Acute effects of cold exposure on central aortic wave reflection

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Edwards, David G., Amie L. Gauthier, Melissa A. Hayman, Jesse T. Lang, and Robert W. Kenefick. Acute effects of cold exposure on central aortic wave reflection. J Appl Physiol 100: 1210–1214, 2006. First published October 13, 2005; doi:10.1152/japplphysiol.01154.2005.—The purpose of this study was to determine the effects of acute cold exposure on the timing and amplitude of central aortic wave reflection and central pressure. We hypothesized that cold exposure would result in an early return of reflected pressure waves from the periphery and an increase in central aortic systolic pressure as a result of cold-induced vasocostriction. Twelve apparently healthy men (age 27.8 ± 2.0 yr) were studied at random, in either temperate (24°C) or cold (4°C) conditions. Measurements of brachial artery blood pressure and the synthesis of a central aortic pressure waveform (by noninvasive radial artery applanation tonometry and use of a generalized transfer) were conducted at baseline and after 30 min in each condition. Central aortic augmentation index (AI), an index of wave reflection, was calculated from the aortic pressure waveform. Cold induced an increase (P < 0.05) in AI from 3.4 ± 1.9 to 19.4 ± 1.8%. Cold increased (P < 0.05) both brachial and central systolic pressure; however, the magnitude of change in central systolic pressure was greater (P < 0.05) than brachial (13 vs. 2.5%). These results demonstrate that cold exposure and the resulting peripheral vasoconstriction increase wave reflection and central systolic pressure. Additionally, alterations in central pressure during cold exposure were not evident from measures of brachial blood pressure.

SYMPTOMS OF ANGINA have been reported to become more severe when patients with cardiovascular disease are exposed to a cold environment (8, 13). Additionally, there is epidemiological evidence that seasonal variation exists in the incidence of cardiac events and deaths, with an increase in winter months (6, 7, 20, 21, 34). Identifying mechanisms by which cold exposure increases the reported incidences of myocardial ischemia may be helpful in explaining this phenomena and assessing possible risk for individuals with cardiovascular disease.

The body’s compensatory responses to cold exposure are aimed at heat conservation for survival. Cold exposure is accompanied by sympathetic activation and cold-induced vasocostriction (CIVC). CIVC lowers the temperature gradient between the skin and environment, decreasing heat loss and helping to maintain core temperature. While serving to maintain core temperature, CIVC may also lead to an increase in the stiffness of the arterial system. Arterial stiffness is known to increase systolic blood pressure as a result of an inability to absorb pulsations from the heart and an increase in wave reflection from the periphery increasing myocardial oxygen demand (24). Pressure waves generated by the heart are buffered by the aorta and large elastic arteries. As pressure waves travel through the arterial system they encounter bifurcations and the arteriole beds, which reflect these waves back to the heart. If the reflected wave arrives early in systole it will add to the pressure generated by the heart and increase systolic and pulse pressures. Because larger elastic arteries buffer pulsations from the heart, muscular arteries can alter the speed of travel of pressure waves along their length and determine when reflected waves return back to the heart, and arterioles serve as major reflecting sites (23, 29), alterations in the stiffness of the arterial system resulting from CIVC may have dramatic effects on the central pressure wave.

The speed and amplitude of reflected waves affect peak central systolic pressure but not peripheral pressure (35). Thus measures of brachial cuff blood pressure will not reveal these effects. Central pressure, the pressure that the left ventricle must overcome, influences wall tension and is a better indicator of myocardial oxygen demand. Therefore, the effect of cold exposure on blood pressure (and myocardial oxygen demand) may be greater than previously thought. The purpose of this study was to determine the effects of acute cold exposure on the timing and amplitude of central aortic wave reflection and central pressure. We hypothesized that cold exposure would result in an early return of reflected pressure waves from the periphery and an increase in central aortic systolic pressure as a result of CIVC.

METHODS

Subjects. Twelve apparently healthy men, as assessed by medical history questionnaire, participated in this study (age 27.8 ± 2.0 yr; weight 81.5 ± 2.3 kg; height 175.4 ± 1.8 cm). All subjects were nonsmokers and refrained from caffeine and ethanol for at least 12 h before testing. All procedures were reviewed and approved by the Institutional Review Board, and all subjects gave written informed consent.

