Cardiovascular responses of blood pressure hyperreactors to the cold pressor test and exercise

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Abstract  The cold pressor test has been used to assess neural control of the cardiovascular system by observing the pressor response during the immersion of one hand in cold water. Previous studies have defined blood pressure hyperreactors to cold stress as individuals who respond with a rise of 15 mmHg or greater in their systolic and/or diastolic blood pressure and who have a higher incidence of hypertension than normal reactors. In this review, the regulatory mechanism of the cardiovascular system during the cold pressor test, and the cardiovascular responses of hyperreactors to both the cold pressor test and an isometric handgrip exercise are described. During the late phase of cold-water immersion for 2 min, the arterial baroreflex resets the heart rate to the control level, but not the peripheral resistance. Although both isometric exercise and the cold pressor test increased blood pressure by the same magnitude, baroreflex resetting of the heart rate was seen during the cold pressor test, but not during the isometric handgrip exercise. Hyperreactors showed larger cardiovascular responses to the cold pressor test than normal reactors, but not to the handgrip exercise. The pain sensation could contribute to greater increases in blood pressure in hyperreactors during cold-water immersion. The incidence of hyperreactors was higher in the middle-aged and elderly (66.7%) than in young adults (27.5%). The pulse pressure of hyperreactors during cold stress was decreased in young adults, but increased in middle-aged and elderly subjects. The onset mechanism of hypertension in hyperreactors remains to be clarified.

Keywords: cardiac contractility, arterial stiffness, pain sensation, incidence of hyperreactors

Introduction

The cold pressor test, first reported by Hines and Brown, has been used to assess neural control of the cardiovascular system by observing the pressor response during the immersion of one hand in cold water. This pressor response is induced by increased cardiac output and by enhanced sympathetic nerve activity. By using \( \frac{dP}{dt}/P \) of the carotid artery pulse, a non-invasive index of cardiac contractility, we have investigated the regulatory mechanism of the cardiac function during a cold pressor test.

Two large, long-term prospective studies using survival analysis have defined blood pressure hyperreactors to the cold pressor test as individuals who respond with a rise of 15 mmHg or greater in their systolic and/or diastolic blood pressure, and they have a higher incidence rate of hypertension than normal reactors. It is assumed that hyperreactors may yield larger cardiovascular responses to the cold pressor test and exercise than normal reactors. Since hypertension may develop with disturbances in arterial stiffness, we have investigated the reactivity of arterial stiffness, i.e., pulse wave velocity (PWV) and an augmentation index normalized to a heart rate of 75 bpm (AIX@75), of hyperreactors to the cold pressor test and isometric handgrip exercise.

In this short review, the regulatory mechanism of the cardiovascular system during the cold pressor test is described along with the characteristics of the cardiovascular responses of hyperreactors to both the cold pressor test and isometric handgrip exercise.

Cold pressor test

Cardiovascular responses. Thirty-four healthy subjects (17 male and 17 female) aged 18-25 years underwent the cold pressor test according to Hines and Brown, which required them to immerse their right hand in water of 4°C for 2 min. Hyperreaction was observed in 12 of the 34 subjects (35.3%): seven of 17 males (41.2%) and five of 17 females (29.4%).

In both normal reactors and hyperreactors, mean blood pressure (MBP) increased maximally at 120 s (seconds) after the onset of cold-water immersion and remained el-
evated until 60 s after the offset of immersion. However, the time course of the heart rate and cardiac contractility differed from that of the MBP. The heart rate and \((dP/dt)/P\) increased maximally at 60 s after the onset of immersion and returned to the control value at 120 s, a phenomenon known as the resetting mechanism of the arterial baroreflex during cold-water immersion\(^{10,15}\), which was more clearly observed in the heart rate than in cardiac contractility\(^{16}\). Hyperreactors produced greater increases in MBP at 60 s and 120 s of immersion and 60 s after the offset of immersion than normal reactors. Although the heart rate and \((dP/dt)/P\) followed almost the same time course, the increases in heart rate, but not cardiac contractility, were larger in hyperreactors than in normal reactors, suggesting that the specific response of cardiac function in hyperreactors is likely to be dominated by parasympathetic withdrawal\(^{10}\).

