Age-related thermoregulatory differences during core cooling in humans

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Cold-induced changes in vasomotor tone depend primarily on norepinephrine (NE) release and α-adrenoceptor-mediated vasoconstriction in the cutaneous vasculature (10, 11). Reasons for impaired thermoregulatory vasoconstriction with aging may be decreased NE release or a decreased vasomotor response for a given amount of NE at its receptors (24, 27). Downregulation of α-adrenoceptor numbers occurs with aging, which may result in decreased vasomotor responsiveness to NE (6). Whether one or both of these mechanisms is responsible for age-related changes in thermoregulatory vasoconstriction has not been determined.

Shivering and the associated increased metabolic heat production are important cold-defense mechanisms that also become less efficient with aging (33). Age-related changes in shivering may reflect the loss of lean body mass with aging, resulting in less available skeletal muscle and less effective shivering. Whether the attenuated shivering response in older people occurs independently from differences in lean body mass is controversial (36), and we aimed to determine this in the current study. Because perceived thermal comfort serves to initiate behavioral thermoregulation, the ability to sense changes in body temperature is important for thermal homeostasis. Whether aging is associated with altered thermal perception during cold challenge is controversial (7, 23), and we also aimed to determine this in the current study.

Thermoregulatory responses can be characterized by threshold, gain, and maximum intensity. Threshold is the core temperature (Tc) at which the thermoregulatory response is initiated. Gain is the change in response magnitude per unit change in Tc, and maximum intensity is the magnitude of response during a given thermal challenge. Each of these response characteristics can be quantitatively assessed to identify age-related changes in thermoregulation. In the current study, we used these methods to compare younger and older individuals given a similar cold thermal...
challenge. The following hypotheses were tested: 1) the intensity of vasoconstriction becomes less with aging due to a reduced vasomotor responsiveness to NE, 2) the intensity of the metabolic response is less in older people, even when adjusted for lean body mass, and 3) perception of thermal discomfort is reduced with aging.

METHODS

Subject selection and study design. With approval from the Committee on Clinical Investigation and after obtaining written informed consent, eight younger (age 18–23) and eight older (age 58–71) male subjects were enrolled. No subject had cardiovascular, pulmonary, renal, or other significant disease, and none were taking medication. All studies were performed in the Outpatient Clinical Research Center between 0800 and 1100. Ambient temperature averaged 23.8 ± 0.5°C, and relative humidity was ~60%. Subjects were dressed in a thin cotton gown and were positioned with their heads elevated ~30°. Percent body fat was estimated by the infrared interactance (Futrex, Hagerstown, MD) over the biceps skinfold, and lean body mass was defined as body weight (kg) · ([100 − percent body fat]/100). This method is highly correlated with measurements obtained by traditional methods (5).

The same protocol was implemented for younger and older subjects. With the use of local anesthesia, a 30-cm, 16-gauge catheter was placed in the right antecubital vein for administration of intravenous fluid. The subjects rested comfortably in the supine position for 30 min before obtaining baseline measurements. The subjects were then monitored for 15 min to obtain baseline data without thermal intervention. A fixed cold thermal stress was delivered over a 30-min period by the infusion of cold (4°C) intravenous fluid (0.9% saline, 40 ml/kg) at a rate of 70 ml/min. A 1-h period of monitoring followed the cold fluid infusion.

Temperature monitoring. Tc was monitored at the tympanic membrane with the use of thermocouple probes (Mon-2-therm, Mallinckrodt Medical, St. Louis, MO). To ensure placement against the tympanic membrane, the probes were inserted until an audible scratching sound was reported by the subject. The external auditory canal was then packed with cotton for insulation. Skin-surface thermocouples (Mallinckrodt) were placed at four sites to allow calculation of a weighted average mean skin temperature defined as 0.3 × (chest + upper arm) + 0.2 × (thigh + calf) (26). All thermocouples were linked to an electronic thermometer (Iso-thermex, Columbus Instruments, Columbus, OH). All temperatures were recorded on a laptop computer at 5-min intervals throughout the study. Precision and accuracy with this thermometry system are to 0.01 and 0.1°C, respectively. The monitoring system was calibrated against a standard mercury in a glass thermometer before this series of experiments.

Subjective thermal comfort. As previously described (13), subjective thermal comfort scores were assessed on a 10-point visual analog scale, with 0 corresponding to “the coldest you have ever been,” 5 corresponding to “neither cold nor warm,” and 10 corresponding to “the hottest you have ever been.” Data were collected at 5-min intervals throughout the studies.