Study design. Testing involved 30 min of rest in two treatment conditions consisting of cold exposure (4°C and wind speed of 6.1 m/s) and temperate exposure (24°C). The environmental treatment protocols were randomly assigned and separated by at least 7 days.

Experimental protocol. A urine specific gravity (USG) of <1.019 (3) was used to verify adequate hydration before each trial. After a seated 20-min equilibration period at 24°C baseline measurements were made. Subjects then entered the environmental chamber and rested in a seated position for 30 min in either the temperate or cold condition.

Physiological measures. During the experimental trials, core (rectal) and mean weighted skin (27) temperatures and oxygen uptake (V̇O2, Vmax 229 metabolic cart, SensorMedics, Yorba Linda, CA) were monitored every 10 min. Brachial blood pressure was assessed by sphygmomanometry in triplicate and averaged at baseline and 30 min.

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wave reflection and a manifestation of overall systemic arterial stiffness. AI is defined as the ratio of reflected wave amplitude and pulse pressure, or \( AI = (P_s - P_i)/(P_s - P_d) \), where \( P_s \) is peak systolic pressure, \( P_d \) is end-diastolic pressure, and \( P_i \) is an inflection point marking the beginning upstroke of the reflected pressure wave. The \( \Delta t \) is a measure of the time it takes for the reflected wave to travel to the periphery and back to the heart and is defined as the time delay from the foot of the pressure wave and the inflection point on the central waveform. A stiffer arterial system results in faster wave travel and quicker return of the reflected wave and thus a lower \( \Delta t \).

**Statistical analyses.** A 2 × 2 (condition × time) analysis of variance with repeated measures was used to compare differences among the trials. A Newman-Keuls post hoc analysis was used to determine significant differences within and between conditions. Paired \( t \)-tests were used to compare \( \dot{V}O_2 \) and skin and core temperatures between conditions. An \( \alpha \)-level of \( P < 0.05 \) was required for significance, and all data are presented as means ± SE.

**RESULTS**

All subjects completed each experimental trial. There were no differences in baseline measurements between conditions. Additionally, subjects were in a well-hydrated state at baseline for both the cold (USG: 1.010 ± 0.002) and temperate (USG: 1.009 ± 0.002) conditions.

**Thermoregulatory responses.** The thermoregulatory responses to cold and temperate exposure are shown in Table 1. Cold exposure induced an average increase of 13% in central systolic pressure, and this increase was different from both baseline and 30-min central systolic pressure in the temperate condition (\( P < 0.05 \)). Cold exposure resulted in an increase (\( P < 0.05 \)) in central systolic pressure, and this increase was different from both baseline and 30-min central systolic pressure in the temperate condition (\( P < 0.05 \)). Cold induced an average increase of 13% in central systolic pressure compared with only 2.5% in peripheral systolic pressure (\( P < 0.05 \), Fig. 2). Consistent with the change in central systolic pressure, central pulse pressure also increased in response to cold exposure (\( P < 0.05 \)) and was greater than both baseline and 30-min central pulse pressure in the temperate condition (\( P < 0.05 \)).

AI significantly increased after 30 min of exposure to the cold (3.4 ± 3.3 vs. 19.4 ± 4.4%, \( P < 0.05 \), Fig. 3). This response was also significantly different compared with the temperate condition (Fig. 2). There was a significant decrease in the \( \Delta t \) from baseline to rest in both the cold and temperate conditions (\( P < 0.05 \)); however, \( \Delta t \) was lower in the cold condition at 30 min compared with the temperate condition (\( P < 0.05 \)).

**Table 1. Physiological variables**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Temperate</th>
<th>Cold</th>
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<tbody>
<tr>
<td>( \dot{V}O_2 ), ml·kg⁻¹·min⁻¹</td>
<td>3.3±0.2</td>
<td>6.0±0.4*</td>
</tr>
<tr>
<td>Mean skin temperature, °C</td>
<td>31.4±0.2</td>
<td>18.8±0.5*</td>
</tr>
<tr>
<td>Core temperature, °C</td>
<td>36.6±0.2</td>
<td>37.3±0.1*</td>
</tr>
</tbody>
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Values are means ± SE. \( \dot{V}O_2 \), oxygen uptake. *\( P < 0.05 \) vs. temperate.
due to shivering and nonshivering thermogenesis in response to a decrease in core temperature. An increase in core temperature shivering response was, in part, responsible for a 0.7°C increase, significantly elevated after 30 min of cold exposure. Additionally, the reflection and indicator of systemic arterial stiffness, was decreased and are consistent with previous reports (18, 25). In addition, subjects began shivering by 5 min of exposure and continued shivering throughout the duration of cold exposure. 

