gauge and forearm vascular conductance (FVC) was calculated as FBF/MAP. Oxygen consumption ($\text{\dot{V}}$O$_2$) and carbon dioxide production were measured via open-circuit spirometry for 3 min every 10 min (TrueOne 2400 Metabolic Measurement system, ParvoMedics, Salt Lake City, UT). The first expired air sampling and FBF measurements were performed after 5 minutes of baseline had elapsed and were repeated every 10 min thereafter. Thermal sensation was assessed every 10 min using a 0-8 scale, where 0=unbearably cold, 4=thermoneutral and 8=unbearably hot (148). All temperature and SkBF data were recorded and stored as 1-min averages using computer software (LabView) and a data-acquisition system (National Instruments, Austin, TX).

**Protocol:** Upon entering the environmental chamber, a 20 min thermoneutral ($T_{db}$ 26.5°C) baseline period began. After the baseline period, $T_{db}$ was steadily reduced at a rate of 0.25°C·min$^{-1}$ for 20 min, followed by a decrease in $T_{db}$ at a rate of 0.05°C·min$^{-1}$ for the remainder of the protocol. The protocol was terminated when sustained involuntary shivering was reported by the subject and/or observed by the investigators.
Calculated variables: Metabolic rate (M) was calculated as: \( M (W \cdot m^{-2}) = 352 \times (0.23 \times RER + 0.77) \times \left( \frac{\dot{V}O_2}{A_d} \right) \) (40). M was corrected for respiratory evaporative and convective heat loss and expressed as \( M_{net} \) (40). Heat storage (S) was calculated as \( S (W \cdot m^{-2}) = M_{net} - (R+C) - E_{diff} \), where \( (R+C) \) represents heat loss due to radiation and convection and \( E_{diff} \) represents heat loss due to water vapor diffusion through the skin (103). \( R+C \) was calculated as \( h(T_{sk} - T_{db}) \), where \( h \) is the combined radiative and convective heat transfer coefficient, calculated according to Parsons (103). \( E_{diff} \) was calculated as \( f_w \times 16.5 \times h_c \times (P_{sk} - P_a) \) (124); \( f_w \) is minimum skin wettedness, assumed as 0.06, \( h_c \) is the convective heat transfer coefficient, \( P_{sk} \) was determined by Antoine’s equation (103) and \( P_a \) was obtained from a standard psychrometric chart. Heat debt (HD) was calculated as \( HD (kJ \cdot m^{-2}) = \sum (M_{net} - (R+C) - E_{diff}) \times \Delta t \), where \( \Delta t \) is the time interval. By convention, HD is usually expressed in kJ, where 1 W·h=3.6kJ. Whole body tissue insulation (\( I_t; \ °C \cdot m^2 \cdot W^{-1} \)) was calculated as \( (T_{es} - T_{sk}) / (M_{net} - S) \).

The mid-region is assumed to encompass all parts of the body not included in the core and skin, specifically fat, connective tissue, muscle and bone. The calculation of \( T_{mid} \) is based on the principle of conservation of heat, which implies that HD must equal the sum of the products of the temperature changes in all body compartments, accounting for their heat capacities and masses. The specific heats of skin, core, fat, and mid-region were 1.02, 1.00, 0.64 and 0.91 W·h·°C⁻¹·kg⁻¹, respectively (129). The mass fractions were calculated as follows: \( f_{fat} = \%fat/100 \), \( f_{sk} = 0.062 \times (1 - f_{fat}) \), \( f_c = 0.159 \times (1 - f_{fat}) \) and \( f_{mid} = 0.779 \times (1 - f_{fat}) \) (129). The change in \( T_{mid} \) was calculated as \(-HD/wt-f_{sk} \times c_{sk} \times \Delta T_{sk}-\).
\[ f_c \cdot c_c \cdot \Delta T_c / (f_{fat} \cdot c_{fat} + f_{mid} \cdot c_{mid}), \]

where wt is body mass in kg and f and c are the whole body fraction and specific heat of each region.

**Statistical Analyses**

Data were analyzed using Student’s t-test for subject characteristics and repeated measures ANOVA and post-hoc t-tests with Bonferroni correction for multiple analyses where appropriate (SAS statistical software, version 9.1, SAS Institute, Cary, NC). Due to the possible interaction of age, gender and %fat, multiple regression analysis was performed to determine if any of these variables predicted the change in T_{es}. Age and sex were included in the regression model as dummy variables, where 0=male, 1=female and 0=young, 1=older. Correlation analysis was performed to test for interrelationships among significant predictors identified by regression analysis. Time to onset of shivering was analyzed using survival curve analysis (Minitab statistical software, version 14, Minitab Inc., State College, PA). Statistical significance was set at \( \alpha = 0.05 \) and data are expressed as mean±SE unless otherwise noted.

**Results**

Subject characteristics are presented in Table 3.1. The 2 age groups were well matched for all variables, except for a statistically significant difference in plasma thyroid stimulating hormone. The wide range of adiposity in each group was representative of the general population, ranging from the 10th to the 85th percentile when compared to
published reference data (3). Multiple regression indicated that age and %fat were significant predictors of ΔT_{es} (p<0.01 for each) but sex was not. Additionally, sex and %fat were significantly correlated (r=0.68, p<0.001) while age and %fat were not; therefore data for men and women were not analyzed separately in the ANOVA model.

During baseline, T_{sk} was 32.6±0.1 and 32.6±0.1°C (p=0.68) and thermal sensation was 4.2±0.1 and 4.1±0.1 (p=0.50), in YS and OS, respectively, indicating sensory thermal neutrality. There was a trend towards a lower T_{es} in OS at baseline (YS: 37.09±0.05, OS: 36.98±0.04°C; p=0.07). The median time to shivering was 81 and 79 min for YS and OS, respectively (p=0.87), and there was no age difference for T_{sk} (YS: 29.4±0.3°C, OS: 29.3±0.2°C, p=0.70) or T_{db} (YS: 20.7±0.2°C, OS: 20.9±0.2°C, p=0.38) at the onset of shivering. During cooling OS failed to maintain T_{es}, decreasing by ~0.2°C (Figure 3.1B). Conversely, YS demonstrated a slight increase in T_{es} (p<0.01 from 45 to 85 min). The difference in T_{es} between groups was significant after 35 min (T_{db}= 23.3±0.1°C) and the gap widened over time. There was no difference in T_{sk} between groups throughout the experiment (p=0.33; Figure 3.1C).

Figure 3.2 depicts the blood flow responses to cooling. CVC was higher in OS throughout the protocol (p<0.001; Figure 3.2A). When expressed as ΔCVC_{%base} OS had an attenuated vasoconstrictor response to cold compared to YS (p<0.01 from 35 min onward), with a maximal vasoconstrictor response of 42±3 ΔCVC_{%base} in OS and 53±4 ΔCVC_{%base} in YS (p<0.01). There was no age difference for FVC throughout the protocol (p=0.25). While OS baseline MAP was ~7 mmHg higher than YS (92±1 vs. 85±1 mmHg, p<0.01), the increase in MAP during cooling was similar between groups, so that the ~7mmHg difference remained throughout cooling.
OS had a lower $M_{net}$ throughout the protocol ($p<0.05$ vs. YS; Figure 3.3A). The lack of significant difference towards the end of the protocol was likely due to reduced statistical power due to subject attrition, rather than a physiological difference. Heat loss by either water vapor diffusion through the skin ($E_{diff}$) or radiation and convection ($R+C$) were not different between age groups (age effect $p=0.82$ and $p=0.37$ for $E_{diff}$ and $(R+C)$, respectively). There were no age differences for HD or predicted $\Delta T_{mid}$ (Figure 3.3B and Figure 3.3C).

Baseline $I_t$ was 0.062±0.002 and 0.063±0.002 °C·m²·W⁻¹ and peak calculated values were 0.092±0.003 and 0.094±0.002 °C·m²·W⁻¹ for YS and OS, respectively ($p=0.95$ for age effect). Thermal sensation did not differ between groups ($p=0.26$), with both groups rating baseline as “comfortable” and reaching “very cold” by cold exposure termination.

Discussion

The purpose of this study was to investigate the mechanisms underlying age-related differences in the defense of $T_c$ during mild passive cooling in a large cohort of young and older subjects. An additional purpose was to extend the ‘mid-region’ temperature concept to older subjects and to mild cold stress. Two subject groups, well matched for relevant anthropometric characteristics but differing in age by almost 50 years, were compared. The principle finding of this study was that OS failed to defend $T_{es}$ during even a mild cold transient. However, a biophysics analysis of the data did not reveal any age-associated differences. Heat production, while lower in the older subjects
during cooling, was also lower at baseline. Heat loss was similar between age groups, even though the older subjects demonstrated an attenuated vasoconstrictor response. The predicted change in mid-region temperature did not help explain the decrease in esophageal temperature in spite of equal heat loss and heat production. However, it has been reported by others (113; 129) that $\Delta T_c$ and HD show a poor relationship to one another. It is only when the rate of change of HD is relatively slow (i.e. during heat balance) that these variables correspond well. Additionally, numerous studies have documented a paradoxical increase in $T_c$ during the first ~30 min of cold exposure, when HD is increasing rapidly.

Examination of the weighting coefficients for core, mid and skin regions may provide an explanation for the lack of a difference in mid-region temperature between groups. Recalling that the relative mass of the mid region is almost 5 times as large as the core region (0.779 vs. 0.159), 1/5th of the change in $T_{es}$ is all that would be required in the mid-region. Considering that the $T_{es}$ difference between YS and OS was ~0.35°C, the difference in predicted $\Delta T_{mid}$ between groups would only be ~0.07°C. We believe that this difference is statistically undetectable, even in a large subject population. Accurate prediction of $\Delta T_{mid}$ may require a relatively large change in $T_{es}$ and empirical measurements of $T_{mid}$ are needed to validate the model. Additionally, as the weighting coefficients were derived from young subjects’ data, different coefficients may be required in older subjects.

Previous studies showing similar decrements in $T_c$ employed more extreme cold stress than in the present study, such as cold air exposure ranging from 5-10°C (13; 30; 64; 75; 133; 134). Furthermore, exposure to these conditions was usually sudden, i.e. the
subject was rapidly introduced to the experimental conditions. Two limitations arise from previous experiment designs: the cold stress has limited application to the conditions normally experienced by adults during everyday living, and the temperature at which groups begin to differ in their responses is unknown. By utilizing a milder cold stress that incorporated a gradual transition from thermoneutral to cool conditions, we attempted to overcome these limitations. When $T_{db}$ was 23.3°C, ~3°C lower than thermoneutral baseline conditions, the OS’ $T_{es}$ was significantly lower than that of the YS, and OS had already begun to show an attenuated cutaneous vasoconstrictor response. These findings indicate that a mild cold stress can elicit an attenuated thermoregulatory response and failure to defend $T_{es}$ in OS. The magnitude of the difference between subject groups continued to increase as $T_{db}$ decreased further.

An attenuated vasoconstrictor response to cold in an aged population has been well documented, despite differences in the cold stimulus and methodology employed (13; 37; 75; 78; 108; 122; 123; 133). Kenney and Armstrong (75), using venous occlusion plethysmography as an index of SkBF, were the first to control for confounding anthropometric characteristics that could affect thermoregulatory responses. Recent research indicates that reflex vasoconstriction is mediated by norepinephrine (NE) and an unknown co-transmitter (115; 123) in young subjects. Our laboratory has recently demonstrated that a loss of co-transmission (123) and decreased sensitivity to NE (122) both contribute to the attenuated vasoconstrictor response in aged healthy human subjects. When the vasoconstrictor effects of NE were blocked, young subjects retained ~40% of their vasoconstrictor capacity, while vasoconstriction was abolished in older subjects, indicating loss of functional co-transmission in these subjects (123).
Administration of exogenous NE revealed blunted vasoconstriction in older subjects, indicating that decreased sensitivity to NE contributes to these subjects’ attenuated vasoconstrictor response (122). However, local cooling responses are maintained in aged subjects (121), suggesting that the attenuated vasoconstrictor response in our subject population is due to reflex rather than local effects.

A failure of older subjects to increase metabolic rate to the same extent as young subjects during a cold stress has been known for many years (64), however most studies have used a severe cold stress to induce shivering. The present investigation differs in that the exposure was terminated when shivering began; therefore our data represent non-shivering conditions throughout the exposure. An increase in $M_{net}$ was not expected, as non-shivering thermogenesis contributes little, if at all, to heat production during cold stress in adult humans (29). Despite the fact that our subject groups were matched for SMM, baseline $M_{net}$ was lower in the older subjects and remained so throughout the experiment. There were no differences for plasma thyroxine or triiodothyronine in our subjects, suggesting that other factors may mediate the difference in $M_{net}$. Lean body mass (LBM) has been reported to account for over half of the variability in metabolic rate (141), while the factors contributing to the remaining variability have yet to be elucidated. Proposed mechanisms include lower fat oxidation, decrease skeletal muscle protein turnover and lower $\text{Na}^+\text{-K}^+$ ATPase activity (141), which may contribute to the difference in resting metabolic rate between young and older subjects. Our $I_t$ results support those of Budd and colleagues (13) who reported no significant relationship between age and $I_t$ in subjects ranging from 26-52 years old. Recalling that $I_t = (T_{es} - T_{sk})/(M_{net} - S)$, age-related differences in any of these variables would determine
differences in tissue insulation. Our findings indicate that the lower $T_{es}$ and $M_{net}$ offset each other, resulting in no age-related differences for $I_t$. The influence of reduced LBM on $I_t$ within an aged population warrants further attention (76; 130).

Simultaneous measurement of $T_c$, $M_{net}$, and SkBF in young and older subjects has been reported in only 4 studies (37; 133-135). Wagner and colleagues (135) did not show any difference in limb blood flow, $M_{net}$ or $T_c$ between young (20-29 yrs) and middle aged (46-67 yrs) men. In a later study, Wagner and Horvath indicated that older subjects failed to maintain $T_c$, but did not demonstrate any age-related attenuation in cutaneous blood flow during the cold stress (133; 134). However, it should be noted that the subject groups in that study differed significantly with respect to body fat, leading the authors to conclude that the changes in $T_c$ were due to body fat differences. Using a cold saline infusion model, Frank and colleagues (37) reported decreased fingertip blood flow when assessed via laser-Doppler flowmetry, an attenuated metabolic response, and a greater drop in tympanic temperature during the cold challenge in older subjects. Cold saline infusion creates a condition in which the core is cooled faster than the skin, which is opposite of the normal physiological response to cold, limiting the generalizability of these results. The present study appears to be the first to simultaneously measure $T_c$, $M_{net}$, and SkBF during environmental cooling in young and older subjects matched for relevant anthropometric characteristics.

