Aging affects the cardiovascular responses to cold stress in humans

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Hess KL, Wilson TE, Sauder CL, Gao Z, Ray CA, Monahan KD. Aging affects the cardiovascular responses to cold stress in humans. J Appl Physiol 107: 1076–1082, 2009. First published August 13, 2009; doi:10.1152/japplphysiol.00605.2009.—Cardiovascular-related mortality peaks during cold winter months, particularly in older adults. Acute physiological responses, such as increases in blood pressure, in response to cold exposure may contribute to these associations. To determine whether the blood pressure-raising effect (pressor response) of non-internal body temperature-reducing cold stress is greater with age, we measured physiological responses to 20 min of superficial skin cooling, via water-perfused suit, in 12 younger [25 ± 1 (SE) yr old] and 12 older (65 ± 2 yr old) adults. We found that superficial skin cooling elicited an increase in blood pressure from resting levels (pressor response; \( P < 0.05 \)) in younger and older adults. However, the magnitude of this pressor response (systolic and mean blood pressure) was more than twofold higher in older adults \( (P < 0.05 \) vs. younger adults). The magnitude of the pressor response was similar at peripheral (brachial) and central (estimated in the aorta) measurement sites. Regression analysis revealed that aortic pulse wave velocity, a measure of central arterial stiffness obtained before cooling, was the best predictor of the increased pressor response to superficial skin cooling in older adults, explaining ~63% of its variability. These results indicate that there is a greater pressor response to non-internal body temperature-reducing cold stress with aging because it may be mediated by increased levels of central arterial stiffness.

Rates of myocardial infarction and cardiovascular-related mortality increase in the winter (1, 25, 28, 34, 35) and are associated with low outdoor temperature (9, 12, 24). The mechanism(s) underlying associations between cardiovascular-related morbidity/mortality and outdoor temperature may involve acute and chronic (i.e., seasonal) changes in cardiovascular system function. Seasonal changes in cardiovascular system function that may increase cardiovascular-related morbidity/mortality in winter include nonfavorable effects on endothelial function (40) and coagulation (26), as well as other traditional risk factors, such as blood pressure (BP) (44) and blood lipids (31). Additionally, cold exposure elicits acute physiological responses (37) that may contribute to cardiovascular events. For instance, cold exposure acutely increases BP (pressor responses), which may help explain why symptoms and severity of angina increase in individuals with cardiovascular disease during cold exposure (20). Importantly, the negative consequences associated with cold exposure increase with advancing age (9, 11, 28, 32, 34). Thus a thorough understanding of acute and chronic physiological responses to cold exposure and how these responses change with age is of biomedical significance.

Physiological responses to moderate levels of cold stress may differ with age (5, 21). For instance, aging has been reported in some (8, 19, 38), but not all (6, 10), studies to include augmented pressor responses to core body temperature-reducing cold stress. It is possible that age-associated increases in arterial stiffness may be a central factor in determining the magnitude of the cold-induced pressor response. For example, arterial stiffness may increase during cold stress, resulting in augmented increases in BP in central (i.e., aorta) compared with peripheral (i.e., brachial) arteries (14). These findings suggest that greater stress may be exerted on the heart during cold exposure than is appreciated on the basis of peripheral BP measurements. The precise effect of aging on these relations is unknown, as are responses to a milder form of cold stress (i.e., non-internal body temperature-reducing) designed not to induce shivering (thermoregulatory response) but, rather, to isolate a vasoconstrictor response. Importantly, exposure to non-internal body temperature-reducing cold stress is likely to be more representative of routine cold exposure experienced by older individuals in a temperate climate. Accordingly, the purpose of the present study was to determine the pressor response to non-internal body temperature-reducing cold stress in younger and older adults. We hypothesized that aging would be associated with an augmented pressor response to cold stress in humans and that this augmentation would be related to levels of central arterial stiffness.

Methods

Subjects

Twenty-four subjects, 12 younger (18–35 yr old) and 12 older (55–75 yr old) adults, participated in this study. All subjects were healthy, normotensive (BP <140/90 mmHg), nonsmokers, and nonobese [body mass index (BMI) <30 kg/m²], and they were taking no medications (Table 1). The Pennsylvania State University College of Medicine Institutional Review Board approved the experimental protocol, and informed consent was obtained from all subjects before testing.