**DISCUSSION**

The purpose of this study was to examine the effect of acute cold exposure on wave reflection and central blood pressure. The major findings demonstrate that AI, a measure of wave reflection and indicator of systemic arterial stiffness, was significantly elevated after 30 min of cold exposure. Additionally, Δt was significantly reduced after cold exposure, indicating that the reflected wave was returning to the heart earlier. Brachial and central systolic pressures were significantly increased with cold exposure compared with the temperate environment. However, the magnitude of the cold-induced change in central systolic pressure was greater than the change in brachial systolic pressure. This change in central pressure waveform can be attributed to cold-induced increases in wave reflection and stiffness of the arterial system. Our findings suggest that cold exposure may increase myocardial oxygen demand through an increase in central systolic pressure due to an increase in wave reflection. Furthermore, the magnitude of the increase in myocardial work, due to cold-induced blood pressure changes, cannot be determined with traditional brachial cuff measurements.

**Thermoregulatory responses.** Exposure to the 4°C environment resulted in skin temperatures that were significantly reduced and are consistent with previous reports (18, 25). In addition, subjects began shivering by 5 min of exposure and continued shivering throughout the duration of cold exposure. 

**Hemodynamic responses.** Wave reflection, as assessed by AI, was increased in the cold condition and was responsible for the greater change in central systolic pressure compared with peripheral systolic pressure. Additionally, central pulse pressure was significantly greater after 30 min of cold exposure as a result of the increase in wave reflection and central systolic pressure. Geleris and colleagues (11) have also reported a significant increase in AI after cold exposure; however, these authors used the cold pressor test (CPT). The CPT is a method of experimentally inducing pain (22) rather than a true cold response. The whole body cooling in the current study may be more physiologically relevant.

The observed increase in AI is a manifestation of an increase in the stiffness of the arterial system during cold exposure. Because an increase in wave reflection affects central, but not peripheral, systolic pressure, the effect of cold exposure was not readily apparent from measurement of brachial cuff pressure. Under conditions of acute increase in arterial stiffness, as in the present study, peripheral systolic pressure changes very little. Due to this small change in systolic pressure, the effects of an increase in central pressure will not be reflected in estimates of myocardial oxygen demand (heart rate × peripheral systolic blood pressure).

CIVC is the likely mechanism by which cold exposure increases the stiffness of the arterial system and subsequently wave reflection and central systolic pressure. Δt was significantly lower in the cold condition, indicating that the reflected pressure wave returned earlier from the periphery. CIVC likely leads to a decrease in diameter of muscular arteries and arterioles, speeding pressure wave travel and potentially altering the site of wave reflection. However, dysfunction of the endothelial nitric oxide pathway may also play a role in the increase in AI. Carnio and Branco (4) observed that the increased pressure in response to acute cold exposure in rats is whole body cooling has been reported by others (36). These data confirm a cold response to the 4°C climate.

**Table 2. Hemodynamic variables**

<table>
<thead>
<tr>
<th></th>
<th>Temperate</th>
<th>Cold</th>
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<tbody>
<tr>
<td></td>
<td>Baseline</td>
<td>30 min</td>
</tr>
<tr>
<td>Heart rate, beats/min</td>
<td>72 ± 3</td>
<td>73 ± 3</td>
</tr>
<tr>
<td>Peripheral SP, mmHg</td>
<td>132 ± 4</td>
<td>129 ± 3</td>
</tr>
<tr>
<td>Peripheral DP, mmHg</td>
<td>85 ± 2</td>
<td>85 ± 2</td>
</tr>
<tr>
<td>Peripheral PP, mmHg</td>
<td>47 ± 4</td>
<td>44 ± 2</td>
</tr>
<tr>
<td>Central SP, mmHg</td>
<td>112 ± 2</td>
<td>114 ± 3</td>
</tr>
<tr>
<td>Central DP, mmHg</td>
<td>86 ± 2</td>
<td>86 ± 2</td>
</tr>
<tr>
<td>Central PP, mmHg</td>
<td>26 ± 2</td>
<td>27 ± 2</td>
</tr>
</tbody>
</table>

Values are means ± SE. SP, systolic pressure; DP, diastolic pressure; PP, pulse pressure; MAP, mean arterial pressure. *P < 0.05 baseline cold; †P < 0.05 vs. baseline temperate; ‡P < 0.05 vs. 30-min temperate.