During exposure to cold, the stimulus for shivering is usually peripheral ($T_{sk}$) rather than central ($T_c$), although shivering has been induced during thermoneutral $T_{sk}$ conditions (14) and direct application of cold to the hypothalamus in experimental animals (63). It should be noted that the present study was not designed a priori to
elucidate time to shivering differences. One of our primary goals was to model the vasoconstrictor response to mild cooling; therefore we choose shivering as our end-point as it is a good indicator that maximal vasoconstriction had been achieved. Inspection of individual CVC curves for each subject indicated that a nadir and plateau was reached prior to the onset of shivering. Therefore we were liberal in our assessment that shivering had begun, and EMG analysis may have indicated a longer time to shivering. Also, while we observed shivering, there was no increase in metabolic rate, which has been used as an indicator that shivering began (77). Kenny and colleagues (77) reported a Tsk shivering threshold ~0.4°C lower than in the present investigation, using a similar cold transient protocol in young subjects. We are unaware of any rigorously controlled studies examining the Tsk threshold for shivering in young vs. older subjects.

We chose not to sub-group the age groups by sex, as others have noted that apparent sex differences during cold stress are actually due to body composition differences (16; 90; 128; 134), which were not present in our study population. Additionally, sex was not a predictor of the change in Tcs. The quantity and distribution of body fat is related to the metabolic response and Ic (16), and to changes in Tsk and Tcs (134). However, other anthropometric characteristics may be relevant, as A47 mass\(^{-1}\) may account for observed sex differences (90; 128). McArdle and colleagues concluded that higher %fat in the women did not appear to provide any protective benefit for maintaining Tc and differences in LBM may also account for some of the gender difference (90).

In summary, older men and women, when exposed to mild cold transients, demonstrated an attenuated vasoconstrictor response and failed to maintain Tcs. These
results appear related to chronological age \textit{per se}, as the groups were well matched for relevant anthropometric characteristics. A biophysical analysis of heat balance failed to yield an explanation for the failure of older subjects to defend $T_{es}$ during mild cold stress.
Table 3.1

Table 3.1: Subject Characteristics. Values are mean ± SE (range). Ad, body surface area; A_d·mass⁻², body surface area to mass ratio; c_b, specific heat of the body; Skinfolds, sum of 7 skinfolds; ASMM, appendicular skeletal muscle mass; TSH, thyroid stimulating hormone; T3, triiodothyronine; T4, thyroxine

<table>
<thead>
<tr>
<th>Variable</th>
<th>Young (N=36)</th>
<th>Older (N=46)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, yr</td>
<td>22±1 (18-30)</td>
<td>71±1 (65-89)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Height, m</td>
<td>1.72±0.02 (1.55-1.99)</td>
<td>1.69±0.01 (1.56-1.89)</td>
<td>.22</td>
</tr>
<tr>
<td>Weight, kg</td>
<td>66.9±1.7 (50-91)</td>
<td>69.2±1.8 (46-99)</td>
<td>.36</td>
</tr>
<tr>
<td>A_d, m²</td>
<td>1.78±0.03 (1.51-2.18)</td>
<td>1.79±0.03 (1.43-2.22)</td>
<td>.87</td>
</tr>
<tr>
<td>A_d·mass⁻¹, cm²·kg⁻¹·10⁻²</td>
<td>2.69±0.03 (2.35-3.06)</td>
<td>2.62±0.03 (2.24-3.13)</td>
<td>.14</td>
</tr>
<tr>
<td>%fat</td>
<td>24.2±1.2 (11.7-37.7)</td>
<td>26.9±1.0 (13.8-43.8)</td>
<td>.09</td>
</tr>
<tr>
<td>c_b, W·h·°C⁻¹·kg⁻¹</td>
<td>0.936±.004 (.890-.980)</td>
<td>0.929±.003 (.877-.970)</td>
<td>.11</td>
</tr>
<tr>
<td>Skinfolds, mm</td>
<td>126±6 (56-209)</td>
<td>124±4 (69-199)</td>
<td>.79</td>
</tr>
<tr>
<td>ASMM, kg·m²</td>
<td>7.01±0.20 (5.00-9.42)</td>
<td>6.90±0.17 (5.05-9.36)</td>
<td>.67</td>
</tr>
<tr>
<td>TSH, mU/L</td>
<td>1.71±0.14 (.50-4.13)</td>
<td>2.97±0.30 (.08-8.56)</td>
<td>.01</td>
</tr>
<tr>
<td>T3, ng/dL</td>
<td>120±5 (74-166)</td>
<td>112±3 (83-149)</td>
<td>.16</td>
</tr>
<tr>
<td>T4, ug/dL</td>
<td>6.9±0.3 (4.7-10.3)</td>
<td>6.5±0.3 (2.3-13.7)</td>
<td>.35</td>
</tr>
</tbody>
</table>
Figure 3.1: Additional X axes indicate number of young and older subjects remaining at each time point. A: Chamber dry-bulb temperature. Main effect for age p=0.58. B: Esophageal temperature. OS had a lower T<sub>es</sub> compared to baseline at all time points from 25 min onward, while YS had an elevated T<sub>es</sub> from 45-85 min, † p<0.01. T<sub>es</sub> was different between groups at all time points from 25 min onward, * p<0.01. C: Mean skin temperature. Main effect for age p=0.34.
Figure 3.2: Additional X axes indicate number of young and older subjects remaining at each time point. A. CVC, units. OS had higher CVC at all time points compared to OS, p<0.01. B. ΔCVC%base. Both groups vasoconstricted significantly compared to baseline, † p<0.001. OS demonstrated an attenuated vasoconstrictor response compared to Y from 35 min onward, * p<0.01 vs YS. C. FVC, units. Both groups reduced FVC compared to baseline (p<0.001 for time effect) but there was no effect of age (p=0.25). There was a trend (p=0.06) towards a higher baseline in YS.
Figure 3.3: Additional X axes indicate number of young and older subjects remaining at each time point. A. Net metabolic rate. There was no time effect for either group, while OS had a lower $M_{net}$ than YS at all time points except 65, 85, 95, and 105 min, * $p<0.05$. B. Heat debt. Main effect for age $p=0.21$; heat debt increased significantly throughout the protocol, $p<0.01$. C. Predicted change in mid-region temperature. Main effect for age $p=0.51$; heat debt increased significantly throughout the protocol, $p<0.01$. See Methods for calculations.
Chapter 4

RESPONSES TO MILD COLD STRESS ARE PREDICTED BY DIFFERENT INDIVIDUAL CHARACTERISTICS IN YOUNG AND OLDER SUBJECTS

Introduction

Epidemiological evidence suggests that older individuals are more susceptible to hypothermia than young individuals, with >50% of deaths due to hypothermia occurring in those aged >65 yrs, an age cohort comprising only ~12% of the US population (20). Cross-sectional studies confirm that aged individuals have a relative inability to maintain core temperature ($T_c$) during cold stress (22; 36; 65). However, one difficulty in interpreting these studies is the confounding influence of body size and composition differences within an age cohort and between age cohorts. Most previous research concerning the thermoregulatory responses due to body composition differences have used the approach of testing two distinct subject populations, matched for all but one relevant individual characteristic, such as muscle mass (47; 130). While this experimental design is useful, it is also flawed in that subjects may also differ in other characteristics, such as surface area to mass ratio ($A_d$·mass$^{-1}$), that may be relevant for cold stress responses (128). Efforts to match young and older subject groups for body composition fail to incorporate changes intrinsic to the aging process (58). An alternative approach is the use of multiple regression analysis, in which a large heterogeneous subject population which varies in several anthropometric parameters is tested, and the relative contribution of individual and combined predictors of $T_c$ are determined (57-60).
Previous studies have shown that $T_c$ may be maintained, decreased or even slightly increased in response to cold stress (24; 128; 134). Young subjects tend to adequately defend $T_c$ during mild (24) but not more severe (128) cold stress. We recently reported that older subjects fail to adequately defend $T_c$ during mild cold stress while young subjects’ $T_c$ actually increased slightly (24). The increase in $T_c$ in the absence of shivering during cold stress is likely due to peripheral vasoconstriction and redistribution of body heat to the core. Inter-individual variability in the $T_c$ response is likely due to body composition characteristics (130; 134) as well as age.

During resting cold stress, there are several plausible variables that may contribute to the $T_c$ response. For example, muscle mass accounts for a large portion of tissue insulation ($I_t$) (26) and may therefore contribute to the defense of $T_c$ (47; 130). The term ‘sarcopenia’ is applied to those individuals whose muscle mass, often quantified as appendicular skeletal muscle mass (ASMM), is $>2$ SD below a reference population mean, and the prevalence of sarcopenia increases with age (6). The development of sarcopenia with advancing age may predispose an individual to a cold-induced $T_c$ drop due to reduced $I_t$ (76), though supporting data are lacking. Similarly, the relation between adiposity and thermoregulation is well known, as individuals with greater subcutaneous fat have a higher $T_c$ (5) and lower metabolic (16) response to cold stress than individuals with relatively less subcutaneous fat, though others have suggested that leaner individuals may compensate with a greater metabolic rate in order to maintain $T_c$ (46). Due to the redistribution of body fat with aging (111; 149), whether % fat or subcutaneous adiposity explains a greater portion of the $T_c$ or $I_t$ variance in older subjects is unknown. While a few studies have noted sex differences in responses to cold stress
(134), these are likely due to sex-related body composition differences (16; 90; 128).

Finally, the thyroid hormones triiodothyronine (T3) and thyronine (T4) may also influence the cold stress response through their effects on metabolic rate (112). Mean thyroid hormone concentrations tend to be similar in young and older subjects, although hypothyroidism prevalence increases with aging (11; 94). When considering the literature regarding cold stress, it is important to note that cold air and cold water impose different physiological stresses, but limited literature in this area precludes limiting the discussion to only cold air exposure studies.

In addition to the normal inter-individual variations in muscle mass and adiposity within an age cohort, there are well known longitudinal changes in muscle and fat mass that occur with aging. The prevalence of obesity increases with aging (21) and an increase in adiposity may provide a protective effect that offsets a decrease in muscle mass. Limited longitudinal data suggest that individuals lose muscle mass and gain fat mass at similar rates, so that body weight remains stable over time (43). The relative importance of these changes on the response to cold stress is unknown.

The purpose of the present investigation was to determine the individual characteristics that influence the response to cold stress, as assessed by esophageal temperature (T_{es}), in heterogeneous young and older subject groups and to determine the relative contributions of the predictors to the response. The individual predictors considered included sex, age in years, weight, ASMM, A_d, A_d·mass^{-1}, sum of skinfolds, %fat, and serum [T3] and [T4]. Because T_c is one of the variables used to calculate I_c, it may be inappropriate to analyze the contribution of the latter on the former. Therefore, an additional purpose was to separately determine the individual characteristics that
influence \( I_t \) and determine the relative contributions of these characteristics. We hypothesized that the individual predictors of \( T_{es} \) and \( I_t \) would differ between age groups, as would the relative contributions of predictors to the explained variance.

### Methods

#### Subjects

Forty-two young (18-30 yr; 21 men, 21 women) and 46 older (65-89 yr; 24 men, 22 women) subjects participated in the study after verbal and written informed consent were obtained. The protocol was approved in advance by The Pennsylvania State University Institutional Review Board. All subjects were normotensive, non-smokers, and not taking any medications that might alter the cardiovascular or thermoregulatory responses to cooling. Young women were eumenorrheic, not taking oral contraceptives, and were tested during days 2-10 of the menstrual cycle. All older women were postmenopausal and not taking hormone replacement therapy. All subjects abstained from alcohol and caffeine for 12 h before reporting to the laboratory on the day of the experiment.

*Preliminary testing.* Subjects underwent a standardized medical screening, including a resting electrocardiogram, blood chemistry analysis (CHEM-24, complete blood count, and thyroid hormone analysis, Quest Diagnostics), and a physical exam. Body composition (%fat) was determined via dual-energy X-ray absorptiometry (DXA; model QDR 4500W, Hologic, Waltham, MA). Appendicular skeletal muscle mass
(ASMM) was taken as the sum of the arm and leg lean masses determined via DXA and expressed relative to height in meters$^2$ (kg·m$^{-2}$) as proposed by Baumgartner (6) in order to eliminate differences in muscle mass due to height differences. Skinfold thickness was measured at the chest, mid-axillary, tricep, subscapular, abdominal, supra-iliac and mid-thigh sites by the same investigator as an estimate of subcutaneous adiposity. Body surface area ($A_d$) was estimated according to Dubois and Dubois (25) and the $A_d$·mass$^{-1}$ ratio was calculated.

**Experimental Protocol.** Subjects arrived at the laboratory between 0800 and 0900 and a copper-constantan thermocouple sealed in a pediatric feeding tube was inserted through the nares a distance equal to ¼ of the subjects standing height for measurement of $T_{es}$ (139). The subject then entered the environmental chamber (dry-bulb temperature ($T_{db}$) = 26.5°C) and was positioned in a semi-recumbent position, dressed only in shorts (men) or shorts and a sports bra (women). Baseline $T_{db}$ was maintained for 20 min; $T_{db}$ was then decreased at a rate of 0.2°C·min$^{-1}$ for 20 min and 0.05°C·min$^{-1}$ thereafter. The protocol was terminated when visible, sustained shivering was observed by the investigators and/or reported by the subject. Temperature data were recorded and stored as 1-min averages using computer software (LabView) and a data-acquisition system (National Instruments, Austin, TX). Tissue insulation ($°C·m^2·W^{-1}$) was calculated as $(T_{es}-T_{sk})/(M_{net}-S)$, described previously (132), where $T_{sk}$ is mean weighted skin temperature ($°C$), $M_{net}$ (W·m$^{-2}$) is metabolic rate corrected for respiratory heat losses and $S$ (W·m$^{-2}$) is heat storage, which is typically negative during cold exposure.
Statistics

Data were analyzed using Student’s t-test for subject characteristics. Considering that the time to shivering varied greatly for each age group, $T_{es}$ and $I_t$ at 60 min were used as the response variables. This approach standardized the exposure time and conditions, avoiding the difficulty of varying time and environmental conditions had data just prior to shivering onset been used, and is consistent with the methodology of previous thermoregulation studies using the multiple regression technique described below (57-60). In order to determine the relative influence of subject characteristics, multiple regression analysis was performed (Minitab statistical software, version 14, State College, PA) in an interactive manner (57-60). All regression analyses were conducted separately for each age group. The first step was to determine which individual predictors correlated with $T_{es}$ or $I_t$ at 60 min. The following individual predictors were considered: sex, age in years, weight, ASMM, $A_d$, $A_d/\text{mass}^{-1}$, sum of skinfolds, %fat, and serum [T3] and [T4]. The predictor with the highest Pearson correlation coefficient was introduced into the regression equation first and the residual variance was calculated and saved. Next, the remaining predictors were correlated with the residual variance of the regression equation and the predictor with the highest Pearson correlation coefficient was regressed against the residual variance. This process was repeated until no significant predictors remained. In effect, a forward stepwise regression analysis was conducted manually, which gave the authors control over the entry of a given predictor into the equation, based on statistical and physiological relevance and independence from other predictors. This process lead to one regression equation for each age group, but there was more than one combination of predictors resulting in
similar explanatory power and these alternatives were explored. Normal probability plots
and residual vs. fitted value plots were obtained for each regression equation to assess
normality of the data and a variance inflation factor (VIF) statistic was calculated to test
for colinearity among the predictors. If VIF was >4.0 colinearity among predictors was
suspected (35). In order to further compare predictor variables between age groups, a
cross-validation of the predictors was performed. In this cross-validation, a combination
of significant predictors for one age group was applied to the other group, regardless of
whether the Pearson correlation coefficients were significant or not.

