Blood Pressure Reactivity to Psychological Stress and Coronary Calcification in the Coronary Artery Risk Development in Young Adults Study

Karen A. Matthews, Sha Zhu, Diane C. Tucker, Mary A. Whooley

Abstract—A longstanding hypothesis is that individuals who exhibit large increases in blood pressure during psychological stress are at risk for atherosclerosis. We tested whether blood pressure changes during psychological stress predict subsequent coronary calcification (CaC) in young healthy adults. We evaluated 2816 healthy black and white women, 20 to 35 years of age, from the Coronary Artery Risk Development in Young Adults Study, who were not using medication for hypertension or diabetes in 1987–1988. Participants completed video game and star tracing tasks while their blood pressure was recorded. Thirteen years later (2000–2001), they completed computed tomography measures of CaC. Overall 9.3% (261 of 2816) had CaC present at follow-up. Each 10 mm Hg change in systolic blood pressure during the video game was associated with a 24% increased odds of having CaC at follow-up (unadjusted odds ratio, 1.24; 95% CI, 1.06 to 1.46; \( P = 0.008 \)). This association persisted after adjustment for age, race, sex, education, smoking, alcohol, family history of myocardial infarction, smoking, daily alcohol consumption, body mass index, and resting or baseline blood pressure (odds ratio, 1.31; 95% CI, 1.08 to 1.58; \( P = 0.006 \)). Blood pressure changes during the star tracing task were not associated with subsequent CaC. Blood pressure changes during a video game predicted the presence of CaC 13 years later. To our knowledge, this is the first study that reports blood pressure reactivity to a stressor being related to calcification in the coronary arteries. Blood pressure reactivity may provide useful prognostic information about future risk beyond standard risk factors. (Hypertension. 2006;47:391-395.)

Key Words: stress ■ risk factors ■ blood pressure ■ coronary artery disease

A longstanding hypothesis is that individuals who are prone to relatively frequent, large increases in blood pressure (BP) during psychological stress are at risk for the development of coronary atherosclerosis.1,2 Few investigations have targeted this question in humans, in part because of the absence of measures of atherosclerosis suitable for studies of individuals without diagnosed or suspected coronary artery disease. Newly available noninvasive techniques can quantify atherosclerosis in the carotid arteries, which is correlated with the degree of systemic atherosclerosis and angiographically determined coronary atherosclerosis.3,4 In several studies of primarily middle-aged white men and women, BP increases from resting levels to levels during psychological tasks, termed BP reactivity to stress, predicted increased carotid atherosclerosis concurrently and over time.5–8 Psychological tasks used in these investigations were diverse and included public speaking, reaction time, tracking, memory, and Stroop Color-Word tasks.

Another noninvasive measure quantifies the extent of calcification in the heart by computed tomography (CT). Measures of cardiac CT are closely related to the amount of coronary atherosclerosis observed by angiography and by the evaluation of pathology specimens.9–11 The extent of coronary calcification (CaC) predicts coronary morbidity and mortality in both symptomatic and asymptomatic individuals.12–14 To our knowledge, there are no studies of BP reactivity to psychological stress and CaC.

In the present study, we examined the association between BP responses to 2 psychological tasks and the presence of CaC measured 13 years later among healthy black and white men and women enrolled in the Coronary Artery Risk Development In young Adults (CARDIA) study. We demonstrated previously that the magnitude of BP responses to the tasks predicted subsequent hypertension in CARDIA.15 We also examined in secondary analyses whether the development of hypertension or the metabolic syndrome (of which BP is 1 component) before measurement of CaC mediated any observed associations between BP responses to the tasks and CaC. For completeness of reporting and because of prior observations that heart rate (HR) responses to challenge were associated with coronary atherosclerosis in the cynomolgus monkey model,16 we also report the associations of HR responses to the tasks and CaC.
Methods

Participants
The CARDIA study is an ongoing prospective, multicenter study of the natural history of cardiovascular risk development in young adulthood. In 1985–1986, 5115 black and white men and women 18 to 30 years of age were recruited and examined at Birmingham, Ala; Chicago, Ill; Minneapolis, Minn; and Oakland, Calif. Participants were recruited to achieve a balance at each site by race (black and white), sex, education (high school degree or less versus more than a high school degree), and age (18 to 24 years and 25 to 30 years).