Thermoregulatory responses. Vasomotor tone was measured with the use of laser Doppler flowmetry (Perimed-PF4, Stockholm, Sweden) at the tip of the left index finger and recorded on a hard disk every 1 s. This device and the laser Doppler probe (Perimed PF-408) were calibrated before each study. Finger-skin blood flow data (in laser Doppler perfusion units) were analyzed as a running average of 1-min epochs. At every 5-min interval, a 1-min average was used as a quantitative measure of blood flow. Blood flow measurements were not obtained in two older subjects and one younger subject due to technical problems. Total body oxygen consumption (ml/min) was assessed at 5-min intervals with the use of indirect calorimetry (Deltatrac, Sensormedics, Anaheim, CA). Metabolic data are reported as raw values (ml/min) and as data normalized to lean body mass (ml·min⁻¹·kg⁻¹·lean body mass). Shivering was assessed by a trained investigator with the use of a four-point scale, where 0 = no shivering, 1 = occasional mild tremors of the jaw and neck, 2 = intensive tremors of the chest, 3 = intermittent vigorous generalized tremor, and 4 = continuous, violent muscle activity (14).

Catecholamine measurements. Plasma concentrations of NE and epinephrine (Epi) were measured in venous blood drawn through the right arm catheter after 10 ml of fluid were discarded to ensure undiluted sampling. Samples were drawn at baseline (before the cold fluid infusion) and at every 0.5°C-increment of Tc during the cold infusion (36.5, 36, 35.5, and 35.0°C). Specimens were stored temporarily on ice in tubes containing EDTA. The plasma was then separated in a refrigerated centrifuge and stored at ~80°C. NE and Epi concentrations were measured with the use of high-pressure liquid chromatography with electrochemical detection after alumina extraction as previously described (11). The sensitivity of this assay is 5 pg/ml, and the intra- and interassay coefficients of variation are <5%.

Data analysis. All morphometric and Tc threshold data were analyzed by unpaired t-tests. Data measured over time were analyzed with the use of repeated-measures ANOVA and dependent-means t-tests. Shivering scores were treated as ordinal data and analyzed by the Mann-Whitney rank sum test. The Tc threshold for vasoconstriction was defined as the Tc at which finger-skin blood flow (laser Doppler) was sustained at or below 50% of the baseline value for more than 1 min. This level of decreased blood flow correlates well with other measures of perfusion (12). The Tc threshold for shivering was defined as the Tc at which total body oxygen consumption increased by 30% above baseline values. This degree of increase correlates well with the visible onset of thermoregulatory shivering (2, 11). The threshold for catecholamine release was defined as the Tc at which the plasma level increased to a statistically significant level above baseline. The gain for the vasoconstriction response was assessed by linear regression of Tc vs. finger-skin blood flow (laser Doppler), and the total body oxygen consumption response was assessed by Tc vs. total body oxygen consumption. The greatest intensity of each thermoregulatory response, which generally occurred on completion of the fluid infusion, was used to define the maximum response. The vasomotor response to NE was determined by linear regression of NE vs. finger-skin blood flow. Logarithmic transformation of NE concentrations was used to obtain linearity of fit between hemodynamic responses and plasma NE levels (35). The regressions used to calculate these gains were generated from data collected during the 30-min period of active cooling. All regressions were performed individually for each subject, and the means of the individual regression line slopes were compared to assess differences in gain between the younger and older groups. All data are reported as means ± SE, except for shivering scores that are reported as median ± interquartile ranges. P < 0.05 was used to define significance.
RESULTS

The older group had significantly greater percent body fat and a lower baseline finger-skin blood flow compared with the younger group, but the groups did not differ for weight, height, lean body mass, baseline Tc, or baseline total body oxygen consumption (Table 1).

The mean Tc threshold for vasoconstriction was lower in the older group (35.5 ± 0.3°C) than in the younger group (36.2 ± 0.2°C) (P = 0.03). The mean Tc threshold for total body oxygen consumption was also lower in the older group (35.2 ± 0.4°C) than in the younger group (35.9 ± 0.1°C) (P = 0.04). Vasoconstriction gain was similar between age groups (P = 0.38) (Table 2). The gain for total body oxygen consumption was lower in the older group, both with the use of raw measurements (P = 0.005) and data normalized for lean body mass (P = 0.03).