Once the regression models were obtained, standardized regression coefficients
were calculated. This enabled the comparison of the relative contribution of individual
predictors to the $r^2$ while controlling for the units of measurement and range of values for
each predictor. The value of the standardized regression coefficient represents the
change of the response variable expressed in units of its standard deviation when the
predictor variable changes by 1 standard deviation. The relative contribution of each
predictor to the variance explained was calculated as: $(|\text{standardized regression
coefficient for predictor}| / \Sigma |\text{all standardized regression coefficients in equation}|) * r^2$.
Absolute values were used, as standardized regression coefficients can be positive or
negative. Adjusted $r^2$ values are given, i.e. $r^2$ corrected for the number of observations
and the number of predictors in the analysis. Comparison of the magnitude of the
residual (unexplained) variance between groups was conducted using the $\chi^2$ test.
Results

Subject characteristics are presented in Table 4.1. Adiposity ranged from 10-44 \%fat, which includes the 10\textsuperscript{th}-90\textsuperscript{th} percentile of published normative values for both age groups (3). Seven young and 14 older subjects met the commonly accepted criteria for sarcopenia. There was a similarly large range for the calculated variables $A_d$ and $A_d\cdot\text{mass}^{-1}$. $[T3]$ and $[T4]$ were within the age- and sex-specific normal range for all subjects. There were no differences in baseline values for $T_{es}$ or $I_t$ ($T_{es}$: 37.05±0.04 vs. 36.95±0.04$^\circ$; $I_t$: 0.065±0.002 vs. 0.065±0.002 for young and older subjects, respectively; $p>0.05$ for both comparisons) and skewness and kurtosis scores indicated that the data were normally distributed; therefore, correction for baseline differences by analyzing the change in $T_{es}$ or $I_t$ was not considered necessary. Additionally, using the absolute values of the response variables was consistent with previous studies using similar multiple regression analysis designs (57-60). The $T_{db}$ at 60 min was virtually identical between groups (21.96±0.09 vs. 21.99±0.08$^\circ$C for young and older subjects, respectively; $p=0.77$), therefore the cold stress was similar for both groups. The young subjects slightly increased $T_{es}$ while older subjects failed to maintain $T_{es}$ (Figure 4.1) (24). For the developed regression equations, there was no colinearity among predictors, based on the VIF statistic.

The physiological responses of these subjects have been previously reported (24). Briefly, there were no differences for mean weighted skin temperature, calculated heat debt or heat storage, while there was an attenuated cutaneous vasoconstrictor response in the older subjects (53±4 vs. 42±3 $\Delta$CVC$_{\%\text{base}}$, i.e. cutaneous vascular conductance, determined via laser-Doppler flowmetry, expressed as percent change from baseline,
p<0.01). Metabolic rate was lower (37.6±0.9 vs. 41.0±1.2 W·m⁻², p<0.05) and mean arterial pressure was higher (96.0±1.2 vs. 86.9±1.6 mmHg, p<0.01) in older vs. young subjects. The correlation matrices for all of the possible predictors and the independent variables are shown in Table 4.2A (young subjects) and Table 4.2B (older subjects). Table 4.3 contains the standardized regression coefficients for all of the subsequent equations, with the equation numbers throughout the text corresponding to the equation numbers in Table 4.3.

**Esophageal temperature**

*Young subjects.* Based on the high observed correlation coefficient with $T_{es}$, the sum of skinfolds was entered into the regression equation first. Correlation with the residual variance of this regression equation indicated that $[T3]$ should be entered next. Once sum of skinfolds and $[T3]$ were entered into the regression equation, no other individual characteristic was correlated with the residual variance. Considering that %fat was also highly correlated with $T_{es}$, a second regression equation was developed starting with this predictor. $[T3]$ was again the 2nd predictor with no additional predictors correlated with the residual variance. Figure 4.2 presents the proportion of the variance explained by each term of *Eq. 1* (panel A) and of *Eq. 2* (panel B). Sum of skinfolds, %fat and $[T3]$ were each positively associated with $T_{es}$. A greater proportion of the variance could be accounted for in *Eq. 1* than *Eq. 2*, due to greater relative influence of sum of skinfolds than %fat.

*Older subjects.* %fat, ASMM, and sex were all similarly correlated with $T_{es}$ therefore 3 regression equations were developed, starting with each of these predictors. After %fat was included in the equation, $A_d$·mass⁻¹ was correlated with the residual
variance. After an equation was started with either ASMM or sex, no remaining predictor was correlated with the residual variance. Figure 4.2, panels C-E show the explained variance for the resulting equations. The residual variance was larger than in the young subjects ($\chi^2 = 5.78, p<0.05$) and ASMM was negatively associated with $T_{es}$.

**Tissue insulation**

ASMM, sum of skinfolds, %fat, and age were the only predictors considered, as a theoretical basis relating other body composition characteristics to $I_t$ is lacking.

**Young subjects.** Based on the correlation coefficients, 2 regression equations were developed. When adiposity was expressed at %fat, muscle mass was not correlated with the residual variance. However, when ASMM was entered first, sum of skinfolds was correlated with the residual variance. The relative contribution to the $r^2$ of each predictor is shown in Figure 4.3, Panels A (Eq. 6) and B (Eq.7). The residual variance for each equation was greater than the residual variance for $T_{es}$, and muscle mass and %fat had similar relative contributions to the $r^2$ as sum of skinfolds alone.

**Older subjects.** ASMM and %fat were the predictors with the largest correlation coefficients and 2 equations were developed. When ASMM was entered into the equation first, the sum of skinfolds was correlated with the residual variance. Alternatively, when %fat was entered first ASMM had the highest correlation with the residual variance. Figure 4.3, Panels C (Eq. 8) and D (Eq.9), shows the relative contribution to the $r^2$ for each predictor. %fat accounted for a greater proportion of the residual variance than sum of skinfolds, and ASMM was negatively associated with $I_t$.

**Cross-validation of predictors**
The results of the cross-validation analysis are shown in Table 44. For $T_{es}$ in the young subjects, ASMM, $A_d \cdot \text{mass}^{-1}$, and sex were non-significant predictors while the relative importance of %fat was unchanged. The sum of skinfolds explained 67% (p<0.001) of the variance in young subjects but only 2% (p>0.05) in the older subjects and the contribution of $[T3]$ dropped from 19-24% (p<0.001) in young subjects to 3-7% (p>0.05) in older subjects. Due to similar original predictors, there was little difference in the cross-validation of $I_t$ predictors. An exception was ASMM, which when combined with %fat in young subjects was non-significant. The greater $r^2$ for $I_t$ ($\chi^2=20.49$, p<0.01) in the older subjects was due primarily to a greater contribution from ASMM.

Discussion

The major findings of the present study are 1) in young subjects, adiposity and $[T3]$ explain most of the variance in the $T_{es}$ response to mild cold exposure 2) in older subjects, either %fat and $A_d \cdot \text{mass}^{-1}$ or ASMM accounted for similar portions of the variability and 3) due to similar explained variance, sex is interchangeable with body composition characteristics in older subjects. While residual (unexplained) variance in $T_{es}$ was greater in older subjects (p<0.01), the residual variance of $I_t$ was greater in the young subjects. ASMM explained a significant portion of the variance in older but not young subjects, though unexpectedly this was a negative relationship.

Previous studies regarding the effects of body composition and/or aging on $T_c$ during cold exposure have either inadequately matched subject groups for relevant anthropometric characteristics (134) or failed in an attempt to match groups for all except one characteristic (128; 130). In contrast, in the present paper we have applied multiple
regression analysis to a large heterogeneous subject population that varied across several characteristics. The use of multiple regression analysis has been successfully employed to examine the relative influence of individual characteristics during heat stress (57-60); to our knowledge the present study is the first application of this technique to cold stress. It is important to point out that the purpose of this multiple regression analysis is not to attempt to globally predict $T_{es}$ or $I_t$ as there are a number of models, ranging from simple to complex, aimed at predicting thermoregulatory responses to cold stress. Rather, this study attempted to quantify the relative contribution of individual characteristics to determination of $T_{es}$ and $I_t$ and how these relationships differ between young and older subjects.

Adiposity had the largest contribution to the $r^2$ for $T_{es}$ prediction in the young subjects, with sum of skinfolds explaining 33% more of the variance than %fat as determined by DXA. Conversely, sum of skinfolds was not correlated with $T_{es}$ in older subjects while %fat was the best predictor. One possible explanation for this is the redistribution of body fat with aging. Cross-sectional studies of young and older subjects (111; 149) have demonstrated that total body and intra-abdominal fat increase with aging while subcutaneous fat decreases and total body mass tends to remain stable. Similar results have been reported in longitudinal studies (67) of elderly men and women. In the present study as a group the older subjects had similar mean sum of skinfolds but a higher mean %fat than the young subjects, which supports the notion of body fat redistribution. Additionally, analysis of limb vs. trunk fat mass from the DXA scans revealed that the older subjects had proportionally less limb fat than the young subjects (46.9±1.0% vs. 49.9±1.0%, p<0.05). Therefore, the lack of a significant correlation between $T_{es}$ and sum
of skinfolds in the older subjects was not surprising in light of this redistribution of body fat. These findings suggest that subcutaneous fat is more important than central or intra-abdominal fat during mild cold stress in older subjects and proportionately less subcutaneous fat may be a disadvantage in older subjects, considering that these subjects failed to defend $T_c$ (Figure 4.1).

Plasma [T3] explained a significant portion of the variance in young but not older subjects; however, possible reasons for this difference are unclear. Thyroid hormones stimulate obligatory thermogenesis, i.e. the heat production due to biological processes such as $\text{Na}^+\text{-K}^+$ ATPase activity, and are essential for facultative (non-shivering) thermogenesis in brown adipose tissue in non-human mammals (112). Most of the variability in basal metabolic rate can be explained by differences in lean body mass, but it has been suggested that thyroid hormones may explain some of the remaining variability (141). Data from animal studies suggest a vasodilatory role for thyroid hormones in the hyperthyroid state, possibly leading to increased heat loss due to greater blood flow. Therefore, in euthyroid individuals, such as those in the present study, the predominant effect of thyroid hormones appears to be heat production.

An unexpected finding was a significant negative relationship between $T_{es}$ and ASMM in older subjects and between $I_t$ and ASMM in young and older subjects. Ducharme and Tikuisis (26) demonstrated that muscle mass may account for up to 92% of tissue insulation in the forearm of young subjects and it has been hypothesized that loss of muscle mass with aging may lead to lower tissue insulation (76), with the assumption that lower tissue insulation would then lead to an impaired defense of $T_c$. Tissue insulation is the result of the passive effects of adipose and muscle tissues coupled
with the dynamic effects of skin and muscle blood flows (74). Either increased adiposity or muscle mass or decreased blood flow increases tissue insulation. However, Jequier et al. (74) proposed that markedly obese subjects have less non-fat (i.e. muscle) insulation that normal weight subjects and suggested that changes in blood flow may be the mediating factor.

In an effort to determine the role of blood flow on tissue insulation, forearm vascular conductance (FVC, ml·100ml⁻¹·min⁻¹·100mmHg⁻¹ determined via strain gauge plethysmography) data (24) were correlated with ASMM. There were significant correlations between FVC and ASMM for young and older subjects (r= 0.61 and 0.57, p<0.01 for young and older, respectively), suggesting that the increased Iᵢ expected due to larger muscle mass is more than offset by higher tissue perfusion, which decreases Iᵢ.

Similarly, Ducharme and Tikuisis (26) showed that during forearm immersion in water >30°C there was a linear relationship between thermal conductivity (the inverse of Iᵢ) and forearm blood flow, such that higher blood flow reduced Iᵢ. Due to colinearity among FVC, ASMM and adiposity, regression modeling of Iᵢ failed to yield a model incorporating all 3 parameters. Additionally, the relationship between tissue insulation and Tₑ is difficult to determine considering that Tₑ is one of the terms in the numerator of the equation to estimate tissue insulation.

Examination of the predictors included in each model and the relative contribution of each to the r² demonstrates the age-dependence of the predictors. The only predictor that was significant for all models (except Eqs. 4-5) was adiposity, the relative contribution of which ranged from 13-67% of the total variance. The residual (unexplained) variance of the Tₑ equations was considerably greater in the older subjects,
suggested greater variability in the responses of the older subjects. Our lab has previously documented greater variability in vasomotor responsiveness to exogenous norepinephrine infusion (122), which may be the result of differential aging, such that a given individual may show impaired physiological function at different chronological ages and at different rates. This phenomenon of differential aging occurs in the cardiovascular system (31) and in the thermoregulatory system as well. That the residual variance for \( I_t \) was greater in the young subjects argues against this conclusion; however, this is difficult to interpret due to a lower relative influence of ASMM.

Numerous studies have suggested a relationship between core cooling and \( A_d \cdot \text{mass}^{-1} \) (80; 90; 105) whereby a larger \( A_d \cdot \text{mass}^{-1} \) (i.e. a smaller size) leads to greater decreases in \( T_c \) during cold stress. Several studies reported that women having higher \( A_d \cdot \text{mass}^{-1} \) but similar adiposity cooled faster compared to men (80; 90). However, there was a strong inverse correlation between %fat and \( A_d \cdot \text{mass}^{-1} \) (\( r = -0.93 \) and -0.95 for men and women respectively) (90). A similar significant correlation was not evident in the present study. In contrast, others have suggested that \( A_d \cdot \text{mass}^{-1} \) has minimal effect on heat transfer in subjects matched for adiposity (130). Additionally, the inclusion of \( A_d \cdot \text{mass}^{-1} \) in models to predict the metabolic response during cold water immersion reduce model precision (126). In the present study \( A_d \cdot \text{mass}^{-1} \) contributed only to the explained variance in \( T_{es} \) in older subjects. Unexpectedly this was a positive relationship and the underlying mechanism for this relationship is not clear. In general, our results support the notion that \( A_d \cdot \text{mass}^{-1} \) has little individual relevance or sole predictive value during mild cold stress.
Sex showed the highest correlation with $T_{es}$ in the older subjects (Table 4.2).