The Institutional Review Boards of the sites approved this study with all of the procedures followed in accordance with institutional guidelines. All of the subjects gave informed consent. This article was approved by the CARDIA Steering Committee. More detailed descriptions of the sampling plan and initial cohort characteristics are available elsewhere.

Participants were reexamined in years 2, 5, 7, 10, and 15 after baseline, with reexamination rates among surviving cohort members of 91%, 86%, 81%, 79%, and 74%, respectively. A total of 4624 participants attended the year 2 (1986–1987) examination, with 4202 participating in all or part of the cardiovascular (CV) reactivity protocol described below. Of the 74% participating in year 15 (2000–2001) examination, 2842 participated in the CT protocol. We excluded 5 participants who reported taking medication for diabetes, 20 who reported using antihypertensive medications, and 1 transsexual participant (based on lack of gender assignment), leaving 2816 for the analysis. A comparison of the 2816 participants in the present analysis with the 556 who had reactivity testing in year 2 and who participated in the year 15 examination but did not participate in the CT protocol showed that the participants in the present analysis were thinner, more educated, more likely to be white, male, and nonsmokers, had no family history of heart disease, and had slightly higher systolic BP (SBP) and HR reactivity scores relative to those who did not enroll in the CT protocol. The groups did not differ in lipids or alcohol consumption.

CV Reactivity Testing
CV reactivity testing included an 8-minute baseline period followed by the presentation of a video game (Atari Breakout) and star tracing task (using a mirror image) in randomized order for 3 minutes each. BP and HR were recorded at 1-minute intervals with an automated BP monitor (2600B Vita-Stat Spacelabs Medical Inc) throughout the tasks and the last 4 minutes of the baseline period. A third and final task, a cold pressor task, is not additionally discussed, because 635 participants who had any CaC were older, white, male, and more likely to smoke and to have a family history of MI. Older participants had no family history of MI, BMI, smoking status, alcohol consumption was classified as at least 2 drinks per day or less. 20 Body mass index (BMI) was calculated as measured weight (kg) divided by height squared (m²). Smoking status was categorized as currently smoking ≥5 cigarettes per week (yes/no). Total and high-density lipoprotein (HDL) cholesterol and triglycerides were measured in fasting blood, 21 with low-density lipoprotein (LDL) cholesterol calculated by the Friedewald equation. Fasting blood glucose was not measured at year 2. Blood glucose was measured at year 0, 7, and 10 examinations, allowing for calculation of the development of the metabolic syndrome using the National Cholesterol Education Program Third Adult Treatment Panel guidelines 22 for years 7 and 10 for the mediational analyses. Hypertension based on both BP readings and self-report of use of antihypertensive medication was evaluated at years 5, 7, and 10 as a possible mediator.

Statistical Analysis
BP and HR reactivity scores were determined by subtracting the average of the final 3 baseline readings from the average levels measured during each task. Cholesterol and triglycerides were log transformed before analysis. Because of the relatively low prevalence of any calcification in the sample, calcification was treated as a dichotomous variable, with participants with any calcification compared with those with no evidence of calcification. t-tests were used to compare the baseline BPs and the BP change scores of the “any calcification” and “no calcification” groups. To determine whether any significant effects could be explained by other variables, logistic regression analyses were performed with the following covariates in the model: age in years, race, sex, education in years, family history of myocardial infarction (MI), BMI, smoking status, alcohol intake, LDL cholesterol, HDL cholesterol, triglycerides, and resting BP or HR. Interaction terms between reactivity scores and race or sex were introduced into the models to test whether the relationships between reactivity scores and calcification varied by race or sex. To test whether the development of hypertension or metabolic syndrome between the year 2 and CT examinations mediated the associations between CV reactivity scores and CaC, additional logistic models were performed adjusting for interim hypertension or metabolic syndrome. P values <0.05 were considered statistically significant.