Experimental Protocol

Subjects were clothed in a high-density tube-lined suit (Med-Eng Systems, Ottawa, ON, Canada), which covered the subject’s whole body, except hands, feet, and head, and were studied in the supine position. A pump in series with an external reservoir tank was used to perfuse the suit with water. The suit was modified with several small (2-inch-square) access windows, at the groin and upper arm, which allowed us to obtain measurements without uncovering large areas of the body. The temperature of the water perfusing the suit could be...
Table 1. Subject characteristics

<table>
<thead>
<tr>
<th>Variable</th>
<th>Younger</th>
<th>Older</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age, yr</strong></td>
<td>25±1</td>
<td>65±2*</td>
</tr>
<tr>
<td><strong>Height, cm</strong></td>
<td>170±2.8</td>
<td>171±1.6</td>
</tr>
<tr>
<td><strong>Body mass, kg</strong></td>
<td>64.9±3.3</td>
<td>72±2.9</td>
</tr>
<tr>
<td><strong>BMI, kg/m²</strong></td>
<td>22.3±0.7</td>
<td>24.6±0.8*</td>
</tr>
<tr>
<td><strong>Body surface area, m²</strong></td>
<td>1.8±0.1</td>
<td>1.9±0.1</td>
</tr>
<tr>
<td><strong>BP, mmHg</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Brachial</td>
<td></td>
<td></td>
</tr>
<tr>
<td>SBP</td>
<td>104±3</td>
<td>121±3*</td>
</tr>
<tr>
<td>DBP</td>
<td>60±1</td>
<td>68±1*</td>
</tr>
<tr>
<td>Central</td>
<td></td>
<td></td>
</tr>
<tr>
<td>SBP</td>
<td>88±2</td>
<td>113±3*</td>
</tr>
<tr>
<td>DBP</td>
<td>61±1</td>
<td>69±1*</td>
</tr>
<tr>
<td>Heart rate, beats/min</td>
<td>58±3</td>
<td>62±3</td>
</tr>
<tr>
<td><strong>PWV, cm/s</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aortic</td>
<td>632±23</td>
<td>927±85*</td>
</tr>
<tr>
<td>Leg</td>
<td>909±65</td>
<td>1,377±148*</td>
</tr>
<tr>
<td>Arm</td>
<td>913±90</td>
<td>1,344±166*</td>
</tr>
<tr>
<td>Augmentation index, %</td>
<td>1±3</td>
<td>32±2*</td>
</tr>
</tbody>
</table>

Values are means ± SE of 12 subjects (6 men and 6 women) in each group. BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; PWV, pulse wave velocity. *P < 0.05 vs. younger.

regulated via a heater in the reservoir tank or by addition of ice directly to the reservoir tank. Except during the cooling period, the suit was perfused with 35°C water. This temperature is slightly above skin surface temperature in a thermoneutral room and helps ensure consistent baseline skin surface temperatures across subjects. Measurements were obtained before and during two separate trials. In trial 1, 35°C water was perfused through the suit at baseline (6 min) and remained at this temperature for an additional 20 min (control trial). In trial 2, after a 6-min baseline period, water perfusion temperature was decreased from 35°C to 15–18°C for 20 min (cooling trial). Trial order was randomized. A minimum 30-min period elapsed before each trial, during which the suit was perfused with 35°C water. Cooling was designed to be mild (i.e., not to induce shivering or alterations in internal body temperature) (13). Measurements obtained before and during the trials were identical. BP and heart rate were measured at 2-min intervals. Sublingual and skin temperatures were recorded at 5-min intervals. Arterial stiffness and wave reflections were measured before (baseline) and during (minutes 12–20) control and cooling trials. An investigator blinded to trial condition (control or cooling trial) and subject group assignment (younger or older adults) performed all analyses.

Measurements

Subjects abstained from food (4 h) and caffeine (12 h) before testing.

BP and heart rate. BP and heart rate were determined using a semiautomated device (Dinamap) with a cuff positioned over the brachial artery under the cooling suit.

Temperature. Sublingual temperature was measured by a thermocouple that was positioned and maintained in the sublingual sulcus. In addition, subjects refrained from breathing through their oral cavity, and skin cooling was not performed on the head, neck, or face, to reduce potential environmental impacts on sublingual temperature (4). Skin surface temperature was determined as the weighted mean of skin surface temperature probes affixed to subject’s chest, arm, thigh, and leg (33).

Pulse wave velocity. Pulse wave velocity (PWV) was used to determine arterial stiffness (3). PWV quantifies the velocity of the pulse wave traveling through an arterial segment based on the measured time delay between the systolic upstroke at a proximal and distal arterial site (Δtime) divided by the measured distance between recording sites (Δdistance). For measurement of PWV, two Doppler signals were simultaneously obtained using nondirectional Doppler flow probes (model 810 A, Parks Medical Electronics). Later off-line analysis determined mean time delay between probes (Δtime) measured over at least six cardiac cycles. PWV was determined in central (i.e., aortic) and peripheral (arm and leg) arterial segments. Recording sites were carotid and femoral arteries for aortic PWV, brachial and radial arteries for arm PWV, and femoral and posterior tibial arteries for leg PWV. The skin over the recording sites was marked to ensure that repeat measurements were obtained over identical arterial segments.