Others have shown that sex differences during cold stress are due to body composition differences (24; 90; 128). After sex was included in the regression equation neither muscle mass nor adiposity were correlated with the residual variance. Conversely, when either ASMM or %fat was entered first, sex was not correlated with the residual variance. Our data support the conclusion that sex differences can be explained by differences in body composition. Therefore, the inclusion of both sexes in the present study allowed for a larger sample size and a greater range of individual characteristics. Fitness level was not considered as a potential predictor as other studies have argued against reduced aerobic capacity as a significant predictor of $T_c$ during resting cold stress (30) and there are no differences between young and older individuals for heat loss, heat production or tissue insulation (13; 24), although one study did suggest an effect of aerobic capacity on metabolic rate during cold stress (10).

In summary, we have shown through multiple regression analysis that the significant predictors as well as the relative contribution of those predictors to the $r^2$ varies by age group. Adiposity and [T3] explain most of the variance in the $T_{es}$ response to mild cold exposure in young subjects while in older subjects either %fat and $A_d \cdot \text{mass}^{-1}$ or ASMM accounted for similar portions of the variability. Due to similar explained variance, sex is interchangeable with body composition characteristics in older subjects. While residual (unexplained) variance in $T_{es}$ was greater in older subjects, the residual variance of $I_t$ was greater in the young subjects. ASMM explained a significant portion of the variance in older subjects though unexpectedly this was a negative relationship, possibly due to higher tissue perfusion and therefore greater heat conductance in those
with greater muscle mass, offsetting the increased passive insulation associated with
greater muscle mass. Other individual characteristics, such as body mass, BMI, and $A_d$,
were not significant predictors. Possibly due to differential aging, in which a given
individual may show impaired physiological function at different chronological ages and
at different rates, the residual (unexplained) variance for $T_{es}$ was considerably greater in
young vs. older subjects.
Table 4.1

Table 4.1: Subject Characteristics. Values are mean ± SE (range). $A_d$, body surface area; $A_d$·mass$^{-2}$, body surface area to mass ratio; Skinfolds, sum of 7 skinfolds; ASMM, appendicular skeletal muscle mass; TSH, thyroid stimulating hormone; T3, triiodothyronine; T4, thyroxine

<table>
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<th>Older (N=46)</th>
<th>P-value</th>
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<td>71±1 (65-89)</td>
<td>&lt;.001</td>
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<td>Height, m</td>
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<td>1.69±0.01 (1.56-1.89)</td>
<td>.13</td>
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<tr>
<td>Weight, kg</td>
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<td>69.2±1.8 (46-99)</td>
<td>.68</td>
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<tr>
<td>$A_d$, m$^2$</td>
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<td>1.79±0.03 (1.43-2.22)</td>
<td>.76</td>
</tr>
<tr>
<td>$A_d$·mass$^{-1}$, cm$^2$·kg$^{-1}$·10$^{-2}$</td>
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<td>2.62±0.03 (2.24-3.13)</td>
<td>.23</td>
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<tr>
<td>%fat</td>
<td>23.0±1.3 (9.5-37.7)</td>
<td>26.9±1.0 (13.8-43.8)</td>
<td>.02</td>
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<tr>
<td>Skinfolds, mm</td>
<td>124±7 (42-209)</td>
<td>124±4 (69-199)</td>
<td>.99</td>
</tr>
<tr>
<td>ASMM, kg·m$^2$</td>
<td>7.19±0.21 (5.00-9.48)</td>
<td>6.90±0.17 (5.05-9.36)</td>
<td>.68</td>
</tr>
<tr>
<td>T3, ng/dL</td>
<td>121±6 (74-166)</td>
<td>112±3 (83-149)</td>
<td>.10</td>
</tr>
<tr>
<td>T4, ug/dL</td>
<td>6.9±0.3 (4.7-10.3)</td>
<td>6.5±0.3 (2.3-13.7)</td>
<td>.47</td>
</tr>
</tbody>
</table>
Table 4.2

Table 4.2: Correlation matrices for young and older subjects. Values are Pearson \( r \) correlation coefficients. \( T_{es} \), esophageal temperature; \( I_t \), tissue insulation; \([T3]\) and \([T4]\), concentrations of T3 and T4, respectively. *p<0.05, **p<0.01.

<table>
<thead>
<tr>
<th></th>
<th>A Young subjects</th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>( T_{es} )</td>
<td>( I_t )</td>
<td>Years</td>
<td>Weight</td>
<td>ASMM</td>
<td>( A_d )</td>
<td>( A_d )-mass(^{-1} )</td>
<td>Skinfolds</td>
<td>%fat</td>
</tr>
<tr>
<td>( T_{es} )</td>
<td>1.00</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>( I_t )</td>
<td>0.43 **</td>
<td>1.00</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Years</td>
<td>0.27</td>
<td>0.11</td>
<td>1.00</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Weight</td>
<td>0.09</td>
<td>-0.11</td>
<td>0.30</td>
<td>1.00</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ASMM</td>
<td>-0.32 *</td>
<td>-0.49 **</td>
<td>0.16</td>
<td>0.75 **</td>
<td>1.00</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>( A_d )</td>
<td>0.03</td>
<td>-0.13</td>
<td>0.27</td>
<td>0.96 **</td>
<td>0.71 **</td>
<td>1.00</td>
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</tr>
<tr>
<td>( A_d )-mass(^{-1} )</td>
<td>-0.18</td>
<td>0.07</td>
<td>0.12</td>
<td>-0.90 **</td>
<td>-0.71 **</td>
<td>-0.77 **</td>
<td>1.00</td>
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<td>Skinfolds</td>
<td>0.75 **</td>
<td>0.43 **</td>
<td>0.14</td>
<td>0.16</td>
<td>-0.30</td>
<td>-0.01</td>
<td>-0.39 *</td>
<td>1.00</td>
<td></td>
</tr>
<tr>
<td>%fat</td>
<td>0.65 **</td>
<td>0.57 **</td>
<td>-0.02</td>
<td>-0.20</td>
<td>-0.62 **</td>
<td>-0.34 *</td>
<td>-0.05</td>
<td>0.86 **</td>
<td>1.00</td>
</tr>
<tr>
<td>([T3])</td>
<td>0.50 **</td>
<td>0.03</td>
<td>0.33</td>
<td>0.16</td>
<td>0.04</td>
<td>0.12</td>
<td>-0.20</td>
<td>0.33 *</td>
<td>0.13</td>
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<tr>
<td>([T4])</td>
<td>0.48 **</td>
<td>0.20</td>
<td>0.28</td>
<td>-0.34 *</td>
<td>-0.33 *</td>
<td>-0.34 *</td>
<td>0.24</td>
<td>0.29</td>
<td>0.26</td>
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<tr>
<td>Sex</td>
<td>0.22</td>
<td>0.56 **</td>
<td>-0.25</td>
<td>-0.65 **</td>
<td>-0.85 **</td>
<td>-0.69 **</td>
<td>0.54 **</td>
<td>0.34 *</td>
<td>0.68 **</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>B Older subjects</th>
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<th></th>
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<th></th>
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<tbody>
<tr>
<td></td>
<td>( T_{es} )</td>
<td>( I_t )</td>
<td>Years</td>
<td>Weight</td>
<td>ASMM</td>
<td>( A_d )</td>
<td>( A_d )-mass(^{-1} )</td>
<td>Skinfolds</td>
<td>%fat</td>
</tr>
<tr>
<td>( T_{es} )</td>
<td>1.00</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>( I_t )</td>
<td>0.39 **</td>
<td>1.00</td>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Years</td>
<td>-0.15</td>
<td>-0.16</td>
<td>1.00</td>
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</tr>
<tr>
<td>Weight</td>
<td>(-0.27)</td>
<td>(-0.36 ) *</td>
<td>(-0.21)</td>
<td>1.00</td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>BMI</td>
<td>-0.15</td>
<td>-0.17</td>
<td>-0.11</td>
<td>0.84 **</td>
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<td></td>
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</tr>
<tr>
<td>ASMM</td>
<td>-0.45 **</td>
<td>-0.67 **</td>
<td>-0.03</td>
<td>0.79 **</td>
<td>1.00</td>
<td></td>
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</tr>
<tr>
<td>( A_d )</td>
<td>-0.29 *</td>
<td>-0.40 **</td>
<td>-0.24</td>
<td>0.97 **</td>
<td>0.77 **</td>
<td>1.00</td>
<td></td>
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<tr>
<td>( A_d )-mass(^{-1} )</td>
<td>0.22</td>
<td>0.23</td>
<td>0.16</td>
<td>-0.94 **</td>
<td>-0.74 **</td>
<td>-0.86 **</td>
<td>1.00</td>
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<td></td>
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<tr>
<td>Skinfolds</td>
<td>0.13</td>
<td>0.31 *</td>
<td>-0.19</td>
<td>0.45 **</td>
<td>0.09</td>
<td>0.32 *</td>
<td>-0.60 **</td>
<td>1.00</td>
<td></td>
</tr>
<tr>
<td>%fat</td>
<td>0.45 **</td>
<td>0.68 **</td>
<td>-0.03</td>
<td>-0.11</td>
<td>-0.55 **</td>
<td>-0.23</td>
<td>-0.08</td>
<td>0.63 **</td>
<td>1.00</td>
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<tr>
<td>([T3])</td>
<td>-0.26</td>
<td>-0.20</td>
<td>0.23</td>
<td>0.25</td>
<td>0.31 *</td>
<td>0.23</td>
<td>-0.24</td>
<td>0.11</td>
<td>-0.15</td>
</tr>
<tr>
<td>([T4])</td>
<td>0.05</td>
<td>0.36 *</td>
<td>-0.21</td>
<td>-0.14</td>
<td>-0.21</td>
<td>-0.15</td>
<td>0.09</td>
<td>0.05</td>
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<td>Sex</td>
<td>0.48 **</td>
<td>0.70 **</td>
<td>0.05</td>
<td>-0.65 **</td>
<td>-0.83 **</td>
<td>-0.70 **</td>
<td>0.55 **</td>
<td>0.05</td>
<td>0.64 **</td>
</tr>
</tbody>
</table>
Table 4.3: Standardized regression coefficients. Table contents are standardized regression coefficients (percent of total variance explained by that predictor). The sum of the percentage of total explained variances equals the $r^2$.

<table>
<thead>
<tr>
<th>Equation #</th>
<th>Independent variable</th>
<th>Constant</th>
<th>ASMM</th>
<th>%fat</th>
<th>Skinfolds</th>
<th>[T3]</th>
<th>$A_d\cdot\text{mass}^{-1}$</th>
<th>Sex</th>
<th>$r^2$</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 (young)</td>
<td>$T_{es}$</td>
<td>36.21</td>
<td></td>
<td></td>
<td>.83 (67)</td>
<td>.23 (19)</td>
<td>.86</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2 (young)</td>
<td>$T_{es}$</td>
<td>36.03</td>
<td></td>
<td>.59 (34)</td>
<td></td>
<td>.42 (24)</td>
<td>.58</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3 (older)</td>
<td>$T_{es}$</td>
<td>35.20</td>
<td>.55 (22)</td>
<td></td>
<td>.36 (14)</td>
<td>.36</td>
<td>.36</td>
<td></td>
<td></td>
</tr>
<tr>
<td>4 (older)</td>
<td>$T_{es}$</td>
<td>37.76</td>
<td>-.53 (28)</td>
<td></td>
<td>.65 (41)</td>
<td>.65</td>
<td>.69</td>
<td></td>
<td>.67</td>
</tr>
<tr>
<td>5 (older)</td>
<td>$T_{es}$</td>
<td>36.75</td>
<td></td>
<td></td>
<td>.65 (41)</td>
<td>.65</td>
<td>.67</td>
<td></td>
<td></td>
</tr>
<tr>
<td>6 (young)</td>
<td>$I_t$</td>
<td>0.055</td>
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<td></td>
<td>.59 (35)</td>
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<td>.35</td>
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<tr>
<td>7 (young)</td>
<td>$I_t$</td>
<td>0.089</td>
<td>-.41 (17)</td>
<td></td>
<td>.30 (13)</td>
<td>.30</td>
<td>.30</td>
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<td></td>
</tr>
<tr>
<td>8 (older)</td>
<td>$I_t$</td>
<td>0.086</td>
<td>-.45 (33)</td>
<td></td>
<td>.50 (36)</td>
<td>.50</td>
<td>.69</td>
<td></td>
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</tr>
<tr>
<td>9 (older)</td>
<td>$I_t$</td>
<td>0.121</td>
<td>-.77 (46)</td>
<td></td>
<td>.35 (21)</td>
<td>.35</td>
<td>.67</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
### Table 4.4

**Table 4.4:** Cross-validation of models presented in Table 4.3. Significant predictors in the young subjects were used to develop regression equations and calculate standardized regression coefficients for the older subjects, and vice versa. Table contents are standardized regression coefficients (percent of total variance explained by that predictor). The sum of the percent of total explained variances equals the $r^2$. * $p>0.05$