Fig. 2. Percent change in systolic pressure induced by cold. Values are means ± SE. *P < 0.05 vs. peripheral.

Fig. 3. Augmentation index and time to wave reflection at baseline and after 30 min in the temperate and cold conditions. Values are means ± SE. *P < 0.05 vs. baseline; †P < 0.05 vs. baseline temperate; ‡P < 0.05 vs. 30 min temperate.
nitric oxide dependant. Although we did not assess the contribution of nitric oxide in the present study, its availability is an important determinant of AI (38). A cold-induced reduction in nitric oxide availability, in conjunction with CIVC, may partly be responsible for the cold-induced changes in AI observed in the present study.

An increase in wave reflection and central systolic pressure elevate the metabolic requirements of the heart in an effort to maintain cardiac output (19) and may potentially explain the occurrence of cold-induced myocardial ischemia. Another potential mechanism for cold-induced myocardial ischemia is a reduction in coronary perfusion due to coronary vasoconstriction. Frank et al. (9) recently reported that mild core hyperthermia in young healthy subjects did not induce coronary vasoconstriction but vasodilation. The authors attributed this response to β-adrenergic receptor-mediated augmentation in myocardial work. These findings, in young healthy subjects with presumably normally responsive coronary arteries, suggest that cold-induced ischemia may be the product of myocardial oxygen demand not being met by the increase in myocardial blood flow (9). Results of Frank et al. (8), in combination with our findings that cold exposure increases AI, suggest that the cold-induced increases in afterload may potentiate the occurrence of ischemia in the cold. Additionally, in the present study we did not observe a reduction in core temperature, suggesting that core temperature does not need to be reduced for deleterious hemodynamic changes to occur. In fact, it appears that it is not a change in body temperature but the compensatory response to cold exposure to maintain core temperature that leads to these changes.

It is important to note that the subjects in the present study were young, healthy volunteers observed at rest and who typically do not experience myocardial ischemia or symptoms of angina. With coronary artery disease (CAD), acute increases in arterial stiffness, resulting in an increase in wave reflection and central systolic pressure, can further increase myocardial oxygen demand and decrease coronary perfusion. In turn, these alterations in myocardial oxygen demand and perfusion can result in myocardial ischemia. In animal studies, the use of bandaging (37) or stiff plastic tube bypass (15, 28) to increase aortic stiffness resulted in increased pulse pressure and cardiac work and a reduction in coronary perfusion. During total coronary occlusion, increased arterial stiffness results in a marked decrease in myocardial function (15). This evidence suggests that aortic stiffness increases myocardial oxygen demand and reduces myocardial perfusion particularly in the setting of CAD. In support of this, a recent investigation by Kingwell et al. (19) found that time to ischemia during treadmill testing was inversely correlated to measures of arterial stiffness in CAD patients. This finding suggests that arterial stiffness is a principal determinant of ischemic threshold in CAD (19). When considering the results of Kingwell et al. with the results of the present study, we hypothesize that an acute cold-induced increase in arterial stiffness may shorten time to ischemia in persons with cardiovascular disease. The increase in whole body VO₂ and heart rate observed in the current study cannot be discounted and likely also contributes to increases in myocardial oxygen demand during cold exposure in CAD.

In summary, we have demonstrated that AI, a measure of wave reflection and indicator of systemic arterial stiffness, was significantly elevated after acute cold exposure. Brachial and central systolic pressures increased with cold exposure; however, the magnitude of the cold-induced change in central systolic pressure was greater than the change in brachial systolic pressure. This is attributable to cold-induced increases in wave reflection and stiffness of the arterial system and suggests that the magnitude of the hemodynamic response to cold exposure cannot be determined with traditional brachial cuff measurements. Cold exposure may increase myocardial oxygen demand through an increase in central systolic pressure secondary to increased arterial stiffness and wave reflection. The present study provides new insight into the cardiovascular and hemodynamic responses to environmental stress. Future research should be aimed at examining the effect of cold exposure on wave reflection and central pressure in an aging and/or CAD populations, to determine clinical significance.

REFERENCES