Radial artery tonometry. Arterial tonometry was used to obtain indexes of arterial stiffness, wave reflection, and myocardial oxygen demand. To obtain these indexes, a tonometer was applied transcutaneously over the radial artery near the styloid process and adjusted to obtain optimal waveforms. Waveforms were calibrated by synthesis of a central (aortic) pressure waveform using a generalized transfer function (Sphygmocor, AtCor Medical, Sydney, Australia) after input of brachial systolic and diastolic BP (17). Derived hemodynamic variables were aortic BP (systolic and diastolic). With use of synthesized central waveforms, aortic augmentation index was estimated as the percent increase in the peak systolic waveform from the systolic shoulder. Rate-pressure product was calculated as brachial and aortic systolic BP times heart rate. Because of technical difficulties, we were unable to obtain radial waveforms in one older subject.

Data Collection and Statistical Analysis

Physiological data were recorded (MacLab 8e, ADInstruments) at 1,000 Hz. Differences in baseline subject characteristics were determined by t-test, and effects of the intervention were determined using a mixed-model ANOVA. Specific contrasts were made using Student-Newman-Keuls tests. Pearson product-moment correlations were used to determine strength of relations between variables. Stepwise multiple regression analysis (F-to-enter 4.00, F-to-remove 3.96, number of steps = 20) was used to identify predictors of responses of interest. Statistical significance was accepted at P < 0.05.

RESULTS

Subject Characteristics

Older subjects tended to weigh more than younger subjects (P = 0.10) and their BMIs were greater (P < 0.05; Table 1). Peripheral (brachial) and central estimates of BP at rest were greater (P < 0.05) in older than in younger subjects. Lastly, measures of arterial stiffness (PWV and augmentation index) at rest were greater (P < 0.05) in older subjects.

Responses to Superficial Skin Cooling

In younger and older subjects, cooling decreased (P < 0.05) mean skin surface temperature without affecting sublingual temperature (Fig. 1). No subject described the cooling trial as painful.

In younger and older subjects, superficial skin cooling elicited a significant pressor response without affecting heart rate (Fig. 2). Brachial pressor responses (systolic and mean BP) to superficial skin cooling were greater in older than in younger subjects (Fig. 2). Similarly, pressor responses (systolic and mean BP) to superficial skin cooling were greater when central estimates of BP were considered (Fig. 3). However, the magnitude of change in brachial and central BP during superficial skin cooling did not differ in younger or older subjects (Fig. 3). Superficial skin cooling-induced increases in peripheral and...
central BP were highly correlated ($r = 0.96$ and 0.98, for systolic and diastolic BP, respectively). Lastly, the slopes of the regressions between the respective changes in peripheral and central estimates of BP were not different from 1.0, indicating no potentiation of the pressor response to cold stress in central arteries of younger or older adults.

Superficial skin cooling elicited divergent effects on measures of arterial stiffness. Superficial skin cooling increased measures of PWV (aortic, arm, or leg) in older, but not younger, adults (Fig. 4). In contrast, superficial skin cooling increased ($P < 0.05$) aortic augmentation index in younger and older adults similarly (Fig. 4). Rate-pressure product was higher in older subjects at rest and increased further during superficial skin cooling in older (7,544 ± 485 vs. 8,728 ± 557 and 6,593 ± 472 vs. 8,155 ± 562 mmHg·min for brachial and central rate-pressure product at baseline and during cooling, respectively, $P < 0.05$), but not younger, adults (6,138 ± 360 vs. 6,645 ± 374 and 5,239 ± 291 vs. 5,820 ± 304 mmHg·min, $P > 0.05$).

Correlates of Augmented Pressor Responses to Superficial Skin Cooling

Pressor responses to superficial skin cooling were correlated with several variables (Table 2). To gain insight into which variables predicted augmented pressor responses to superficial skin cooling, we performed stepwise multiple regression using changes in brachial and central systolic BP as the dependent variable and other baseline subject characteristics (age, height, weight, BMI, body surface area, skin temperature, and oral temperature), hemodynamic variables (heart rate and brachial and central BPs at rest), and indexes of arterial stiffness (PWVs and augmentation index) as independent variables. This analysis revealed that aortic PWV (63%) and brachial systolic BP (15%) at rest explained 78% of the variability in the pressor response to superficial skin cooling.