Despite a lower Tc nadir in the older group (34.9 ± 0.2°C) than in the younger group (35.5 ± 0.2°C, P = 0.001), the maximum intensities of both vasoconstriction (52 ± 32 vs. 12 ± 2 laser Doppler units, P = 0.03) and total body oxygen consumption (360 ± 30 vs. 495 ± 40 O₂ ml/min, P = 0.006) were less in the older group (Fig. 1). When normalized for lean body mass, mean maximum total body oxygen consumption was greater in the younger group (8.1 ± 0.5 O₂ ml · min⁻¹ · kg⁻¹ lean body mass) than in the older group (5.9 ± 0.6 O₂ ml · min⁻¹ · kg lean body mass⁻¹) (P = 0.05). The mean maximum shivering score was also lower in the older group (2 ± 0) than in the younger group (3 ± 0) (P = 0.01). Subjective thermal comfort scores were similar in the two age groups (3 ± 0 and 3 ± 0, P = 0.82) despite the lower Tc in the older group. Mean skin-surface temperature was 0.7 ± 0.2°C lower (P = 0.01) before core cooling and 0.7 ± 0.2°C lower (P = 0.01) immediately after core cooling in the older group. Mean skin-surface temperature decreased 0.7 ± 0.1°C in both the younger and older groups over the course of the 30-min cooling period (P = 0.02 for change over time).

At baseline Tc, the mean plasma NE concentration was greater in the older individuals (261 ± 26 vs. 149 ± 18 pg/ml, P = 0.03). NE was significantly increased above baseline when Tc fell to 36.0°C in the

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Table 1. Morphometric data

<table>
<thead>
<tr>
<th>Age Group</th>
<th>Age, yr</th>
<th>Wt, kg</th>
<th>Height, cm</th>
<th>Body Fat, %</th>
<th>Lean Body Mass, kg</th>
<th>Baseline Tc, °C</th>
<th>Baseline Finger-Skin Blood Flow, Laser Doppler PU</th>
<th>Baseline Total Body O₂ Consumption, ml O₂/min</th>
</tr>
</thead>
<tbody>
<tr>
<td>Older (n = 8)</td>
<td>63 ± 4</td>
<td>75 ± 4</td>
<td>167 ± 4</td>
<td>29 ± 2</td>
<td>54 ± 5</td>
<td>36.6 ± 0.1</td>
<td>137 ± 29</td>
<td>240 ± 20</td>
</tr>
<tr>
<td>Younger (n = 8)</td>
<td>21 ± 1</td>
<td>75 ± 7</td>
<td>175 ± 2</td>
<td>20 ± 2</td>
<td>60 ± 5</td>
<td>36.7 ± 0.1</td>
<td>217 ± 24</td>
<td>270 ± 20</td>
</tr>
<tr>
<td>P value</td>
<td>0.0001</td>
<td>0.97</td>
<td>0.06</td>
<td>0.003</td>
<td>0.36</td>
<td>0.49</td>
<td>0.05</td>
<td>0.37</td>
</tr>
</tbody>
</table>

Data are given as means ± SE. Tc, core temperature; PU, perfusion units.

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Table 2. Comparison of gain for thermoregulatory responses in younger and older subjects

