Consistency of Hemodynamic Responses to Cold Stress in Adolescents

Robert M. Kelsey, Stephen M. Patterson, Marie Barnard, Bruce S. Alpert

Abstract—Laboratory research on hypertension often is performed with cold stress to elicit vasoconstriction and increases in blood pressure. Several studies have shown that cardiovascular responses to the cold pressor test predict the development of hypertension. We extended this research by comparing cardiovascular responses to a traditional forehead cold pressor test and a naturalistic whole-body cold exposure. We evaluated blood pressure and impedance cardiographic measures of cardiac output and total peripheral resistance in healthy black (n = 69) and white (n = 47) adolescents (mean age, 14.7 years) during forehead cold pressor (3°C to 4°C) and passive whole-body exposure to a cold chamber (8°C to 10°C). Both tasks elicited increases in vascular resistance and blood pressure, but forehead cold elicited an increase in cardiac output, whereas whole-body cold elicited a decrease in cardiac output (P<0.05). Consistent with previous research, there was a tendency toward greater vasoconstrictive reactivity to cold stress in blacks than in whites, particularly during whole-body cold exposure (P<0.05). Cardiovascular reactivity correlated significantly between tasks, but substantial intertask consistency occurred only for cardiac and vascular reactivity in male subjects (r>0.30) but not in female subjects (r<0.15). These gender differences might reflect diminished adrenergic receptor function in female subjects. We conclude that whole-body cold exposure offers a viable, relatively naturalistic alternative to traditional cold pressor tests for the assessment of cardiovascular reactivity. (Hypertension. 2000;36:1013-1017.)

Key Words: stress n vasoconstriction n cardiac output n blood pressure n hemodynamics n adolescents

Cold stress is often used to elicit α-adrenergic vasoconstriction and pressor responses (ie, blood pressure [BP] increases) in laboratory research on hypertension.1–5 The most commonly used cold stressor is some variation of the cold pressor test, which involves the immersion of a limb in ice water or the placement of a bag of ice water on the forehead.1,4–9 A number of studies have shown that cardiovascular responses to the cold pressor test predict future resting BP and the development of hypertension.10–12 Furthermore, studies of both adults and children indicate that blacks, who are at increased risk for early hypertension development,13,14 exhibit greater vascular reactivity during limb and forehead cold pressor tasks relative to whites.15–21

Traditional laboratory cold pressor tasks typically involve limited regional body surface exposure to very cold and often painful ice water slurries (≈4°C),6–9 so it is not clear whether the cardiovascular effects of such tasks can be generalized to more naturalistic environmental cold exposure (CE). However, in a recent study of adolescents,3 we demonstrated that whole-body CE (8°C to 10°C) elicited increases in total peripheral vascular resistance and BP similar to those elicited by traditional cold pressor tasks and that cardiac and vascular responses to whole-body CE were greater in blacks than in whites. This study extends this research by providing a direct evaluation of the consistency of cardiac and vascular reactivity during forehead cold pressor and whole-body CE.

Subjects
Normotensive male (n = 51; 32 black and 19 white) and female (n = 65; 37 black and 28 white) adolescents (mean age, 14.7±1.6 years) were recruited from the Memphis, Tennessee, area for a study on early markers of hypertension. Children identified as having significant medical conditions or taking medications that would affect BP responses were excluded from the study. Informed consent and assent were obtained from the adolescent and the parent or legal guardian. The University of Tennessee Institutional Review Board approved the protocol, and all procedures conformed to institutional guidelines. Information on the date of last menses was collected from female subjects, but no attempt was made to control for menstrual cycle phase. Each subject received $60 for participating.

Cardiovascular Measures
Systolic BP (SBP, mm Hg) and diastolic BP (DBP, mm Hg) were measured during each rest and task period with a SunTech automated BP monitor (model 4240, SunTech Medical Instruments, Inc) with a cuff appropriate to the subject’s arm size. This BP monitor is an auscultatory device that uses phase 5 Korotkoff sounds to determine DBP and ECG R-wave gating to enhance measurement accuracy. Mean arterial pressure (MAP, mm Hg) was calculated as (1/3×SBP)+(2/3×DBP). Cardiac output (CO, L/min) was measured with a Minnesota impedance cardiograph (model 304B, Instrumentation for Medicine, Inc) and a Tetrapolar band-electrode system according to established guidelines.22 Impedance cardiographic data were acquired and scored with commercial software (COP 4.0, Bio-Impedance Technology, Inc). Total peripheral resistance (TPR,
dyne \cdot s/cm^2) was derived from concurrent measures of CO and BP by the formula TPR=(MAP/CO)\times 80.