Responses During the Control Trial

Values obtained at baseline during the control and cooling trials were similar within each subject group (younger and older), although some age-associated differences existed at baseline. During the control trial, all variables were unchanged in younger and older subjects, indicating that responses observed during the cooling trial were the result of superficial skin cooling.

DISCUSSION

In this study, we demonstrate that aging is associated with an augmented systolic and mean BP response to non-internal body temperature-reducing cold stress in humans and that these responses are strongly associated with increased levels of central arterial stiffness (i.e., aortic PWV). Our findings importantly extend previous findings showing greater pressor responses to core body temperature-reducing levels of cold stress in older than in younger adults (7, 8, 19, 38) by showing that pressor responses to a much less severe (i.e., non-internal body temperature-reducing) level of cold stress induces marked and consistently higher systolic and mean BP responses in older than in younger adults.

The mechanism(s) underlying the greater systolic, but not diastolic, BP response to non-internal body temperature-reducing cold stress in older adults may involve central arterial stiffness. As expected, central arterial stiffness was higher in older than in younger adults before superficial skin cooling (Fig. 4, Table 1). Structural changes in the aorta with age (29) would be expected to reduce the ability of the vasculature to buffer pressure fluctuations across the cardiac cycle, resulting in increased systolic BP and widening of pulse pressure at rest and, possibly, in response to stress (16, 22). These effects may help explain why indexes of central arterial stiffness, before cooling, were consistently related to the magnitude of the systolic and diastolic BP response to cold stress.
pressor responses to superficial skin cooling (Table 2). Although our study design does not allow us to definitively identify increased levels of arterial stiffness as an underlying factor in the greater pressor response to skin surface cooling in older adults, the results of statistical analysis showing that aortic PWV, measured at rest before cooling, was the strongest predictor of this response are consistent with this concept. We cannot determine whether further increases in PWV observed during superficial skin cooling in older adults were the cause or the result of the augmented systolic BP response to superficial skin cooling, although we suspect that the latter may be the case (29).

Our findings suggest another reason why cardiovascular-related morbidity and mortality may increase in winter. Increased levels of central arterial stiffness may lead to greater increases in myocardial oxygen demand during cold exposure in older adults. During superficial skin cooling, increased systolic BP (afterload) results in increased rate-pressure product, which was not observed in younger adults, and, presumably, stroke work (since BP is increased and stroke volume is unchanged during cooling) (42, 43) in younger and older adults. These effects are more pronounced in older adults on the basis of their augmented systolic BP responses to superficial skin cooling. Additionally, increases in preload associated with superficial skin cooling (43) may increase ventricular wall stress further in older adults secondary to decreases in left ventricular compliance with age (2). It is possible that left ventricular contractility may need to increase in older adults because of a reduced efficiency of the Frank-Starling mechanism to maintain stroke volume in the face of increased afterload during cooling (2). These findings suggest that superficial skin cooling results in greater increases in myocardial oxygen demand in healthy older adults and may help explain the
relations between cold outdoor temperatures, acute cardiovascular events, and aging in humans (9, 11, 28, 32, 34).

Pressor responses to superficial skin cooling were not augmented in central (estimated in the aorta) compared with peripheral (brachial) arteries in younger or older adults. These data are in contrast to previous data in younger adults demonstrating greater increases in central than in peripheral artery systolic BP during a more severe cold stress (14). Although we did not see this amplification during superficial skin cooling in younger or older adults, we did observe greater age-associated increases in central than in peripheral systolic BP at rest, as previously reported (29). These effects of aging on the relation between central and peripheral BP are thought to be due to enhanced effects of wave reflections (41). Responses in central systolic BP to superficial skin cooling are important to document, because pressure within the aorta, rather than the brachial artery, should be a better determinant of left ventricular workload (39). We are aware that the use of a transfer function to reconstruct central aortic waveforms from radial waveforms is controversial (18, 30). However, these data were used only to supplement data collected using other more established and widely accepted methods of assessing arterial stiffness, such as PWV (23).

Other factors that may contribute to pressor responses during superficial skin cooling include sympathetic nervous system activation. Cold stress increases plasma norepinephrine levels (13). We are not aware of any data comparing indexes of whole body sympathetic outflow in younger and older adults during the type of cold stress used in the present study. However, in a previous study in which core body temperature was decreased during cooling, increases in norepinephrine were twice as great in younger (4-fold increase from baseline) as in older (2-fold increase from baseline) adults, and epinephrine was unchanged (15). Thus it would appear unlikely that an augmented sympathoexcitatory response to superficial skin cooling would explain the augmented pressor response we observed in older adults during superficial skin cooling in the present study. Additionally, splanchnic vasoconstrictor responses to upright tilt are greater in older than in younger subjects (27). Inasmuch as we previously showed splanchnic vasoconstriction during superficial skin cooling in younger healthy adults (42), this response may be augmented with age.