<table>
<thead>
<tr>
<th>Subject</th>
<th>Change in Finger-Skin Blood Flow (PU) per °C Change in Tc</th>
<th>Change in Total Body O₂ Consumption (Vₐₒ₂/min) per °C Change in Tc</th>
<th>Change in Total Body O₂ Consumption (Vₐₒ₂/lbm⁻¹ · min⁻¹) per °C Change in Tc</th>
<th>Change in Finger-Skin Blood Flow (PU) per °C Change in Plasma NE [log NE (pg/ml)]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Younger group</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>65.03</td>
<td>-237.45</td>
<td>-2.98</td>
<td>-0.53</td>
</tr>
<tr>
<td>2</td>
<td>77.96</td>
<td>-184.71</td>
<td>-3.67</td>
<td>-2.13</td>
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<tr>
<td>3</td>
<td>100.98</td>
<td>-172.59</td>
<td>-1.67</td>
<td>-3.79</td>
</tr>
<tr>
<td>4</td>
<td>34.02</td>
<td>-156.46</td>
<td>-2.4</td>
<td>-1.99</td>
</tr>
<tr>
<td>5</td>
<td>88.73</td>
<td>-253.56</td>
<td>-3.21</td>
<td>-1.31</td>
</tr>
<tr>
<td>6</td>
<td>134.26</td>
<td>-108.39</td>
<td>-1.77</td>
<td>-1.4</td>
</tr>
<tr>
<td>7</td>
<td></td>
<td>-88.14</td>
<td>-1.79</td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>86.33</td>
<td>-349.39</td>
<td>-6.63</td>
<td>-0.19</td>
</tr>
<tr>
<td>Means ± SE</td>
<td>83.9 ± 9.8</td>
<td>-193.8 ± 25.7</td>
<td>-3.01 ± 0.47</td>
<td>-1.62 ± 0.33</td>
</tr>
<tr>
<td>Older group</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>54.78</td>
<td>-27.55</td>
<td>-0.65</td>
<td>-0.28</td>
</tr>
<tr>
<td>2</td>
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<td>-176.61</td>
<td>-2.07</td>
<td>0.01</td>
</tr>
<tr>
<td>3</td>
<td>78.55</td>
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<td>-2.18</td>
<td>-0.06</td>
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<tr>
<td>4</td>
<td></td>
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<td>-2.47</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>43.29</td>
<td>26.29</td>
<td>0.37</td>
<td>-0.41</td>
</tr>
<tr>
<td>6</td>
<td>84.16</td>
<td>-58.73</td>
<td>-0.99</td>
<td>-0.04</td>
</tr>
<tr>
<td>7</td>
<td>73.57</td>
<td>-89.42</td>
<td>-1.98</td>
<td>-0.26</td>
</tr>
<tr>
<td>Means ± SE</td>
<td>70.7 ± 10.6</td>
<td>-73.4 ± 5.7</td>
<td>-1.4 ± 0.47</td>
<td>-0.18 ± 0.33</td>
</tr>
<tr>
<td>P value</td>
<td>0.38</td>
<td>0.005</td>
<td>0.03</td>
<td>0.01</td>
</tr>
</tbody>
</table>

Values in table represent regression coefficients from simple linear regressions. Finger-skin blood flow was measured in laser Doppler PU. Vₐₒ₂, metabolic heat production measured by indirect calorimetry; lbm, lean body mass; NE, plasma norepinephrine concentration. Two older and one younger subject had missing data for blood flow.
younger subjects \((P = 0.04)\) but was not increased above baseline until \(T_c\) fell to 35.0°C \((P = 0.008)\) in the older subjects, indicating a lower NE release threshold for \(T_c\) in the older group (Fig. 2). The maximum response for NE was fourfold above baseline in the younger group but only twofold above baseline in the older group. Plasma Epi concentrations were similar in the younger and older groups at baseline and did not change during core cooling. The older group had smaller vasomotor responses for a given increment change in plasma NE concentrations. This is demonstrated by a decreased slope of the regression line of best fit in the older group (Fig. 3) and by a significant difference in the slope of the regression line in the two groups \((P = 0.01)\) (Table 2).

**DISCUSSION**

The results of the current study indicate multiple age-related changes in systems determining thermoregulatory responses. Compared with younger individuals, older individuals had 1) a decreased threshold for and decreased maximum response for vasoconstriction, 2) decreased threshold, maximum response, and gain for total body oxygen consumption, and 3) similar thermal comfort scores despite a lower \(T_c\) in the older group. Underlying mechanisms for the age-related impairment of the vasomotor responses were both a lower \(T_c\) threshold for NE release and a decreased vasomotor response for a given change in NE. The decreased shivering and total body oxygen consumption cannot be explained by differences in body composition alone, which suggests the intrinsic heat production response to core hypothermia is altered by the aging process.

The above findings support each of the hypotheses that we proposed to test regarding the mechanisms for impaired thermoregulation in older humans. All three major cold-defense responses are in some way impaired with age; the vasomotor response and total body oxygen consumption are clearly reduced in intensity. Behavioral thermoregulatory responses are likely to be impaired as well because these depend on changes in perceived thermal comfort. Our findings suggest the perception of cold thermal comfort is decreased with age because thermal comfort scores were similar in the older subjects despite a significantly lower \(T_c\).
Under baseline conditions, Tc is similar in younger and older individuals (17). Most studies (3, 8, 16) have shown a greater extent of core hypothermia in older subjects given the same cold exposure as younger subjects. This susceptibility to hypothermia is especially evident during anesthesia and surgery in the elderly (9). In contrast, other studies have shown either similar changes of Tc (31) or even smaller changes in the older individuals subjected to cold challenge (25), especially when the two age groups are matched for body composition. The present results indicate that a given core thermal challenge also results in more hypothermia in older individuals. By delivering the cold challenge directly to the core thermal compartment, we eliminated the confounding variable of greater surface insulation from increased subcutaneous fat in the older group.