### Cold Stress

The cold pressor (CP) task occurred in the Pediatric Clinical Research Center (P-CRC). Subjects sat upright in a comfortable chair while the experimenter applied a plastic bag containing crushed ice and water (~3°C to 4°C) to their forehead for 3 minutes.

A walk-in refrigerated chamber located in a laboratory of the Adult Clinical Research Center (A-CRC) served as the whole-body CE stimulus. A refrigerated ventilation system maintained the cold chamber at a constant temperature of 8°C to 10°C (85% to 95% humidity). Subjects sat upright in a comfortable chair in the cold chamber for 10 minutes. The temperature and exposure duration for CE were based on previous studies of healthy children and children with chronic diseases during rest and strenuous exercise in ambient temperatures as low as 5°C.23,24 Subjects were continuously observed through large observation windows during CE.

### Procedure

The laboratory sessions were conducted in the morning 1 to 2 hours after subjects consumed their normal breakfast. Informed consent and assent were obtained in the cardiovascular laboratory of the P-CRC, which was maintained at a temperature of 22°C. Subjects then removed their shoes, shirt, and other upper outer garments and changed into a hospital gown. They were not required to remove lower garments. The experimenter measured the height and weight of the subject and then connected the subject to the automated BP monitor, ECG, and impedance cardiograph. Subjects sat quietly in a comfortable chair for a 20-minute baseline rest period before performing the 3-minute CP task. Cardiovascular data were recorded during the last 3 minutes of the baseline rest period and during each minute of CP.

After completing the laboratory procedures in the P-CRC, subjects were taken by wheelchair to the laboratory in the A-CRC that housed the cold chamber. Subjects were connected to identical cardiovascular recording devices at the A-CRC and then sat quietly in a euthermic laboratory area (22°C) for another 20-minute baseline rest period before performing the 10-minute CE task. Cardiovascular data were recorded during the last 3 minutes of the baseline rest period and during minutes 1, 2, 5, 6, 9, and 10 of CE. After CE, subjects returned to the euthermic laboratory area. After completion of all laboratory procedures, the cardiovascular recording devices were removed and any remaining questions by the subject and/or parent were answered. Once the subjects stated that they were again comfortable, they were escorted back to the P-CRC to complete the remainder of the study protocol.

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<th>TABLE 1. Age, BMI, and Baseline Cardiovascular Levels in Adolescents</th>
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Values are mean±SD.

**Data Reduction and Analysis**

Data from the last 3 minutes of each baseline rest period were averaged to compute baseline means for CO, TPR, and MAP. Similarly, data from the 3 minutes of CP and the 6 sampled minutes of CE were averaged to compute task means. Cardiovascular reactivity was evaluated by subtracting the means for the appropriate baseline rest period from the means for each task period. Baseline cardiovascular function was evaluated in a 2 (race)\times2 (gender)\times2 (period) multivariate ANOVA, whereas cardiovascular reactivity during CP and CE was analyzed in a 2 (race)\times2 (gender)\times2 (task) multivariate ANOVA. The inclusion of age and body mass index (BMI, kg/m²) as covariates in these analyses did not alter the results, so only unadjusted results are reported.

Significant multivariate effects were followed by univariate and stepdown F tests. Stepdown F tests use hierarchical ANCOVA techniques to determine the relative contribution of each cardiovascular measure to a multivariate effect after controlling for prior measures in the analysis.25,26 The a priori ordering of the measures for the stepdown tests was based on presumed autonomic influences on cardiovascular function: (a) a significant effect for CO, assessed first in a univariate ANOVA, presumably reflects parasympathetic and \(\beta\)-adrenergic sympathetic effects on the heart; (b) a significant effect for TPR, assessed second in a univariate ANCOVA with CO as the covariate, presumably reflects residual \(\alpha\)-adrenergic effects on the vasculature; (c) a significant effect for MAP, assessed last in a univariate ANCOVA with both CO and TPR as covariates, probably reflects nonautonomic influences on BP. A value of \(P<0.05\) (2-tailed) was considered significant for these analyses.

Pearson product-moment correlation coefficients were computed to assess the consistency of CO, TPR, and MAP reactivity between CP and CE. These correlations were computed for the total sample and separately by race and gender. A value of \(P<0.05\) (1-tailed) was considered significant for these analyses.