It was not an aim of this study (i.e., this study was not powered) to directly examine sex-related effects. Some previous studies have reported sex-related differences in response to cold stress, although others have observed no such effect (36, 37). In the present study, we observed no baseline differences in BP measures between men and women within their respective age group. However, during superficial skin cooling, increases in systolic and mean BP, pulse pressure, and rate-pressure product were greater in older women than in older men. No such sex-related effects appeared in the younger group. These data are partially consistent with those of Wagner.

Fig. 3. Changes in brachial (peripheral) and central estimates of blood pressure from baseline to 12–20 min after initiation of superficial skin cooling in younger (filled bars) and older (open bars) adults. Values are means ± SE. *P < 0.05 vs. baseline. †P < 0.05 vs. young.
and Horvath (38), who identified cold-induced increases in rate-pressure product in older women compared with younger women and older men but no significant differences in BP responses between these groups. Future studies appear warranted to more definitively examine these potential important differences in older men and women.

The diet of the volunteers in the days leading up to the experimental session was not controlled. Additionally, we did not measure cholesterol levels of volunteers, nor did we measure hydration status before data collection. These are all acknowledged limitations of the present study.

In conclusion, our findings provide support for the concept that aging is associated with augmented pressor responses (systolic and mean BP) to non-internal body temperature-reducing cold stress in humans. Importantly, age-associated increases in arterial stiffness may be a critical factor underlying this augmented BP response in older individuals, as suggested by the strong correlation between these measures. Thus it may be important for future studies to consider the role of arterial stiffness when interpreting the effects of cold exposure in other subject populations. Moreover, the present findings may help explain the associations between increased cardiovascular morbidity and mortality during the cold winter months, particularly in older adults.

**GRANTS**

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### Table 2. Univariate correlates of the pressor response to superficial skin cooling

<table>
<thead>
<tr>
<th>Variable</th>
<th>Change in Brachial BP</th>
<th>Change in Central BP</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Systolic</td>
<td>Diastolic</td>
</tr>
<tr>
<td>Age</td>
<td>0.75*</td>
<td>-0.04</td>
</tr>
<tr>
<td>Height</td>
<td>0.07</td>
<td>0.30</td>
</tr>
<tr>
<td>Weight</td>
<td>0.17</td>
<td>0.14</td>
</tr>
<tr>
<td>BMI</td>
<td>0.20</td>
<td>-0.01</td>
</tr>
<tr>
<td>Body surface area</td>
<td>0.24</td>
<td>0.27</td>
</tr>
<tr>
<td>Skin temperature</td>
<td>-0.11</td>
<td>-0.09</td>
</tr>
<tr>
<td>Oral temperature</td>
<td>-0.38</td>
<td>-0.19</td>
</tr>
<tr>
<td>Augmentation index</td>
<td>0.67*</td>
<td>0.46*</td>
</tr>
<tr>
<td>Aortic PWV</td>
<td>0.80*</td>
<td>0.69*</td>
</tr>
<tr>
<td>Arm PWV</td>
<td>0.11</td>
<td>-0.06</td>
</tr>
<tr>
<td>Leg PWV</td>
<td>0.25</td>
<td>-0.15</td>
</tr>
<tr>
<td>Brachial SBP</td>
<td>0.56*</td>
<td>0.45*</td>
</tr>
<tr>
<td>Brachial DBP</td>
<td>0.54*</td>
<td>0.39</td>
</tr>
<tr>
<td>Brachial MAP</td>
<td>0.59*</td>
<td>0.45*</td>
</tr>
<tr>
<td>Central SBP</td>
<td>0.62*</td>
<td>0.46*</td>
</tr>
<tr>
<td>Central DBP</td>
<td>0.52*</td>
<td>0.39</td>
</tr>
<tr>
<td>Central MAP</td>
<td>0.59*</td>
<td>0.45*</td>
</tr>
<tr>
<td>Heart rate at rest</td>
<td>0.13</td>
<td>-0.21</td>
</tr>
</tbody>
</table>

Values in the matrix are Pearson product-moment correlation ($r$) values. Skin and oral temperatures were measured during superficial skin cooling. BP, blood pressure; MAP, mean arterial blood pressure. *Significant univariate correlation ($P < 0.05$).
REFERENCES