<table>
<thead>
<tr>
<th>Equation #</th>
<th>Independent variable</th>
<th>Constant</th>
<th>ASMM</th>
<th>%fat</th>
<th>Skinfolds</th>
<th>$[T3]$</th>
<th>$A_d\cdot\text{mass}^{-1}$</th>
<th>Sex</th>
<th>$r^2$</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 (older)</td>
<td>$T_{es}$</td>
<td>37.33</td>
<td></td>
<td>.16 (2) *</td>
<td>-.28 (3) *</td>
<td>.05 *</td>
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</tr>
<tr>
<td>2 (older)</td>
<td>$T_{es}$</td>
<td>36.84</td>
<td>.42 (14)</td>
<td>.20 (7) *</td>
<td>.21</td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>3 (young)</td>
<td>$T_{es}$</td>
<td>37.13</td>
<td>.64 (34)</td>
<td>-.14 (7) *</td>
<td>.41</td>
<td></td>
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<td></td>
</tr>
<tr>
<td>4 (young)</td>
<td>$T_{es}$</td>
<td>37.61</td>
<td>-.32 (8) *</td>
<td>.08 *</td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>5 (young)</td>
<td>$T_{es}$</td>
<td>37.05</td>
<td></td>
<td>.22 (2) *</td>
<td>.02 *</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>6 (older)</td>
<td>$I_t$</td>
<td>0.043</td>
<td>.68 (45)</td>
<td></td>
<td></td>
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<tr>
<td>7 (older)</td>
<td>$I_t$</td>
<td>0.121</td>
<td>-.77 (46)</td>
<td>.35 (21)</td>
<td>.67</td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>8 (young)</td>
<td>$I_t$</td>
<td>0.076</td>
<td>-.23 (11) *</td>
<td>.43 (21)</td>
<td>.32</td>
<td></td>
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<td></td>
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</tr>
<tr>
<td>9 (young)</td>
<td>$I_t$</td>
<td>0.089</td>
<td>-.41 (17)</td>
<td>.30 (13)</td>
<td>.30</td>
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</tbody>
</table>
Figure 4.1: $T_{es}$ responses to mild cooling in young (●) and older (○) subjects. * p<0.01 vs. baseline, † p<0.01 vs. young subjects. Data are mean±S.E.
Figure 4.2: Results of multiple regression analysis for $T_{es}$ after 60 min of cold exposure. Panels A-B: Young subjects, equations 1-2. Panels C-E: Older subjects, equations 3-5. Each pie chart segment shows the relative importance of each predictor, as defined by its standardized regression coefficient, and the residual (unexplained) variance, expressed as percentage of the total variance. (+) positive correlation, (-) negative correlation.
Figure 4.3: Results of multiple regression analysis for I, after 60 min of cold exposure. Panels A-B: Young subjects, equations 6-7. Panels C-D: Older subjects, equations 8-9. See Figure 4.2 legend for explanation of pie charts.
Chapter 5

MODELING HUMAN CORE TEMPERATURE DURING A UNIQUE CROSS-DESERT EXPEDITION

Introduction

Numerous models of human thermoregulation exist to predict body core temperature ($T_c$) with an acceptable degree of accuracy. These models are useful for assessing the cumulative physiological strain of environmental and exercise stressors, for the prediction of water losses and subsequent fluid requirements, and when coupled with real-time measurement of environmental conditions and estimated metabolic heat production, for the prediction of impending heat casualties. Some models are described as rational, or bioengineering; familiar examples include the Pierce lab 2-node model (39) and the Stolwijk 25-node model (117). Rational models consist of a passive controlled system and an active controlling system. The passive system defines the geometry of the body, sub-dividing the body into several tissue compartments, the specific number varying among models, and calculates temperature distributions and heat transfer rates within the tissue compartments and between the body and the environment. The active system defines the physiological control mechanisms, such as sweating, shivering, and cutaneous vasoconstriction and vasodilation that attempt to control the rate of heat transfer within the passive system.

Development and validation of the active system control equations is conducted using existing laboratory data from multiple studies covering a wide range of
environmental and exercise intensity conditions; the cumulative sample size is often greater than 30 subjects. Validation studies are usually not more than 2 h in duration, conducted under tightly controlled conditions were $T_c$ can be measured. Rational models function in the time domain, in which incremental changes are algebraically summed over time. Minor errors in the calculation of these incremental changes may not be apparent in relatively short-term exposures but may be revealed in longer simulations, leading to less accurate predictions. With the development and validation (79; 97) of the ingestible core temperature telemetry pill ($T_{pill}$) and the availability of Global Positioning Satellite (GPS) receivers for the accurate calculation of speed, grade and altitude, field validation of these models has become possible, but are rare (147).

Data collected under field conditions will likely differ from laboratory data in several respects. 1) Due to time of day effects dry-bulb ($T_{db}$), wet-bulb ($T_{wb}$) and mean radiant temperatures (MRT) and relative humidity will fluctuate. Unless the field study is conducted under strictly controlled conditions, terrain conditions, grade, and movement speed may vary as well. 2) Estimated metabolic heat production (M) may vary between models due to different M prediction equations within each model (9; 28; 101). 3) The length of the exposure may be longer than the exposures used to validate the models. 4) The ability of the models to accurately predict $T_c$ in small sample sizes becomes relevant when a larger sample size is not possible, such as during individual athletic or occupational activities.

Recently, three accomplished ultra-endurance athletes embarked on a unique expedition in which they attempted to run across the entire Sahara Desert together, beginning in Saint-Louis, Senegal and finishing in Cairo, Egypt, approximately 90-100
days later, traveling ~80 km per day. These men have frequently either won or finished among the leaders in numerous desert races, including the Marathon des Sables, the Badwater Ultra-marathon, and the Gobi March. In spite of their previous experience and accomplishments, they recognized that they could benefit from expert advice regarding hydration and nutrition strategies and better knowledge of thermoregulatory processes during exercise in the heat if they were to be successful in their attempt. The present paper represents part of an advisory effort that was invited to conduct physiological testing on, and provide advice to, the runners. Consequently, we were invited to accompany the runners for several days at the start of their expedition, providing us with the opportunity to determine if existing models of human thermoregulation, developed and validated from large sample sizes under laboratory conditions, accurately predicts individual and group $T_c$ in a small subject sample during a unique field environment.

Therefore, the purpose of the present study was to collect the environmental and physiological data necessary for input into three models of thermoregulation, including two which were recently developed (34; 146) and that have not as yet been subjected to extensive validation. We hypothesized that due to the variability inherent to field studies, the root mean squared deviation (RMSD; a statistic describing the mean difference between predicted $T_c$ ($T_{pred}$) and $T_{pill}$) would be greater than during laboratory studies, though still within acceptable limits, even for 3 individuals. Additionally, we hypothesized that 1) different estimates of metabolic rate would yield similar $T_{pred}$ when input into the same model, and 2) predictive accuracy of the models would be greater during the first 2 h of the run than during the entire run.
Methods

Baseline Testing: Approximately 3 months prior to the expedition the runners visited the Gatorade Sports Science Institute (GSSI) for 2 days of consultation meetings and baseline testing. The experimental procedures were explained to the subjects and verbal and written informed consent was obtained. Height (m) was measured to the nearest 0.5 cm and body mass (kg) was measured to the nearest 0.1 kg. Body composition was estimated using the BodPod air displacement plethysmography system (Life Measurement, Inc, Concord, CA). Peak oxygen consumption (VO$_2$peak; MOXUS system, AEI Technologies, Pittsburgh, PA) was measured using a modified Balke protocol during which the subject self-selected speed and grade was increased 2% every 2 min. The test was terminated upon volitional exhaustion, and a valid VO$_2$peak was considered when a subject achieved commonly accepted criteria (3). On the following day, each subject ran for 2 h in the heat (45-47°C, 30-40% RH) at a self-selected speed, similar to the speed when they run in ultra-endurance races, in order to determine sweat rate and composition. During this test, oxygen consumption was measured periodically via collection in Douglas bags and oxygen consumption, carbon dioxide production and respiratory exchange ratio were subsequently calculated (S-3A/I and CD-3A analyzers, AEI Technologies, Pittsburgh, PA). Subject characteristics are presented in Table 5.1.

Field Observations: This was an observational study and no attempt was made to influence start or stop times of any run, stop and restart times within a given run, or movement speed or distance. The only exception was for occasional stops requested by other researchers accompanying the expedition. On day one, the runners traveled 44.1
km in 6 h 10 min, which after accounting for total stop time of 41 min averaged 8.0 km/h. Due to logistical considerations, difficulties crossing the Senegal/Mauritania border, and the runners desire to log significant distance this day, they did not start until after sundown and they continued until ~0220 h local time. Approximately 9 h after the conclusion of run 1 (NIGHT), the runners started run 2 (DAY) at 1120 h local time. Total run time was 7 h 50 min, ending at 1910 h, covering 38.3 km, and after accounting for 141 min of stop time, average run speed was 7.0 km/h. Stop time was greater for DAY due to requested stops by other researchers, to replenish fluid supplies and to eat, and an extended stop due to quadriceps muscle cramps in one runner. Clothing worn by the subjects during each run was recorded and any changes in clothing ensemble were noted. On each day the running surface was either asphalt or hard-packed dirt.

*Environmental Monitoring:* $T_{db}$, $T_{wb}$ and globe ($T_g$) temperatures were measured and % RH was calculated with a portable data-logging heat stress monitor (QuesTemp 34, Quest Technologies, Oconomowoc, WI) and air velocity ($V_{air}$), along with $T_{db}$ and % RH, were recorded with a handheld personal weather monitor (Kestral 4000 pocket weather tracker, Nielsen-Kellerman, Boothwyn, PA). Data was automatically recorded once per minute for both instruments. MRT was estimated using the following equation (48):

$$MRT = (1+0.222*V_{air}^{0.5})*(T_g-T_{db})+T_{db}$$

*Physiological measurements:* On the evening prior to the first run, each subject ingested a temperature telemetry capsule (CorTemp, HQ Inc, Palmetto, Fl) for measurement of core temperature (79; 97). Subsequently, the presence or absence of a $T_{pill}$ was determined whenever a subject had a bowel movement and a new $T_{pill}$ was
administered if necessary. During the run, subjects wore a Polar heart rate sensor and $T_{pill}$ and HR data were recorded by the CorTemp datalogger once per minute. Prior to each run, hydration status was estimated using morning body weight compared to the previous days body weight and urine specific gravity (USG), where USG>1.020 was considered hypohydrated (4; 85).

Movement speed. One of the subjects wore a GPS receiver (Magellan eXplorist 600, Thales Navigation, San Dimas, CA) continually. Data was downloaded daily and time and location data were converted to movement speed (Magellan MapSend Worldwide V1.30). The 3 runners remained together throughout each run, therefore the movement speed for one was assumed for all 3.

Prediction Models. SCENARIO is a rational model of human thermoregulation developed (81) and revised (82-84; 147) at the US Army Research Institute of Environmental Medicine (USARIEM). Another rational model developed at USARIEM is the Initial Capability Decision Aide (ICDA) (146), which is an abridged model incorporating components of the SCENARIO and Pierce models. The latest versions of the ICDA and SCENARIO models were run at USARIEM. A new rational model of human thermoregulation was developed by Fiala, consisting of 15 body segments, 7 possible tissue types per segment, and utilizing regression modeling to fine-tune the algorithms for sweating, shivering, vasoconstriction and vasodilation (33; 34). A version of this model written in Microsoft Excel was obtained from Dr. Fiala. Table 5.2 details the inputs required by each model. Each individual’s baseline $T_{pill}$ was input to the SCENARIO and ICDA models; the Fiala model does not have the option of overriding the default value of 36.84°C. Baseline $T_{sk}$ for ICDA was set to 33°C, which is similar to
the default values assumed by the SCENARIO and Fiala models. All environmental and metabolic data were supplied to each model as 5-min averages and outputs were requested at 5-min intervals.

Metabolic rate. The ICDA has an integrated equation developed by Berglund (9) for predicting metabolic rate in MET units from heart rate ratio (activity HR:resting HR) and T\text{db} as follows:

\[ \text{MET} = 0.68 + 4.69(\text{HRR}-1) - 0.052(\text{HRR}-1)(\text{T}_{\text{db}}-20). \]

SCENARIO has integrated equations in which metabolic rate is predicted from movement speed, grade, and load carriage (the Pandolf equation (101)):

\[ M(W) = 1.5W + 2.0(W+L)(L/W)^2 + \eta(W+L)(1.5V^2 + 0.35V*G) \]

Where W is body weight in kg, L is load carried, \( \eta \) is the terrain coefficient (1.2 for asphalt or hard-packed surfaces), V is walking speed and G is the fractional grade. This equation is valid for slow movement speeds (<2.2 m/s or 7.9 km/h) and an equation extending this to 3.2 m/s or 11.5 km/h was subsequently developed (28):

\[ M_r = M_w - 0.5(1-0.01L)(M_w-15L-850) \]

Where \( M_r \) is the running metabolic rate and \( M_w \) is the walking metabolic rate calculated by the Pandolf equation. Alternatively, metabolic rate in watts (W) can be directly input into the model by the user if determined by another method.

In the present study, SCENARIO simulations for each day and runner were conducted twice, once using the Pandolf equation (denoted as SCEN-P) and again using the METS predicted by ICDA (SCEN-I), in which METS were converted to W by the equation \( W = \text{METS} \times 58.2 \times A_d \), where 58.2 W·m\(^{-2}\)=1 MET (38) and \( A_d \) is the individuals Dubois body surface area (25). The Fiala model does not include a calculation of
metabolic rate and only requires input in METS. Therefore, 2 simulations using the Fiala model were run, one using METS predicted by ICDA (Fiala-I) and the other using Watts predicted by the Pandolf equation within SCENARIO (Fiala-P) and converted to METS, where \( \text{METS} = \text{Watts} \times \text{Ad}^{-1} \times 58.2^{-1} \).

**Statistics.** Haslam and Parsons proposed using the RMSD for comparison of \( T_{\text{pred}} \) vs. \( T_c \) (54). The RMSD is defined as follows:

\[
\text{RMSD} = \sqrt{\frac{1}{n} \sum_{i=1}^{n} d_i^2}
\]

Where \( d_i \) is the difference between measured and predicted temperature at each time point and \( n \) is the number of time points. This statistic enables comparison of predicted vs. observed data in the units of the variable of interest. The interpretation of this statistic is that a model’s goodness of fit is acceptable when the RMSD is less than the standard deviation (SD) of the measured data. We calculated the RMSD and the SD for the total time of each run, and in order to test our third hypothesis, for the first 2 h of each run.

**Results**

Complete \( T_{\text{pills}} \), HR, and environmental data were collected on 2 consecutive days. No replacement \( T_{\text{pills}} \) were administered within 2 hours of the start or during a given run. Average, minimal and maximal environmental conditions for each day are shown in Table 5.3. \( T_{\text{db}} \) was considerably higher and %RH lower on day 2 due to time of day effects. Sunset was at 1832 h on day 2, approximately 40 min before the conclusion of the run.
Individual and group absolute and delta $T_{\text{pill}}$ data for both days are shown in Figure 5.1. The $T_{\text{pill}}$ SD was 0.34 and 0.51°C for NIGHT and DAY, respectively. When the first 2 h period of each run was analyzed, the SD was marginally lower, 0.33 and 0.49°C. Urine specific gravity from the first morning void indicated that runners 2 and 3 on NIGHT and runner 3 on DAY were moderately hypohydrated (USG>1.020), otherwise the runners were euhydrated and SCENARIO was configured appropriately. Due to the runners’ fitness level and heat exposure in the days and weeks leading up to the expedition, all runners were considered fully heat acclimatized. The runners wore the same shorts and t-shirt combination each day and the default clothing insulation and moisture vapor permeability values for this clothing ensemble were used for ICDA and SCENARIO simulations. A clothing file for Fiala was configured using the same values as the other models; therefore there was no difference in clothing input between the three models.