In both normal reactors and hyperreactors, no changes were noted in stroke volume or cardiac output, whereas total peripheral resistance (TPR) increased at 60 s or 120 s after the onset of immersion in cold-water\(^{10,17}\). However, the time course did not differ in terms of the stroke volume, cardiac output, or TPR between the two groups.

As regards arterial stiffness, the aortic PWV and carotid Alx@75 followed almost the same time course in both groups of subjects; they remained unchanged during the first 30 s, but increased to a maximum at 90 - 120 s after the onset of cold-water immersion, and then remained elevated for as long as 30 s after the offset of immersion\(^{16}\). The time courses were similar to that of muscle sympathetic nerve activity (MSNA)\(^{3,8}\), suggesting that cold- and/or pain-induced vasoconstriction increases arterial stiffness and the PWV, which leads to increases in wave reflection from the periphery, the Alx@75\(^{18,19}\). The increases in PWV and Alx@75 during cold-water immersion were greater in hyperreactors than in normal reactors. The specific response of PWV and Alx@75 in hyperreactors may be ascribed to greater increases in arterial stiffness caused by increased MBP, which occurs with either the increased heart rate by parasympathetic withdrawal\(^{10}\) or vasoconstriction of muscular arteries by sympathetic activation\(^{18}\), or with both of them.

**Cold and pain sensation.** Both cold and pain sensations were evoked during cold-water immersion. Cold sensation, which originates from cutaneous cold receptors, becomes maximal at around 1 min of cold stress and produces an increase in blood pressure\(^{20,21}\). Pain sensation, which originates from cutaneous nociceptors, modifies the cold pressor reactions\(^{20,21}\). Peckerman et al.\(^{22}\) have reported that the increase in blood pressure during the cold pressor test depends on the intensity of the perceived pain. Every 30 s during the cold-water immersion for 2 min, the cold sensation was evaluated on an interval scale of 7 steps (1: very cold, 2: cold, 3: slightly cold, 4: neutral, 5: slightly warm, 6: warm, 7: hot), and the pain sensation on an interval scale of 4 steps (1: very painful, 2: painful, 3: slightly painful, 4: no pain)\(^{10,23}\). Both the cold and pain sensations became stronger throughout cold-water immersion in both normal reactors and hyperreactors. Although no different time course was observed in the cold sensation between the two groups, the pain sensation was stronger in hyperreactors than normal reactors at 60 s during immersion in cold water. Therefore, the pain sensation could contribute to greater increases in blood pressure in hyperreactors.

### Isometric handgrip exercise

A cardiovascular response to exercise is induced both by direct action of the cardiovascular center activated from the efferent copy of motor command and by the exercise pressor reflex originating from active muscles\(^{24}\). To examine whether hyperreactors yield larger cardiovascular responses to exercise than normal reactors, the isometric handgrip exercise was performed at 30% maximal voluntary contraction for 2 min\(^{10}\). The increase in MBP was the same level during isometric exercise as during the cold pressor test. However, the decreases in heart rate and \((dP/dt)/P\) seen during the late phase of the cold pressor test were not observed during the isometric exercise, suggesting that the baroreflex resetting of the heart rate and cardiac contractility is likely to be mediated via the central command at the onset of isometric exercise\(^{25,26}\).

The aortic PWV and carotid Alx@75 remained unchanged during the first 30 s, but increased to a maximum at 60 s after the onset of exercise, and then remained elevated until 30 s after the offset of exercise\(^{10}\). These time-courses were similar to that of MSNA\(^{27-29}\), suggesting that vasoconstriction elicited by exercise pressor reflex increases arterial stiffness and PWV, causing an increase in Alx@75\(^{18,30}\).