Results
Prevalence of CaC and Associations With Risk Factors
At 13-year follow-up, 9.3% (261 of 2816) had CaC. Among those participants with CaC, CaC scores ranged from 0.8 to 807.7, with 4.7% (132 of 2816) having scores ≥20. Participants who had any CaC were older, white, male, and more likely to smoke and to have a family history of MI. Older males were particularly likely to have any CaC. Compared with those who had no CaC at follow-up, those with CaC had lower HDL cholesterol and higher BMI, resting SBP, DBP, HR, and log -transformed triglycerides and LDL cholesterol at year 2 (Table 1).

Covariates and Mediators
Covariates were from year 2 concurrent with the reactivity testing unless noted otherwise. At all of the examinations, 3 seated BP measurements at 1-minute intervals were taken on the right arm using a Hawksley random zero sphygmomanometer (WA Balm Company) after a 5-minute rest. SBP and diastolic BP (DBP) were recorded as phase I and phase V Korotkoff sounds, and the latter 2 measures were averaged. Standardized questionnaires were used to collect self-reported diagnosis and treatment of hypertension, diabetes, other chronic conditions, and health behaviors. Family history of either parent having a heart attack before the age of 60 had been reported at year 0 (baseline) examination only. Only 9.8% reported an alcohol consumption equivalent to ≥2 drinks per day at year 2, so alcohol consumption was classified as at least 2 drinks per day or less. 20 Body mass index (BMI) was calculated as measured weight (kg) divided by height squared (m²). Smoking status was categorized as currently smoking ≥5 cigarettes per week (yes/no). Total and high-density lipoprotein (HDL) cholesterol and triglycerides were measured in fasting blood, 21 with low-density lipoprotein (LDL) cholesterol calculated by the Friedewald equation. Fasting blood glucose was not measured at year 2. Blood glucose was measured at year 0, 7, and 10 examinations, allowing for calculation of the development of the metabolic syndrome using the National Cholesterol Education Program Third Adult Treatment Panel guidelines 22 for years 7 and 10 for the mediational analyses. Hypertension based on both BP readings and self-report of use of antihypertensive medication was evaluated at years 5, 7, and 10 as a possible mediator.
Association Between CaC and CV Reactivity
CaC groups did not differ in the changes observed during the star tracing task but did differ in the changes observed during the video game (Table 2). Participants who had any CaC had greater increases in SBP during the video game than did those with none. The association between having any CaC and SBP reactivity during the video game remained statistically significant in the multivariate logistic regression model (Table 3).

The tests for interactions between race or gender and SBP reactivity during the video game were nonsignificant (all P values >0.20). Analyses were repeated adding fasting glucose from year 0 and physical activity to the multivariate model; they were also repeated excluding participants who had SBP >140 or DBP >90 at year 2. Neither analysis altered the primary findings (data not shown).

Participants who had any CaC had smaller increases in HR during the video game than did those with no CaC (Table 2), but this association was not significant after adjustment for potential confounders (P=0.37). Test for interaction between sex and HR reactivity was nonsignificant. However, the test for the interaction between race and HR reactivity was significant (P=0.0003). Multivariate logistic analyses in blacks and whites separately showed that the higher HR reactivity (per 10 bpm) during the video game was associated with a lower risk of subsequent calcification in blacks [odds ratio (OR), 0.45; 95% CI, 0.28 to 0.73; P=0.001] but not in whites (OR, 1.12; 95% CI, 0.92 to 1.54; P=0.19).