RMSD values are shown in Table 5.4 along with the $T_{\text{pill}}$ SD for each day. The most accurate models, on both individual and group levels, were SCEN-P and SCEN-I at NIGHT and SCEN-P and ICDA during DAY. Model prediction differences for these models from $T_{\text{pill}}$ are shown in Figure 5.2 (NIGHT) and Figure 5.3 (DAY). During DAY, N=2 runners for ICDA, SCEN-I and Fiala-I due to poor heart rate data quality for one runner. All of the models performed better during NIGHT than DAY, i.e. in the absence of a solar heat load; however, none of the models RMSD was less than the SD of 0.34. When the first 2 h of NIGHT were analyzed, all of the models predictions improved except for SCEN-I, though the RMSD for all model simulations was still greater than the $T_{\text{pill}}$ SD. ICDA and SCEN-P had the lowest RMSD during DAY (0.70 and 0.66,
respectively), but these values were greater than the SD of 0.51. Analyzing the first 2 h of DAY, the RMSD for ICDA and SCEN-P increased (0.70 to 1.02 and 0.66 to 0.69, respectively), though SCEN-P was still the best model.

Comparison of metabolic rate estimation is presented in Figure 5.4A (NIGHT) and Figure 5.4B (DAY). Mean metabolic rate was 5.1 METS calculated by ICDA and 6.3 METS from SCENARIO (t-test p<0.01) during NIGHT and 4.1 and 4.2 METS, respectively, during DAY (p=0.66). There were greater oscillations in metabolic rate estimated by SCENARIO, causing the varying T_{pred}-T_{pill} difference in the plot of SCEN-P in Figure 5.2 and Figure 5.3 compared to the relatively stable T_{pred}-T_{pill} differences for SCEN-I in Figure 5.2 and for ICDA in Figure 5.3.

Discussion

Rational models of human thermoregulation, such as the SCENARIO, ICDA and Fiala models used in the present study, have been validated using laboratory data collected over relatively short durations. The present study represents the first evaluation of the ICDA and Fiala models using field data greater than 2 h in duration. SCENARIO has undergone limited field validation (147), during which US Marine officers conducted marksmanship training for ~2 h followed by a road march for ~30 min; this is the only previous evaluation of any of these models using field data. The data for the present study represents 2 bouts of intermittent moderate intensity exercise for 6 h during warm-humid nighttime conditions and for almost 8 h during hot-dry conditions. None of the model’s T_{pred} was within acceptable limits of agreement; however, all models except
SCEN-I during NIGHT and ICDA and SCEN-P during DAY yielded lower RMSD when only the first 2 h of the exposure was modeled. Model accuracy was relatively independent of the equation used to estimate metabolic heat production, as SCENARIO (which allows for the greatest degree of individualization) consistently produced lower RMSD values than Fiala, regardless of which estimate of metabolic heat production was used. The $T_{pred}$ RMSD of the ICDA model was greater than SCENARIO but less than Fiala, consistent with the hypothesis that greater individualization at input leads to more accurate $T_{pred}$.

The $T_{pill}$ SD in field studies is larger than those reported in laboratory studies. The $T_c$ data from the laboratory studies used in the validation of the SCENARIO (81), ICDA (146) and Fiala (34) models each had a SD<0.25°C; several of the data sets used in the validation of these models had sample sizes between 3 and 5. In contrast, in the present study the SD were 0.34 and 0.51°C for NIGHT and DAY, respectively, and others (147) reported a SD of 0.46°C during military field training in a sample size of 5. These findings suggest that there is greater individual $T_c$ variability during field studies that is not explained solely by the small sample size in the present study and it may be more difficult to accurately predict an individual’s $T_c$ outside of the laboratory.

The factors affecting the accuracy of a given model’s prediction can be categorized into 1) what data are requested/required for execution of the model and 2) how the model uses those data. Mean radiant temperature is required as an estimate of solar heat load and inaccurate estimation from $T_{db}$, $T_g$ and $V_{air}$ may be a source of error affecting the data supplied to the model during field studies. During laboratory exposures, MRT is usually assumed to equal $T_{db}$ and errors in MRT estimation does not
affect the outcome. In field studies, accurate estimation of MRT is critical for calculating heat loss or gain due to radiation and convection, in which MRT and $T_{db}$ are first used to calculate operative temperature ($T_o$):

$$T_o = \frac{(h_c * T_{db} + h_r * MRT)}{(h_c + h_r)}$$

where $h_c$ is the convective heat transfer coefficient and $h_r$ is the radiant heat transfer coefficient. Radiant and convective heat transfer ($R+C$) is then estimated by:

$$R+C = \frac{(T_{sk} - T_o)}{R_{clt}}$$

where $R_{clt}$ is the dry thermal resistance between the skin and the environment specific to the clothing ensemble.

The importance of accurately estimating MRT is evident when comparing NIGHT vs. DAY in the present study, in which there was full solar radiation during DAY and the model predictions were less accurate. Solar radiation during full sunlight has been estimated to add ~100 W·m$^{-2}$ of heat strain to the individual (12) that would need to be dissipated to the environment. Our finding of greater over-prediction of $T_c$ during DAY suggests that the MRT equation we used overestimated the actual solar radiation. We re-ran the SCENARIO simulations for DAY, identical to the original simulation in all respects except a different calculation of MRT was used (103). Average MRT for the entire run was 54.0°C using this equation, which was 7.3°C higher than the result from the original equation, and consequently model prediction was considerably worse, as the RMSD increased to 2.89 compared to 0.66 for the original simulation.

Each of the models used requires input of similar environmental data, but differ considerably in the subject data required (Table 5.2). ICDA allows for input of the subjects height, weight, and baseline $T_{sk}$ and $T_c$, while SCENARIO requires input of the
most comprehensive individual characteristics and indicators of physiological state. The input of acclimation status (none, partial or full) in SCENARIO reduces the baseline $T_c$ by 0.0, 0.25 or 0.50°C, respectively; however, providing the individual’s actual baseline $T_c$, if known, overrides this function. Additionally, the algorithm for sweating rate varies based on the individual’s hydration status, in which the $T_c$ threshold for sweating increases and the slope of the $T_c$: sweat rate relationship decreases with hypohydration (92). In earlier versions of SCENARIO, the algorithms for skin blood flow and sweat rate were modified to account for an individual’s fitness level (84), but these improvements are not present in the version (v1.0b3, 2003) of the model currently in use at USARIEM and employed in the present study, suggesting a possible avenue for future model improvement. This is supported by data demonstrating that an individual’s maximal oxygen consumption ($VO_{2max}$) explained 27-36% of the variability in $T_c$ between subjects exercising at the same absolute intensity in warm-humid and hot-dry conditions (57). Havenith’s individualized version of the Pierce 2-node model (61), which incorporates an increase in the slope of the $T_c$: sweat rate relationship and increased maximal skin blood flow with increasing fitness level, yielded a lower mean error between measured and predicted $T_c$ values, reinforcing the importance of $VO_{2max}$ on the heat stress response.

In contrast to ICDA and SCENARIO, the Fiala model assumes standard individual dimensions of 73.5 kg body weight, 1.72 m height, 1.86 m² $A_d$ and 14% body fat, and does not allow for any individualization of body characteristics or physiological state. As a method to test the importance of individualization, the SCENARIO model was re-run for DAY with runner anthropometric characteristics and physiological state
set to match those assumed by the Fiala model and the results compared with the original, individualized, SCENARIO simulation. The RMSD increased to 0.82, compared with 0.66 for the original SCENARIO simulation, demonstrating greater error when standard individual anthropometric characteristics are input. It should be noted that the Fiala model performed well when validated with laboratory data (34), in which the RMSD ranged from 0.07-0.45 under a variety of climatic and exercise conditions.

Differences in the algorithms that cumulatively estimate $T_c$ are apparent in the oscillations in $T_{\text{pred}}-T_{\text{pill}}$ in figures 2 and 3. Examination of Figure 5.4B indicates that the runners were resting at ~1530 hrs and again at ~1700 hrs, while Figure 5.3 at the same time points shows a rapid decrease in the $T_{\text{pred}}-T_{\text{pill}}$ difference, suggesting that the rate of cooling at rest is overestimated. Fiala reported that $T_{\text{pred}}$ in his model responded more quickly than actual $T_c$ changes when exercise stopped (34), which is supported by our data. SCENARIO incorporates an equation accounting for change of state lag time, irrespective of whether workload is increasing or decreasing. However, Givoni and Goldman’s empirical model of thermoregulation describes different time lags at the start and at the cessation of exercise (44), suggesting a possible area of improvement for other models. It is interesting to note that these oscillations in $T_{\text{pred}}-T_{\text{pill}}$ are less obvious when metabolic rate is estimated by ICDA, suggesting that metabolic rate is more closely related to heart rate than to movement speed. In addition to the likely over-estimation of metabolic rate contributing to the high $T_{\text{pred}}$, it is also possible that heat loss due to radiation, convection and evaporation may be underestimated. However, the present study does not allow us to determine if over-estimation of heat production, under-estimation of heat loss, or a combination thereof, results in the high $T_{\text{pred}}$. It should be
noted that in situations in which the prevention of heat casualties is of primary concern, as in military applications, over-estimation of $T_c$ may provide an acceptable margin of safety (17) and is preferable to under-estimation of $T_c$.

Rational models of thermoregulation operate in the time domain, in which incremental changes in $T_c$ are compiled over time. Our finding of a lower RMSD during the first 2 h of the exposure suggests that minor errors in the estimation of these incremental changes become more important during longer exposures. For example, consider the theoretical example of over-estimating the $T_c$ increment by only 0.003 °C·min$^{-1}$. At the end of a 6 h exposure this will lead to an over-prediction of $T_c$ by more than 1.0 °C and increase the RMSD. Model improvements that show only minor, seemingly undetectable reductions in $T_{\text{pred}} - T_{\text{pill}}$ during short duration exercise may result in dramatic improvements in model accuracy during longer duration exposures.

Using unique field data, we have shown that the SCENARIO, ICDA, and Fiala models of human thermoregulation do not predict $T_c$ as accurately as during shorter duration laboratory studies; this inaccuracy was greater during DAY compared to NIGHT. When only the first 2 h of each exposure was analyzed, the RMSD decreased in 7 out of 10 simulations. A greater degree of individualization within a model led to a lower RMSD compared to models with less individualization, as demonstrated with the SCENARIO model. Future improvements in model performance may be realized through greater individualization, especially concerning the effects of aerobic fitness.
Table 5.1

Table 5.1: Subject Characteristics. \( A_d \), Dubois body surface area; \( VO_{2\text{peak}} \), peak oxygen consumption.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Subject 1</th>
<th>Subject 2</th>
<th>Subject 3</th>
<th>Mean ± SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, yrs</td>
<td>43</td>
<td>37</td>
<td>30</td>
<td>36.7±6.5</td>
</tr>
<tr>
<td>Height, m</td>
<td>1.81</td>
<td>1.72</td>
<td>1.64</td>
<td>1.72±0.09</td>
</tr>
<tr>
<td>Weight, kg</td>
<td>79.4</td>
<td>69.0</td>
<td>57.8</td>
<td>68.7±10.8</td>
</tr>
<tr>
<td>( A_d ), m(^2)</td>
<td>1.99</td>
<td>1.81</td>
<td>1.62</td>
<td>1.81±0.19</td>
</tr>
<tr>
<td>( VO_{2\text{peak}} ), L/min</td>
<td>4.33</td>
<td>4.01</td>
<td>3.54</td>
<td>3.96±0.40</td>
</tr>
<tr>
<td>( VO_{2\text{peak}} ), mL/kg/min</td>
<td>54.5</td>
<td>58.1</td>
<td>61.4</td>
<td>58.0±3.5</td>
</tr>
<tr>
<td>Body fat, %</td>
<td>11.3</td>
<td>15.8</td>
<td>10.6</td>
<td>12.6±2.8</td>
</tr>
</tbody>
</table>
Table 5.2

Table 5.2: Inputs required by each model. Hydration status is either euhydrated, or moderate or severe dehydration. Acclimation status is full, partial, or none. ¹Watts calculated from speed, grade, load carriage (Pandolf 77, Epstein 87) input by user if determined by other means; ²No built-in equation, METS estimated by method of user’s choice; ³METS estimated from heart rate ratio and Tdb (Berglund 77).

<table>
<thead>
<tr>
<th>Variable</th>
<th>SCENARIO</th>
<th>Fiala</th>
<th>ICDA</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Individual</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Height</td>
<td>X</td>
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<td></td>
</tr>
<tr>
<td>Weight</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Body fat %</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline T&lt;sub&gt;c&lt;/sub&gt;</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline T&lt;sub&gt;sk&lt;/sub&gt;</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Resting HR</td>
<td></td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Hydration status</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Acclimation status</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Time of day</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Environment</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>T&lt;sub&gt;db&lt;/sub&gt;</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>MRT</td>
<td>X</td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>V&lt;sub&gt;air&lt;/sub&gt;</td>
<td>X</td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>RH, %</td>
<td>X</td>
<td></td>
<td>X</td>
</tr>
<tr>
<td><strong>Metabolism</strong></td>
<td>Watts&lt;sup&gt;1&lt;/sup&gt;</td>
<td>METS&lt;sup&gt;2&lt;/sup&gt;</td>
<td>METS&lt;sup&gt;3&lt;/sup&gt;</td>
</tr>
</tbody>
</table>
Table 5.3: Environmental Conditions. Data are mean (minimum- maximum). $T_{db}$, dry-bulb temperature; $T_{wb}$, wet-bulb temperature; $T_g$, globe temperature; MRT, mean radiant temperature; RH, relative humidity; $V_{air}$, air velocity

<table>
<thead>
<tr>
<th>Variable</th>
<th>NIGHT</th>
<th>DAY</th>
</tr>
</thead>
<tbody>
<tr>
<td>$T_{db}$ °C</td>
<td>24.7 (22.6-26.9)</td>
<td>37.8 (30.8-41.0)</td>
</tr>
<tr>
<td>$T_{wb}$ °C</td>
<td>20.8 (20.0-23.8)</td>
<td>21.5 (18.7-24.1)</td>
</tr>
<tr>
<td>$T_g$ °C</td>
<td>23.9 (22.1-26.0)</td>
<td>45.9 (28.7-54.6)</td>
</tr>
<tr>
<td>MRT, °C</td>
<td>23.8 (22.0-25.9)</td>
<td>46.7 (28.5-56.1)</td>
</tr>
<tr>
<td>RH, %</td>
<td>75 (57-89)</td>
<td>17 (11-31)</td>
</tr>
<tr>
<td>$V_{air}$ m/sec</td>
<td>2.0 (0.0-3.1)</td>
<td>1.4 (0.0-2.4)</td>
</tr>
</tbody>
</table>
Table 5.4

Table 5.4: Model comparison analysis results. Data are the root mean squared deviation, except for $T_{pill}$, which is the standard deviation of the measured $T_c$ values.