Geleris et al.\(^{31}\) have reported that subjects with greater PWV and Alx responses to the cold pressor test also had greater responses to the isometric handgrip exercise. However, the time courses of the MBP, heart rate, \((dP/dt)/P\), aortic PWV, and carotid Alx@75 did not differ between normal reactors and hyperreactors, suggesting that neither group of reactors differs in cardiovascular responses to isometric handgrip exercise. It is likely in isometric handgrip exercise that the increase in sympathetic nerve activities elicited by the direct action of the cardiovascular center and by an exercise pressor reflex does not differ between normal reactors and hyperreactors, and parasympathetic withdrawal does not dominantly affect cardiovascular responses in hyperreactors.

### Characteristics of blood pressure hyperreactors to cold pressor test

Eighty young adults (38 male and 42 female) aged 18-23 years and 15 middle-aged and elderly subjects (3 male
and 12 female) aged 45-67 years underwent the cold pressor test according to Hines and Brown\(^1\), which required them to immerse their right hand in 4°C water for 1 min. Hyperreactors accounted for 22 of the 80 subjects in young adults (27.5%) and 10 of the 15 subjects in the middle-aged and elderly subjects (66.7%), indicating that the incidence of hyperreactors is higher in the middle-aged and elderly subjects than in young adults \((P<0.05, \chi^2\text{-test})\). Of the 22 young adult hyperreactors, 10 were male and 12 were female, whereas of the 10 hyperreactors in the middle-aged and elderly subjects, two were male and eight were female. There was no difference in the incidence of hyperreactors between male and female in the two groups of subjects.

The responses of blood pressure, heart rate, and cold and pain sensation to the cold pressor test were measured and compared between the young adults and middle-aged and elderly subjects (Tables 1 and 2). In both normal reactors and hyperreactors, the heart rate during cold stress increased significantly in young adults, but not in middle-aged and elderly subjects. In hyperreactors, the pulse pressure during cold stress decreased significantly in young adults, whereas it increased significantly in middle-aged and elderly subjects, suggesting that the arteries of hyperreactors in the middle-aged and elderly may be stiffer and less compliant during cold stress\(^{11}\).

The cold and pain sensations in hyperreactors were weaker in middle-aged and elderly subjects than in young adults, who participated in the cold pressor test for 2 min (mentioned earlier) using data at 60 s during immersion in cold water \((P<0.05, \text{Mann-Whitney } U\text{-test})\). And, the enhanced pain sensation was seen in young adult hyperreactors, but not in the middle-aged and elderly hyperreactors (Table 2). In the middle-aged and elderly subjects, therefore, the pain sensation may not contribute to greater increases in blood pressure in hyperreactors when compared to young adults.

Hyperreactors can be classified into three subtypes based on changes in blood pressure to the cold pressor test. Of the 22 hyperreactors in young adults, four were systolic hyperreactors having an systolic blood pressure (SBP) response of more than 15 mmHg (18.2%), eight were diastolic hyperreactors having a diastolic blood pressure (DBP) response of more than 15 mmHg (36.4%),

### Table 1. Changes in blood pressure and heart rate during a cold pressor test in young adults and middle-aged and elderly subjects