![Graph](http://hyper.ahajournals.org/content/156/6/1014/F1.large.jpg) CO, TPR, and MAP responses (% change from baseline) to forehead CP and whole-body CE in adolescents.
Baseline
Table 1 presents age, BMI, and baseline cardiovascular data for each group. There were no significant racial differences in any of these measures. There were no significant gender differences in age or BMI, but baseline MAP was higher overall in male subjects than in female subjects (P < 0.01). Moreover, the decrease in CO and the increase in TPR over baseline periods (both P < 0.001) were greater in male subjects than in female subjects (both P < 0.025).

Cold Stress
Magnitude of Cardiovascular Reactivity
Table 2 presents mean CO, TPR, and MAP reactivity during CP and CE for each group. Both stressors elicited significant increases in TPR and MAP across groups (both P < 0.05), but they had opposite effects on CO reactivity: CP elicited an increase in CO (P < 0.001), whereas CE elicited a slight decrease in CO (P < 0.05). A significant multivariate task effect (P < 0.0005) indicated that the differential impact of CP versus CE extended to all 3 measures (all univariate F[1, 112] > 4.74, P < 0.05). For illustrative purposes, the figure depicts the cardiovascular responses to CP and CE in terms of percent change from baseline. As the figure indicates, CE elicited the greatest increase in TPR, whereas CP elicited the greatest increases in CO and MAP. Stepdown F tests indicated that the task difference in CO reactivity (stepdown F[1, 112] = 18.14, P < 0.0005) largely accounted for the task difference in TPR reactivity (stepdown F[1, 111] < 1, P = NS) but that neither component completely accounted for the difference in MAP reactivity between tasks (stepdown F[1, 110] = 16.56, P < 0.0005).

There were no significant differences in cardiovascular reactivity as a function of gender. Although the multivariate test of racial differences was not significant (P < 0.15), stepdown F tests suggested a tendency toward greater overall TPR reactivity in blacks (CO-adjusted M = 143 dyne · s/cm²) than in whites (CO-adjusted M = 94 dyne · s/cm²), (F[1, 111] = 4.16, P < 0.05). Similarly, the multivariate race by task interaction fell short of significance (P < 0.10), but stepdown F tests suggested that the differential impact of CP versus CE on CO reactivity was greater in blacks than in whites (F[1, 112] = 4.74, P < 0.05).

Consistency of Cardiovascular Reactivity
Table 3 presents the correlations between cardiovascular responses to CP and CE for the total sample and separately by race and gender. The correlations between CP and CE were significant albeit modest for all 3 measures in the total sample. The correlations for blacks and whites were similar to each other and to those for the total sample. In contrast, the correlations for male subjects and female subjects differed markedly, with significant correlations emerging for CO and TPR reactivity in male subjects (both r > 0.30) but not in female subjects.

Discussion
Both CP and CE elicited significant increases in vascular resistance and BP, as expected, but they elicited divergent

| TABLE 2. Cardiovascular Responses (Changes From Baseline) During Cold Stress in Adolescents |
|----------------------------------|--------|--------|--------|--------|
|                                  | Black   | White  |
|                                  | Male Subjects | Female subjects | Male Subjects | Female Subjects |
|                                  | (n=32)  | (n=37) | (n=19) | (n=28) |
| CP                               |         |        |        |        |
| CO, L/m                          | 0.6±0.9 | 0.2±0.9 | 0.2±0.9 | 0.0±0.6 |
| TPR, dyne · s/cm²                | 19±177  | 115±180 | 65±115 | 138±174 |
| MAP, mm Hg                       | 9±9     | 9±6    | 7±6    | 7±8    |
| CE                               |         |        |        |        |
| CO, L/m                          | −0.1±0.7| −0.3±0.6| −0.1±0.7| 0.0±0.8 |
| TPR, dyne · s/cm²                | 163±283 | 227±300 | 100±217 | 120±269 |
| MAP, mm Hg                       | 5±8     | 6±7    | 3±7    | 5±5    |

Values are mean±SD.

| TABLE 3. Correlations Between Cardiovascular Responses to Forehead Cold Pressure and Whole-Body Cold Exposure in Adolescents |
|---------------------------------------------------------------|--------|--------|--------|--------|
|                                  | Total   | Black  | White  | Male Subjects | Female Subjects |
|                                  | (n=116) | (n=69) | (n=47) | (n=51) | (n=65) |
| CO                              | 0.18*   | 0.21*  | 0.18   | 0.36†  | 0.01  |
| TPR                             | 0.21†   | 0.23*  | 0.25*  | 0.31†  | 0.13  |
| MAP                             | 0.15*   | 0.15   | 0.13   | 0.18   | 0.12  |