Possible Mediators of CaC and SBP Reactivity
We examined whether interim development of hypertension between the SBP reactivity measure in 1987–1988 and CaC measure in 2000–2001 was a pathway by which SBP reactivity resulted in increased risk for having any CaC. After additional adjustment for interim hypertension (SBP ≥160, DBP ≥95, or use of antihypertensive medications) at year 5 (1990–1991), year 7 (1992–1993), or year 10 (1995–1996), the association between SBP change (per 10 mm Hg increase) and subsequent CaC remained significant (Table 3 OR plus interim hypertension, 1.33; 95% CI, 1.10 to 1.61; P<0.004). Virtually identical results were obtained when interim hypertension was considered to be SBP ≥140 or DBP ≥90. Similarly, after additional adjustment for interim metabolic syndrome at year 7 (1992–1993) or year 10 (1995–1996), the association between SBP change (per 10 mm Hg increase) and subsequent CaC remained significant (Table 3 OR plus interim metabolic syndrome at year 10, 1.35; 95% CI, 1.11 to 1.64).

### Table 1. Characteristics of Participants by Presence of CaC

<table>
<thead>
<tr>
<th>Variable</th>
<th>Any Calcification</th>
<th>No Calcification</th>
<th>t Test or χ²</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean (SD) age at enrollment, y</td>
<td>27.0±3.1</td>
<td>25.1±3.6</td>
<td>&lt;0.0001</td>
<td></td>
</tr>
<tr>
<td>Men, %</td>
<td>73</td>
<td>43</td>
<td>&lt;0.0001</td>
<td></td>
</tr>
<tr>
<td>White, %</td>
<td>66</td>
<td>55</td>
<td>0.0007</td>
<td></td>
</tr>
<tr>
<td>Mean (SD) BMI, kg/m²</td>
<td>26.0±4.9</td>
<td>24.8±4.7</td>
<td>0.0001</td>
<td></td>
</tr>
<tr>
<td>Mean (SD) education, y</td>
<td>14.3±2.5</td>
<td>14.4±2.3</td>
<td>0.2322</td>
<td></td>
</tr>
<tr>
<td>Family history of MI, %</td>
<td>19</td>
<td>11</td>
<td>&lt;0.0001</td>
<td></td>
</tr>
<tr>
<td>Smoking status, %</td>
<td></td>
<td></td>
<td>&lt;0.0001</td>
<td></td>
</tr>
<tr>
<td>Nonsmoker</td>
<td>49</td>
<td>62</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ex-smoker</td>
<td>14</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Current smoker</td>
<td>37</td>
<td>24</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alcohol intake per day at least equivalent of 2 drinks, %</td>
<td>18.2</td>
<td>8.9</td>
<td>&lt;0.0001</td>
<td></td>
</tr>
<tr>
<td>Mean (SD) LDL cholesterol, mg/dL</td>
<td>129.4±37.3</td>
<td>111.8±32.1</td>
<td>&lt;0.0001</td>
<td></td>
</tr>
<tr>
<td>Mean (SD) HDL cholesterol, mg/dL</td>
<td>50.3±13.5</td>
<td>55.5±14.0</td>
<td>&lt;0.0001</td>
<td></td>
</tr>
<tr>
<td>Mean (SD) triglycerides, mg/dL</td>
<td>100.2±68.7</td>
<td>75.8±46.8</td>
<td>&lt;0.0001</td>
<td></td>
</tr>
</tbody>
</table>

### Table 2. Unadjusted Mean (SD) of Baseline and Task Minus Baseline Changes in BP and HR for Those With and Without Any CaC