<table>
<thead>
<tr>
<th>Model</th>
<th>NIGHT</th>
<th>DAY</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Total time</td>
<td>1st 2 h</td>
</tr>
<tr>
<td>$T_{pill}$ (SD)</td>
<td>0.34</td>
<td>0.33</td>
</tr>
<tr>
<td>ICDA</td>
<td>0.64</td>
<td>0.49</td>
</tr>
<tr>
<td>SCEN-I</td>
<td>0.36</td>
<td>0.43</td>
</tr>
<tr>
<td>Fiala-I</td>
<td>0.91</td>
<td>0.69</td>
</tr>
<tr>
<td>SCEN-P</td>
<td>0.45</td>
<td>0.40</td>
</tr>
<tr>
<td>Fiala-P</td>
<td>1.65</td>
<td>0.91</td>
</tr>
</tbody>
</table>
Figure 5.1: Individual and group mean $T_{pill}$ data for NIGHT, panel A and DAY, panel B. Data are 5 min averages. Inset: individual and group $T_{pill}$ data expressed as change from baseline.
Figure 5.2: $T_{\text{pred}}-T_{\text{pill}}$ differences for SCEN-P and SCEN-I at NIGHT. Panels A, B, and C correspond to subjects 1-3 and panel D are the group means. Positive values indicate $T_{\text{pred}}>T_{\text{pill}}$. 
Figure 5.3: $T_{pred} - T_{pill}$ differences for SCEN-P and ICDA during DAY. Panels A, B, and C correspond to subjects 1-3 and panel D are the group means. Positive values indicate $T_{pred} > T_{pill}$. 
Figure 5.4: Comparison of metabolic rate estimation methods for NIGHT, panel A and DAY, panel B. Watts estimated by Pandolf equation converted to METS. See methods section for calculation details.
Chapter 6

CONCLUSIONS

The purposes of the studies comprising this dissertation were to 1) determine the influence of primary human aging in a relatively large subject population on the defense of core temperature ($T_c$) during a mild cold transient stress, 2) determine the individual characteristics that influence the $T_c$ and tissue insulation ($I_t$) responses to cold stress in heterogeneous young and older subject groups in order to determine the relative contributions of the predictors to the responses and 3) validate three rational models of thermoregulation during long duration exercise performed by 3 ultra-endurance athletes. The aim of this chapter is to summarize the results of these studies and to suggest features avenues of research.

Aging and Cold Stress

The principal finding of the study entitled “Impaired defense of core temperature in aged humans during mild cold stress” (Chapter 3) is that older subjects fail to maintain $T_c$ during mild cold stress, while young subjects maintain, and even slightly increase, $T_c$. The underlying mechanism(s) for this difference is difficult to determine, as neither group demonstrated a change in metabolic rate, although the older subjects had a lower $M$ at baseline and throughout the exposure. Older subjects demonstrated an attenuated vasoconstrictor (VC) response, but this did not result in increased skin temperature ($T_{sk}$) or increased dry heat loss. Additionally, calculation of the change in mid-region temperature ($\Delta T_{mid}$) region failed to provide an explanation for the decreased $T_c$ in older
subjects. This may have been due to the very small difference (<0.06°C) in \(T_{\text{mid}}\) between groups, which is not detectable physiologically or statistically. Direct measurement of \(T_{\text{mid}}\) has not been performed in young or older subjects and such measurement is needed to evaluate this hypothesis.

An analysis of the individual characteristics that influence the responses to mild cold stress (“Responses to mild cold stress are predicted by different individual characteristics in young and older subjects”; Chapter 4) led to the following conclusions 1) adiposity and [T3] explain 86% of the variability of the \(T_e\) response in young subjects while 2) in older subjects, either percent body fat and body surface area/mass (36%) or appendicular skeletal muscle mass (ASMM; 28%) explained the variability of the \(T_e\) response and 3) sex is interchangeable with body composition characteristics in older subjects, due to similar explained variability. The coefficient for ASMM was negative, that is, an increase in muscle mass resulted in lower \(T_e\) (older subjects only) and lower tissue insulation (young and older subjects). This finding is discordant with the literature, which suggests a protective effect of greater muscle mass during cold exposure (76; 130). However, forearm vascular conductance was greater in subjects with greater muscle mass, suggesting that the increased passive \(I_t\) provided by muscle was more than offset by greater perfusion of that muscle mass.

**Prediction Core Temperature during Exercise in the Heat**

We used data collected from 3 individuals performing long duration exercise in desert conditions to compare 3 rational models of human thermoregulation and found that
each over-predicted $T_c$ (“Modeling human core temperature during a unique cross-desert expedition”, Chapter 5). The magnitude of the over-prediction was greater during day time conditions, suggesting an over-estimation of the effects of solar radiation by all 3 models. The Fiala model, which does not allow for any individualization, resulted in the least accurate predicted $T_c$ ($T_{\text{pred}}$), while SCENARIO, which enables the greatest degree of individualization, was the most accurate, though the root mean squared deviation was still greater than the $T_{\text{pill}}$ standard deviation. The models were relatively insensitive to the method used to estimate metabolic heat production, though there were oscillations in $T_{\text{pred}}-T_c$ when $M$ was estimated via movement speed as opposed to heart rate and dry-bulb temperature. When the anthropometric characteristics assumed by the Fiala model were used as standardized input for the SCENARIO model and compared with the original output from SCENARIO, the RMSD increased from 0.66 to 0.82°C, illustrating the importance of individual anthropometric characteristics in obtaining accurate predictions from rational models of human thermoregulation.

**Future Research Directions**

Several avenues of research are suggested by the findings presented in this dissertation. There is a lack of empirical evidence demonstrating the expected loss of heat via radiation and convection due to attenuated vasoconstriction. We attempted to demonstrate this relation using estimated $R+C$ in Chapter 3 but were unable to demonstrate such an effect.
An alternative approach to better address this question may be to use the technique of Ferretti et al (32) to estimate conduction and convection from the skin during cold stress. Applying the calculations outlined in their paper (32) would enable direct calculation of convective heat transfer, rather than estimation, through the skin to compare young and older subjects. We hypothesize that any increase in convection in the older subjects would be due to attenuated vasoconstriction.

The direct measurement of $T_{\text{mid}}$ has not been successfully performed. Tikuisis has attempted to do so during severe cold stress causing vigorous shivering, but motion artifact introduced considerable noise in the temperature signal (P. Tikuisis, personal communication). In order to validate the 3 region model, direct measurements of $T_{\text{mid}}$ are needed. Additionally, due to attenuated cutaneous VC in older subjects, the temporal disconnect between stabilization of $T_c$ and heat balance (129) may be increased in older individuals. Such an increase in time for $T_c$ to stabilize may have implications for models of survival time during cold water immersion.

The results from the project applying models of human thermoregulation during heat stress lend themselves to several follow-up studies. Numerous equations exist to estimate mean radiant temperature (48; 103), however it is unknown which of these is most accurate when applied to models of human thermoregulation. An alternative approach is to reconsider the equal weighting coefficients for $T_{\text{db}}$ and MRT in the calculation of operative temperature.

The experimental conditions in chapter 5 extended the limits of models of thermoregulation in 3 ways, by introducing the effects of solar radiation, varying exercise intensity and extending the exposure duration. Due to the poor prediction of each of the
models utilized in this study, it is important to assess the effects of these variations individually. In order to examine the latter effect, tentative plans have been made using archival laboratory data at USARIEM to further validate the ICDA model.

Finally, a recommendation for those who may develop or revise prediction models in the future. In cases where several model improvements have been implemented at once (61; 83; 84; 147), it would be advisable to implement and evaluate the effects of each change or addition on an individual basis. As a result, only the changes that actually improved model performance could be included in the revised model.
Bibliography


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Appendix A

INFORMED CONSENTS

Informed consent for the aging and cold stress studies (Chapters 3 and 4):

INFORMED CONSENT FORM FOR CLINICAL RESEARCH STUDY
The Pennsylvania State University

Title of Project: Age and Control of Human Skin Blood Flow – (R2) Age and Lean Body Mass (IRB# 16376)

Principal Investigator: W. Larry Kenney, Ph.D.
Address: 102 Noll Laboratory
Phone: (814) 863-1672

Other Investigators: Jane Pierzga, M.S., Research Assistant
Lacy Holowatz, M.S., Doctoral Candidate
David DeGroot, M.S., Doctoral Candidate

This is to certify that I, __________________ have been given the following information with respect to my participation as a volunteer in a program of investigation under the supervision of Dr. W. Larry Kenney.

1. Purpose of the study: Past research has shown that my body’s protective response to cold stress lessens as I age. Also, as people age, their muscles often get smaller. Doctors call this low muscle mass “sarcopenia.” A smaller body mass may make it even more difficult for older people to maintain their body temperature in the cold. This study will compare younger and older people who have normal and low body mass. The study will explore whether some of these groups are better able to tolerate a cold stress than others.

2. Procedures: I may request a staff member of the same gender as myself to apply any probes or run any tests where I feel uncomfortable working with someone of the opposite sex.

Day 1: Blood Draw: I will not eat anything after midnight during the night before my exam. I report to the General Clinical Research Center (GCRC). When I arrive, the nurses will draw 15 ml (1 Tbsp) of blood from a vein in my arm. The medical staff gives me an exam including a check-up, blood pressure, and heart rate. They also measure my height and weight. My percent body fat is measured using a tool that looks like tongs. The tongs gently measures the thickness of skin folds at several places on my body. The medical staff monitors my heart with an electrocardiograph (ECG) while I rest. If I am a female of childbearing age, I will submit a urine sample for a pregnancy test.
**Day 2: Screening and DXA Scan:** A clinician gives me an exam including a medical history. A Dual-Energy X-Ray Absorptiometry (DXA) test measures the fat, muscle, and bone in my body. I need to remove my jewelry for this test. During the test, I lay on a table without moving for 10 minutes while a scanner moves past my body.

**Day 3: Experiment:** I will avoid alcohol or caffeine (i.e. coffee, tea, cola) for 12 hours before the experiment. The medical staff records my blood pressure and heart rate when I arrive. I don exercise clothing. Then I sit in a chair in a room that is 25°C (77°F) with 30% humidity. The researcher will take several measurements during the experiment:

- **Heart Rate:** The researcher uses a heart rate monitor that straps around my chest.
- **Blood Pressure:** The researcher uses the same method as that used by a doctor.
- **Skin Temperature:** The researcher tapes wires to my arm, chest, thigh, and calf.
- **Body Temperature:** A temperature sensor is sealed in a tube that looks like a strand of spaghetti. The researcher inserts the tube through my nose and into my throat. While the researcher guides the tube, I will drink water through a straw until the tube is properly placed. The length of tube inserted into my throat is equal to ¼ of my height. I may have the tube coated with gel to make the tube slippery and numb the tissue around the tube.
- **Forearm Blood Flow:** The researcher places a blood pressure cuff around my wrist and upper arm. The researcher places a strain gauge that looks like a rubber band around my forearm between the cuffs. During the experiment, a series of measurements are performed every 5 minutes. Each series lasts 1 minute. For each series, the wrist cuff inflates to stop blood flow to my hand. The upper arm cuff inflates allowing blood flow into my arm while blocking blood flow out. This causes a slight increase in size of my forearm that can be seen by the gauge. During each series, the wrist cuff remains inflated while the upper arm cuff will switch 4 times between inflation (10 seconds) and deflation (5 seconds). Then both cuffs are deflated.
- **Skin Blood Flow:** The researcher tapes two probes with their holders to the skin of my arm. A machine attached to the probes shines a low-energy laser light into my skin.
- **Metabolic measurements:** I will breathe into a tube every 10 minutes for 3 minutes so the researcher may collect some of my expired air. The researcher measures the volume of the air I breathe out. The researcher also measures the amount of oxygen and carbon dioxide in the air I breathe out.

When the experiment begins, I sit quietly for the 20-minute baseline period. Then the temperature in the room will decrease to 20°C (68°F) for 20 min. Then the room temperature will decrease at a rate of 1°C (1.8°F) every 20 minutes. I must try to relax and not move during the experiment. When I start to shiver or wish to stop, the experiment ends. While I am rewarmed, the researcher heats the laser probes’ holders to 42°C (108°F) for 30 minutes. This creates the greatest amount of blood flow possible.

**3. Discomforts and risks:**

- **Blood Draw:** Blood draws often cause mild pain, bruising, swelling, or bleeding. There is also a slight chance of infection. I may feel lightheaded. To keep the chance of infection minimal, the medical staff uses the same techniques used in hospitals.

- **Percent Body Fat:** The measure is performed in private room so I will not feel self-conscious.
**ECG:** The ECG’s wires are taped to my body to measure the electrical activity of my heart. There are no risks, but the tape may temporarily redden or irritate my skin.

**DXA Scan:** The DXA scan exposes me to a small amount of radiation where the x-ray beam crosses my body. The radiation is the same as a whole body dose of about 1.5 mrem. A mrem is a unit of whole body radiation dose. For comparison, 1.5 mrem is less than I would receive from a routine chest x-ray. Also, 1.5 mrem is less than that from the cosmic rays I would receive during a coast-to-coast flight. Five days of local, normal background radiation is more than 1.5 mrem.

**Heart Rate:** The monitor is in a band placed around my chest. This measure has no risk.

**Blood Pressure:** The researcher uses the method used in a doctor’s office. During the short time the cuff is inflated, my arm may feel tingly or numb. Rarely, the cuff may cause a temporary bruise.

**Skin Temperature:** The wires taped to my skin are not harmful, but the tape may irritate.

**Body Temperature:** The researcher will describe the procedure in detail and the feelings to expect. During placement of the tube, there is a small chance that the soft tissue of my nose and throat could be irritated. I may choose that the tube be coated with a thin layer of lidocaine gel to make it slippery and to reduce the chance of irritation. Water may be used to moisten the tube instead. Although vomiting is rare, brief gagging may occur during tube placement until the end of the tube is beyond my upper throat. Once the tube has been placed, I will have a feeling like that of having a vitamin stuck in the back of my throat. This is normal and usually fades during the experiment. The tube will not stop me from swallowing or talking.

**Lidocaine gel:** Although no bad effects to the gel used in this fashion have been recorded, there remains a small chance of a bad reaction that could include rash, swelling, itching, redness, difficulty in swallowing, heart, or breathing trouble. If I have had a bad reaction to Lidocaine or Novacaine in the past, I will not have the gel put on the probe.

**Forearm Blood Flow:** My arm and wrist may feel numb when the cuffs are inflated, and the cuffs may cause temporarily bruising.