The cutaneous vasomotor response is an important thermoregulatory mechanism that allows the skin to serve as a functional heat exchanger. During cold exposure, studies have shown either similar (33) or reduced (1, 4, 19, 20) vasoconstriction in the elderly compared with the young. Underlying adrenergic mechanisms for the age-related changes have not been determined. Although the NE response to cold stress has been reported to be similar in younger and older humans (29, 32), the NE measurements in these studies were not taken at similar body temperatures in the two age groups, and the vasoconstrictor response for a given NE concentration was not determined.

The results from the current study indicate that baseline cutaneous blood flow decreases with aging, resulting in less capacity to change blood flow from baseline levels. Furthermore, we have identified an explanation for the decreased cutaneous vasoconstriction response on the basis of NE release and vasomotor responsiveness to NE. Although the plasma NE concentration was greater at baseline in older subjects, the Tc threshold that triggered a significant change in NE from baseline was 1°C lower in the older than in the younger group. Once the NE response was initiated, the magnitude of NE change from baseline was also less, and the vasomotor response to a given change in NE was reduced in the older subjects. The latter may reflect downregulation in α-adrenoceptor-mediated responses with aging (15, 18).

The absence of a significant Epi response in both the younger and older groups suggests that the sympathetic neural rather than the adrenomedullary system is primarily responsible for body temperature homeostasis during a fall in Tc. It is only when aggressive cooling of both the core and the skin surface is applied that an Epi response is observed (13).

Shivering increases heat production and maintains Tc during cold challenge. Most previous studies have shown a decreased baseline metabolism (30) and a decreased shivering response in the elderly (21, 33). This is in part due to the decrease in lean body mass that occurs with aging. Others have shown either no change or even increased shivering with aging when the subjects have been matched for body composition (22). Our results indicate that all the measured characteristics of the shivering response (threshold, gain, and maximum response) are reduced with aging when thermal insulation is bypassed by direct core cooling. Even when heat production was normalized for lean body mass, an age-related difference in gain and maximum response remained, confirming an age-related impairment of the shivering response, independent of changes in body composition.

Previous studies suggest that in addition to physiological thermoregulatory impairment with aging, there may be behavioral thermoregulatory impairment as well. The elderly are more likely to maintain a lower ambient temperature in their homes compared with younger individuals (34), suggesting decreased ability to perceive cold (23, 28). Other investigators (7) have shown no difference in thermal perception with aging during exposure to mild cold ambient temperatures. Our findings suggest that the ability to sense thermal changes is reduced with aging because thermal comfort scores at any given Tc were greater in the older individuals.

In the present study, skin temperature was not “clamped” but instead was allowed to decrease slightly during core cooling. Although mean skin temperature was lower in the older subjects before and after core cooling, skin temperature decreased to the same extent in both younger and older groups, minimizing any confounding effects of altered skin temperature per se. Age-related impairment in thermoregulatory responses was noted despite both lower core and skin temperatures in the older group. A concern with the intravenous fluid infusion is the possible effects of increased intravascular volume on the measured responses. We have demonstrated that a normothermic control group, given similar volumes of saline at body temperature (37°C), did not experience vasomotor, metabolic, or thermal comfort changes thus further validating the intravenous fluid model of cold challenge (11).

In summary, aging is associated with reduced intensity of the vasoconstriction and shivering responses during cold challenge. The ability to perceive cold is also somewhat impaired. The decreased vasoconstriction response is explained by a delayed and reduced NE response as well as a decreased vasomotor responsiveness for a given amount of endogenous NE. Shivering and the associated heat production are decreased in older individuals, with decreased threshold, gain, and maximum response that cannot be attributed solely to differences in lean body mass. These findings contribute to our understanding of why older people are susceptible to core hypothermia during cold challenge.

Perspectives

Studies have shown that older people have less ability to maintain body temperature during cold challenges (3, 8, 21, 34). Although age-related changes in vasomotor function have been implicated (20), the un-
derlying mechanisms are not understood. The current findings describe an age-related reduction in sympa-
thoneural and vasomotor responsiveness, which in combination attenuate cutaneous vasoconstriction during
cold stress. This finding along with a decreased intensity of metabolic heat production and decreased
thermal perception during core hypothermia indicates that all three major cold-defense mechanisms are
impaired with aging.

The authors express sincere gratitude to Susan Kelly for assistance with data collection and analysis. We also thank Arrow International for donating the intravenous catheters.

This study was supported in part by the National Institutes of Health Grants NS-26363, Outpatient Department General Clinical Research Center 5-MO1-RR-00722, and the International Anesthesia Research Society.

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