*P<0.05, 1-tailed.
†P<0.015, 1-tailed.
‡P<0.005, 1-tailed.
cardiac responses. Convergent increases in TPR and CO contributed to the increase in BP during CP, whereas an increase in TPR contributed to the increase in BP during CE despite a drop in CO. As a result, the increase in BP during CP exceeded that during CE despite a larger increase in vascular resistance during CE. Stepdown tests indicated that the task difference in CO reactivity accounted for the task difference in TPR reactivity, suggesting that β-adrenergic vasodilation partially masked α-adrenergic vasoconstriction during CP.3,5,7 Furthermore, consistent with previous research,15–17,19,20 there was a tendency toward greater vasoconstrictive reactivity to cold stress in blacks than in whites, particularly during CE. This racial difference in TPR reactivity,3,5,7 during CP.3,5,7 Furthermore, consistent with previous research,15–17,19,20 there was a tendency toward greater vasoconstrictive reactivity to cold stress in blacks than in whites, particularly during CE. This racial difference in TPR reactivity emerged only after controlling for CO reactivity in stepdown tests, suggesting that β-adrenergic vasodilation masked racial differences in α-adrenergic vasoconstriction.3

Although CP and CE elicited opposite changes in CO, these changes were relatively small and were near the limits of measurement error for the impedance cardiography system used in this study.5,22 Most previous studies have reported either no change or a decrease in CO during forehead CP,9,19,20 but some studies have observed increases in CO during limb CP tests.1,5 The sources of differences in cardiovascular reactivity to various types of regional and whole-body cold stress remain unclear, but likely candidates include variations in the intensity and duration of cold stress,3,6,9 the amount and location of the exposed skin surface,3 painfulness of the cold stimulus,7,8 body posture during stimulation,9,10 and proximity of the experimenter to the subject during stress.27,28 These factors might differentially influence various mechanisms that mediate increases in BP, including β-adrenergic and α-adrenergic vasoactive mechanisms, as well as nonadrenergic vasoactive mechanisms involving substances such as angiotensin II and endothelin-1.29–31 Moreover, stepdown tests on the present data suggest that factors other than CO and TPR may contribute to variations in BP reactivity to different types of cold stress.

There was a significant decrease in CO and a significant increase in TPR but no significant change in MAP across baseline rest periods. Logistical considerations precluded random counterbalanced ordering of CP and CE in this study, so we cannot determine whether these baseline shifts resulted from carryover effects of prior stress, differences in experimental setting (P-CRC versus A-CRC), or general effects of time in the laboratory. Recent studies have demonstrated that cardiac performance tends to decrease and vascular resistance tends to increase over baseline periods regardless of prior exposure to stress and that these baseline shifts have little impact on subsequent cardiovascular reactivity to stress.25,28 However, the baseline shifts in the present study were greater than in those studies. Nevertheless, baseline CO and TPR did not correlate significantly with CO and TPR reactivity for either stressor in the present study, and controlling for baseline levels in covariance analyses did not alter the results for CO and TPR reactivity to stress. Thus, CO and TPR responses to cold stress were apparently independent of baseline levels. The case was different for MAP reactivity, which correlated inversely with baseline MAP for both stressors (r = −0.28 for CP and r = −0.61 for CE, both P < 0.002). Thus, elevations in MAP during baseline might have constrained increases in MAP during cold stress.

Despite differences in the intensity and extent of cold stress during CP and CE and differences in the cardiovascular profiles preceding and during these different stressors, the cardiovascular responses to these two tasks correlated significantly. The magnitudes of the intertask correlations were similar for blacks and whites, although there was some attenuation of statistical power because of the reduction in sample size for analyses by race. In contrast, the intertask correlations for CO and TPR reactivity were substantially different for male subjects and female subjects, with significant correlations emerging only for male subjects. These gender differences might reflect variations in adrenergic receptor function between male subjects and female subjects, because previous studies suggest that peripheral vascular adrenergic receptor function and the heritability of vascular reactivity are diminished in female subjects.32,33 Gender differences in hormonal factors, including hormonal variations over the menstrual cycle in female subjects, might contribute to gender differences in adrenergic receptor function and the intertask consistency of cardiovascular responses.32

In conclusion, forehead CP and whole-body CE evoked similar vasoconstrictive and pressor reactions but opposite cardiac reactions. Cardiovascular reactivity correlated significantly between tasks, but substantial intertask consistency occurred only for CO and TPR reactivity in male subjects. The cold stress involved in whole-body CE was less intensive but more extensive than that involved in traditional limb and forehead CP tests. Thus, whole-body CE is a relatively naturalistic form of environmental cold stress that offers a viable alternative to traditional CP tests for the assessment of cardiovascular reactivity, especially when the avoidance of painful stimuli is desirable, as in evaluations of children.

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