**Laser Doppler Flowmetry:** I understand that weak lasers can hurt my eye if I stare into the light for a long time. The laser is not turned on until the probes are taped to a surface. The tape may irritate my skin.

**Local Heating:** The researcher will measure the temperature of my skin under the holders. The skin will feel very warm but will not hurt. The heating will make the skin of my arm under the holders red like when I take a hot bath. The redness will not last more than several hours. Some people may be more sensitive to the heating than others. If my arm feels too hot, I will tell the researcher and the heat will be turned down or discontinued.

**Metabolic Measurements:** There are no risks to this procedure.
Whole body cooling: I know that cooling may cause goose bumps, shivering and chilly sensations. I understand that the cooling will affect only my skin and will not cool the inside of my body. I know that I may stop the experiment at any time.

4. **Benefits to me:**

I receive a medical screening and measure of my body composition that could inform me about my health. I could also gain some knowledge about how my body works during thermal stress.

   **b. Potential benefits to society:**
   This study helps us to learn more about how cold affects older people’s bodies and about how low body mass may compound these effects. These results could encourage researchers to explore ways to prevent this loss. Also, these results could be used to alert people caring for the elderly that individuals with low body mass are prone to lowered body temperatures in cold environments.

5. **Alternative procedures that could be utilized:** The researcher could measure my temperature with a probe inserted in my rectum, under my tongue or in my ear. These techniques are less accurate for the purposes of this project. The other techniques in the study are used in research worldwide. They are the best means by which to meet the goals of this study with minimal discomfort and risk to me.

6. Time duration of the procedures and study: I visit the Noll Lab on 3 days. The blood draw on Day 1 lasts no longer than 20 minutes. The screening and DXA on Day 2 lasts no longer than 1.5 hours. The experiment on Day 3 last no longer than 5 hours.

7. **Statement of confidentiality:** The data is available only to the investigators. Volunteers are coded by an identification number for statistical analyses. All records are kept in a secure location. All records associated with my participation in the study will be subject to the usual confidentiality standards applicable to medical records (e.g., such as records maintained by physicians, hospitals, etc.), and in the event of any publication resulting from the research no personally identifiable information will be disclosed. The Office for Research Protections and the Biomedical Institutional Review Board (IRB) may review records related to this project.

8. **Right to ask questions:** If I have any questions or concerns about the research or my participation in the present investigation, I may contact Lacy Holowatz (W: 814-863-2948, 861-6255), David DeGroot (W: 814-863-2948, 237-5873), or Jane Pierzga (W: 814-865-1236, H: 814-692-4720). If there are findings during the research that could relate to my wanting to help with the study, I will be told of the findings. I may contact the Office for Research Protections, 212 Kern Graduate Building, University Park, PA 16802, (814) 865-1775 for additional information concerning my right as a research participant.

   I have been given an opportunity to ask any questions I may have, and all such questions or inquiries have been answered to my satisfaction.

9. Compensation:

I receive $60.00 for completing experiment. I get a T-shirt.
If I am an employee of Penn State University, the compensation I receive for participation will be treated as taxable income and therefore taxes will be taken from the total amount. If I am not employed by Penn State University, total payments within one calendar year that exceed $600 will require the University to annually report these payments to the IRS. This may require me to claim the compensation that I receive for participation in this study as taxable income.

10. Injury Clause: I understand that medical care is available in the event of injury resulting from research but that neither financial compensation nor free medical treatment is provided. I also understand that I am not waiving any rights that I may have against the University for injury resulting from negligence of the University or investigators.

11. Voluntary participation: I understand that my participation in this study is voluntary, and that I may withdraw from this study at any time by notifying the investigator. My withdrawal from this study or my refusal to participate will in no way affect my care or access to medical services. I may decline to answer specific questions. However, my acceptance into the study may be contingent upon answering these questions. My helping with the study may be ended without my consent if the researcher deems that my health or behavior adversely affects the study or increases risks to me beyond those approved by the Penn State Institutional Review Board (IRB) and agreed upon by me in this document.

12. In the event that abnormal test results are obtained, I will be apprised of the results immediately and recommended to contact my private medical provider for follow-up.

This is to certify that I am 18 years of age or older and I consent to and give permission for my participation as a volunteer in this program of investigation. I understand that I will receive a signed copy of this consent form. I have read this form, and understand the content of this consent form.

Volunteer __________________________ Date ______________

I, the undersigned, have defined and explained the studies involved to the above volunteer.

Investigator _________________________ Date ______________
Informed consent for the study “Modeling human core temperature during a unique cross-desert expedition” (Chapter 5):

PROJECT:  Fluid, electrolyte, and caloric balance and thermoregulatory response to running for five days in the Sahara desert.

RESEARCHERS:  GSSI Research Team
              Team Leader:   Beth Stover, M.S. 847-304-2499
              Additional Scientists: John Eric Smith, MS and Dave DeGroot, MS

Please read the following information carefully and feel free to ask questions.

Sign the final page (release and waiver) only when you are satisfied that all procedures and risks have been sufficiently explained to you.

PURPOSE OF THE STUDY: To observe the thermoregulatory response and determine if fluid, electrolyte and caloric balance can be maintained when running 50 miles a day for five days in the Sahara desert.

GENERAL TEST PROCEDURES: During the first five days of your run through the Sahara we will be monitoring several variables to determine your fluid and electrolyte losses and intake, your caloric intake, and how your body responds to the heat while running. A full explanation of the procedures will be given verbally prior to participating in the experiment. We will also provide you with general instructions. This will give you an opportunity to ask questions about the project.

FLUID AND ELECTROLYTE BALANCE:

**THESE MEASURES WILL BE TAKEN DURING BOTH THE MORNING AND EVENING RUN**

- Before and after running, your bodyweight will be measured in dry shorts on a portable, platform scale.

- All fluid containers will be weighed prior to and after running. You are allowed to drink fluids freely from these containers during the run.

- Any food, gels, or supplements you plan to use during the run will need to be weighed (before and after) as well.

- If you need to urinate or defecate during the run, you will need to be weighed before and after going to the bathroom.

- Halfway through each run, sweat patches (small paper patches) will be placed on several specific anatomical sites (head, forearm, upper chest, back, thigh) to aid in determination of sweat electrolyte concentrations. We will remove them as they become filled with sweat. We will try to minimize interrupting your run. This should not involve more than 2 minutes of stopping.

TOTAL BODY WATER AND FLUID TURNOVER:

- You will ingest a small amount (1/2 gram per kg of your body weight; less than 1 oz) of deuterium oxide (D2O) the night before the start of the first day of running and in the evening of the fifth day of running. You will do so after emptying your bladder and having a small amount of that urine stored. D2O, or heavy water, is a safe substance that looks, tastes and behaves like water in his body. Because it can be detected in urine, D2O allows the scientist to measure your hydration status. You will collect all urine from the time after you drink the D2O until the next morning, including the urine when you first awaken. The scientists will provide a large bottle for collecting
the urine. You will deliver the urine bottle to the scientist the next morning and then collect an additional urine sample at that time. Urine samples will be discarded after they are measured for D\textsubscript{2}O content and urine specific gravity, an index that predicts hydration status.

- Each subsequent day for four days when you arise in the morning, you will provide the scientists with a sample of urine. The urine will be measured for D\textsubscript{2}O. The dilution of the D\textsubscript{2}O during days of running will tell the scientists your fluid turnover each day.

**CALORIC BALANCE:**
- These measures will be recorded throughout the day each of the five days.
- A record of all of the foods and fluids you consume and your daily activities will be kept by the scientists. Please make an effort to notify them of all foods and fluids consumed and the amount.
- All foods and fluids will be weighed by the researchers before and after consuming them.
- Your body weight and skin fold measures will be taken each morning by one of the researchers. Shin folds are measured using a tool that looks like tongs. The tongs gently measure the thickness of skin folds at several places on your body. We will be taking measures at your back (by the shoulder), tricep, and abdomen.

**THERMOREGULATORY RESPONSE:**
- Your heart rate will be monitored during your runs using a Polar Monitor: The researcher straps a Polar Monitor belt around your chest to measure heart rate.
- Your core temperature will be monitored using a small, ingestible pill (T-pill): The T-Pill is about the size of a multi-vitamin and has been used for many years. Researchers have used the pill in astronauts, fire fighters, scuba divers, and people climbing mountains. The system has 2 parts:
  1. T-pill – The T-pill is a small sensor that uses a radio signal to report the temperature in your body. On the night before each trial, you will wake the battery in the T-pill by removing and throwing away the T-pill’s wrapper. You then swallow the T-pill with water as if it were a vitamin. The T-pill stays inside of your body for about 12 – 15 hours. It is eliminated from your body via a bowel movement. You will not know when it has been passed. We will check with our recorder and notify you.
  2. The recorder – The recorder reads and stores the radio signal from the T-pill. The researcher straps the recorder around your waist. You will need to wear the recorder during your runs.

**HEALTH RISKS:**

All experimental procedures used in this study have been routinely used in this and other exercise physiology laboratories, and present minimal risk to your health. However, you should be aware that there are risks involved in any laboratory procedure and with these tests. It is imperative that you notify the research staff of any unusual physical symptoms that may develop during or after the testing procedures. Emergency procedures will be coordinated through the on-site physician. All precautions needed to minimize risks to your health will be taken. All staff attending to this experiment are trained as 'first responders' and are certified to provide basic life support. Also keep in mind that you are free to discontinue participation in this study at any time, for any reason.

- **Core Body Temperature:** The ingestible temperature sensor telemetry system (CorTemp 2000, HTI Technologies, Inc.), that will be used in this study, provides a valid measure of core temperature during rest and exercise. It was developed by the Johns Hopkins University Applied Physics Laboratory, in collaboration with NASA's Goddard Space Flight Center. This sensor is listed with the Food and Drug Administration for one-time use and has been safely and
comfortably used in a number of other research studies in human subjects and in children. Swallowing the T-pill presents risks like that of taking a vitamin pill such as choking or gagging on the pill or water. The pill becomes slippery when wet so you must be careful. There have been no reports of abdominal problems with the T-pill. However, the pill could cause cramps, irritation, blockage, or infection. Magnetic Resonance Imaging (MRI) is a medical test that can cause the T-pill to overheat and be dangerous. You cannot have an MRI within 2 weeks after having swallowed a T-pill unless you have seen the T-Pill pass from your body. If you need an MRI and have not seen the T-Pill pass, you will tell your doctor that you have swallowed a T-Pill.

- **Skin Fold Measurements:** You may feel embarrassed having this measure. The researcher makes this measure in a private and professional way.

- **Heart Rate (Polar Monitor):** There are no risks to this measurement.

- **Body Weight, Urine Sample:** Your may feel embarrassed having this measure. The researcher makes this measure in a private and professional way.

**SUBJECT COMPENSATION:** After all testing is completed, you will receive a report with your individual results including recommendations for future running events similar to the one in which you are participating.

**CONFIDENTIALITY OF TEST RESULTS:** Your test results will be kept in the Gatorade Sports Science Institute. Grouped or blind-coded data may be used for publication in scientific journals or for marketing claims. Personal confidentiality will not be breached. Case study data may be used for publication in scientific journals. In the case of media, you are free to use specific reports that will be sent to you following the testing. Determination of use of photographs and other results learned while at the Quaker Oats facility must be handled on a case-by-case basis with your primary contact or tour leader.

**PUBLICITY RELEASE:** As part of my participation in testing by Gatorade Sports Science Institute (hereinafter "Gatorade Lab") I understand that photographs, videotapes and/or drawings or other likenesses of me may be taken and used from time to time by the press or by Gatorade for public relations or other publicity or advertising purposes. I hereby grant full permission to The Quaker Oats Company and its subsidiary Stokely-Van Camp, Inc., maker of Gatorade Thirst Quencher, and their respective officers, directors, employees, agents, successors and assigns or anyone authorized by any of them, to use my name, photograph, video image, voice, likeness and biographical data, in whole or in part, in any and all media for the purposes of publicity, advertising, trade or news purposes and in connection therewith I hereby release them and each of them from all liability.

I have read each and every word of the foregoing prior to my execution of this release and am fully familiar with the contents thereof.
Appendix B

SUPPLEMENTAL DATA

Several variables were measured or calculated that were either not included or not presented in their entirety in the manuscripts comprising chapters 3-5 and are presented here. From the aging and cold stress studies, survival curve analysis were performed to test for a difference in subject time to shivering and subsequent protocol termination and ratings of thermal sensation where obtained to quantify the sensory response to mild cooling. Baseline and final values (Chapter 3) and the value at 60-min (Chapter 4) were given for tissue insulation ($I_t$); complete data for young and older subjects are provided here.

The figures depicting the predicted core temperature ($T_{pred}$) during exercise in the heat (Chapter 5) included the best 2 models for NIGHT and for DAY. The plot of $T_{pred}$ vs. time for all 5 model simulations for each day is included in this appendix.
Figure B.1. Survival curve analysis of time to onset of visible, sustaining shivering during mild stress in young and older subjects. There was no difference in time to shivering when assessed by either the Wilcoxin (p=0.53) or log-rank (p=0.87) tests.
Figure B.2. Subjective ratings of thermal sensation for young and older subjects. The numerical values of 4, 3, 2, 1 and 0 corresponded to comfortable, cool, cold, very cold, and unbearable cold, respectively. There was no difference in the rating of thermal sensation (p=0.26 for age effect).
Figure B.3. Tissue Insulation, calculated as \((T_{es}-T_{sk})/(M_{net}-S)\). The progressive lower \(T_{es}\) in the older subjects (Figure 3.1) was offset by lower \(M_{net}-S\), such that there was no age effect (\(p=0.95\)).
Figure B.4. Predicted core temperature ($T_{\text{pred}}$)-actual core temperature ($T_{\text{pill}}$) for each of the 5 model simulations during NIGHT. Panel A presents the model predictions using metabolic rate as predicted by the equation of Berglund integrated into the ICDA model, while panel B presents the model predictions using metabolic rate as estimated by the Pandolf equation within SCENARIO.
Figure B.5. Predicted core temperature (T\text{pred})-actual core temperature (T\text{pill}) for each of the 5 model simulations during DAY. Panel A presents the model predictions using metabolic rate as predicted by the equation of Berglund integrated into the ICDA model, while panel B presents the model predictions using metabolic rate as estimated by the Pandolf equation within SCENARIO.
VITA

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   Ph.D., Physiology
University of New Hampshire  Dec 1996
   M.S., Kinesiology
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Professional Affiliations:
1999-present:  Student member, American Physiological Society
1995-present:  Member, American College of Sports Medicine

Publications:

DeGroot DW, Havenith G and Kenney WL, Responses to mild cold stress are predicted by different individual characteristics in young and older subjects, J Appl Physiol 101: 1607-1615, 2006


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