<table>
<thead>
<tr>
<th></th>
<th>Young adults</th>
<th>Middle-aged and elderly</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Normal reactors</td>
<td>Hyperreactors</td>
</tr>
<tr>
<td></td>
<td>((n=58))</td>
<td>((n=22))</td>
</tr>
<tr>
<td>SBP (mmHg)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>rest</td>
<td>110.9±1.5</td>
<td>111.4±9.2</td>
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<tr>
<td>cold</td>
<td>116.4±1.8***</td>
<td>127.6±13.1***</td>
</tr>
<tr>
<td>DBP (mmHg)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>rest</td>
<td>68.0±8.9</td>
<td>68.6±7.9</td>
</tr>
<tr>
<td>cold</td>
<td>73.6±9.3***</td>
<td>91.0±10.9***</td>
</tr>
<tr>
<td>MBP (mmHg)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>rest</td>
<td>82.3±9.3</td>
<td>82.9±7.6</td>
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<tr>
<td>cold</td>
<td>87.8±9.3***</td>
<td>103.2±10.5***</td>
</tr>
<tr>
<td>Pulse pressure (mmHg)</td>
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<td></td>
</tr>
<tr>
<td>rest</td>
<td>43.0±7.3</td>
<td>42.8±7.4</td>
</tr>
<tr>
<td>cold</td>
<td>42.9±9.0</td>
<td>36.6±10.6**</td>
</tr>
<tr>
<td>Heart rate (beats/min)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>rest</td>
<td>63.8±10.0</td>
<td>68.9±8.8</td>
</tr>
<tr>
<td>cold</td>
<td>65.1±10.5*</td>
<td>76.7±11.3**</td>
</tr>
</tbody>
</table>

Data are mean±SD. SBP, systolic blood pressure; DBP, diastolic blood pressure; MBP, mean blood pressure. 
***, **, * Significantly different from rest: \(P<0.001, P<0.01, P<0.05\), respectively.

### Table 2. Changes in cold and pain sensation during a cold pressor test in young adults and middle-aged and elderly subjects

<table>
<thead>
<tr>
<th></th>
<th>Young adults</th>
<th>Middle-aged and elderly</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Normal reactors</td>
<td>Hyperreactors</td>
</tr>
<tr>
<td></td>
<td>((n=12))</td>
<td>((n=8))</td>
</tr>
<tr>
<td>Cold sensation</td>
<td></td>
<td></td>
</tr>
<tr>
<td>rest</td>
<td>4 (all 4)</td>
<td>4 (all 4)</td>
</tr>
<tr>
<td>cold</td>
<td>1 (1-3)**</td>
<td>1 (all 1)**</td>
</tr>
<tr>
<td>Pain sensation</td>
<td></td>
<td></td>
</tr>
<tr>
<td>rest</td>
<td>4 (all 4)</td>
<td>4 (all 4)</td>
</tr>
<tr>
<td>cold</td>
<td>2 (1-3)**</td>
<td>1 (all 1)**+</td>
</tr>
</tbody>
</table>

Data are median (range). **, * Significantly different from rest: \(P<0.01, P<0.05\), respectively.
† Different between normal reactors and hyperreactors at time indicated: \(P<0.05\).
and ten were systolic and diastolic hyperreactors having both SBP and DBP responses of more than 15 mmHg (45.5%). In contrast, of the 10 hyperreactors in middle-aged and elderly, six were systolic hyperreactors (60.0%) and four were systolic and diastolic hyperreactors (40.0%). The incidence of the three subtypes of hyperreactors was different in the two subject groups (P<0.05, Fisher’s exact test). The higher incidence of systolic hyperreactors and no incidence of diastolic hyperreactors in the middle-aged and elderly group may reflect stiffer and less compliant arteries during cold stress11).

Conclusion

Blood pressure hyperreactors yield specific cardiovascular responses to the cold pressor test. The increases in MBP, heart rate, PWV, and AIX@75, but not cardiac contractility, during cold-water immersion are greater in hyperreactors than in normal reactors, and the pain sensation is stronger in hyperreactors than in normal reactors. However, hyperreactors do not differ from normal reactors in cardiovascular responses to isometric handgrip exercise. Moreover, hyperreactors have a higher incidence rate of hypertension than normal reactors, but the onset mechanism of hypertension in hyperreactors remains to be clarified. If the mechanism is clarified, the incidence of hyperreactors could be reduced, which would help in the prevention of hypertension.

Conflict of Interests

The author declares that there is no conflict of interests regarding the publication of this article.

References