<table>
<thead>
<tr>
<th>Variable</th>
<th>Calculated</th>
<th>Resting</th>
<th>Star Tracing</th>
<th>Video Game</th>
</tr>
</thead>
<tbody>
<tr>
<td>Systolic BP</td>
<td>Yes</td>
<td>116.8 (11.4)</td>
<td>12.7 (9.7)</td>
<td>11.1 (9.3)</td>
</tr>
<tr>
<td></td>
<td>No</td>
<td>111.2 (10.7)</td>
<td>11.5 (8.2)</td>
<td>9.7 (7.7)</td>
</tr>
<tr>
<td>Diastolic BP</td>
<td>Yes</td>
<td>67.8 (11.1)</td>
<td>11.4 (7.6)</td>
<td>9.0 (7.2)</td>
</tr>
<tr>
<td></td>
<td>No</td>
<td>64.3 (10.3)</td>
<td>10.8 (7.6)</td>
<td>8.8 (7.3)</td>
</tr>
<tr>
<td>Heart rate</td>
<td>Yes</td>
<td>68.2 (9.6)</td>
<td>6.3 (8.3)</td>
<td>4.4 (7.1)</td>
</tr>
<tr>
<td></td>
<td>No</td>
<td>69.5 (9.8)</td>
<td>6.1 (7.3)</td>
<td>5.5 (7.4)</td>
</tr>
</tbody>
</table>

*P<0.001 from t tests comparing calcification groups.
†P<0.05.
Discussion

We found that BP reactivity to a video game predicted the presence of CaC 13 years later among young- to middle-aged adults who were free of hypertension and diabetes. This association persisted after adjustment for other atherosclerosis risk factors, including age, race, sex, smoking, obesity, family history of MI, cholesterol, and physical activity. Moreover, the association between BP reactivity to a video game and subsequent CaC was not because of interim development of hypertension or the metabolic syndrome in the 13 years between the measurements of stress reactivity and CaC. To our knowledge, this is the first study to test the association of BP reactivity and CaC.

In contrast, BP reactivity to the star tracing task did not predict subsequent CaC. It is unclear why the association between BP reactivity and CaC differs by type of stressor. One factor may be that BP reactivity to the video game may be a more reliable characteristic of the individual than BP reactivity to the other tasks. This is an unlikely explanation, because numerous studies show that BP reactivity to a variety of tasks is a reliable characteristic of normotensive adults, with correlations for BP change scores averaged across a number of tasks ranging from 0.0.71 to 0.81 across 5 studies with intervals of 1 week to 1 month. Another possibility is related to differences in SBP reactivity by sex and race. As reported elsewhere, men had larger increases in SBP during the video game and star tracing tasks, especially among whites, than had women. Given that men and whites more often had any CaC relative to women and blacks, perhaps the association between SBP reactivity during the video game and any CaC is illusory. Arguing against this notion is that we adjusted for sex and race in the multivariable analyses. A final explanation is related to the low prevalence of CaC in the CARDIA sample. The association of SBP reactivity to star tracer task and CaC may simply be less robust, because the association did approach conventional levels of significance in univariate analyses (P<0.08). Perhaps the effects with SBP reactivity to the star tracing task would be stronger in a sample with a higher prevalence of atherosclerosis.

Strengths of this study include state-of-the-art methods in CARDIA for measuring CV risk factors; a standardized reactivity protocol using well-characterized laboratory stressors; a large population-based, multiethnic sample; 13-year follow-up of participants from young adulthood into middlelife; and high quality measurement of CaC. Having any CaC was associated with a number of CV risk factors, including atherogenic lipid values, smoking, race, sex, resting BP, and family history, providing internal validity to our calcification results.

Several limitations should be considered in interpreting our results. The measure of HR was based on a single HR at the time of BP measurement. Continuous measures of HR and HR variability during stress were unavailable and may be important to understanding the development of atherosclerosis, given other findings in animal and human studies. The very low prevalence of CaC in the sample of healthy adults reduced the power to detect associations that may be obtained in a sample with a greater prevalence of disease. Finally, although BP reactivity to the video game was assessed 13 years earlier than CaC, we could not rule out the possibility that BP reactivity to the video game was a consequence of even earlier changes in the arterial wall. Perspectives

Our data show that SBP changes to one of the psychological stressors predict subsequent CaC among healthy participants. These data partially support the hypothesis that BP reactivity to stress may lead to CaC. BP reactivity predicts CaC, as well as standard resting BP in our study. BP reactivity protocols should be added to future epidemiological protocols to additionally evaluate the role of BP reactivity in coronary atherosclerosis.

Acknowledgments

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References


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