Blood Pressure Reactivity to Psychological Stress Predicts Hypertension in the CARDIA Study

Karen A. Matthews, PhD; Charles R. Katholi, PhD; Heather McCreath, PhD; Mary A. Whooley, MD; David R. Williams, PhD, MPH; Sha Zhu, PhD; Jerry H. Markovitz, MD, MPH†

Background—A longstanding but controversial hypothesis is that individuals who exhibit frequent, large increases in blood pressure (BP) during psychological stress are at risk for developing essential hypertension. We tested whether BP changes during psychological stress predict incident hypertension in young adults.

Methods and Results—We used survival analysis to predict hypertensive status during 13 years of follow-up in a sample of >4100 normotensive black and white men and women (age at entry, 18 to 30 years) enrolled in the CARDIA study. BP responses to 3 psychological challenges—cold pressor, star tracing, and video game tasks—were measured. Hypertensive status was defined as use of antihypertensive medication or measured BP ≥140/90 mm Hg. After adjustment for race, gender, covariates (education, body mass index, age, and resting pressure), and their significant interactions, the larger the BP responses were to each of the 3 tasks, the earlier hypertension occurred (P<0.0001 to <0.01). The systolic BP effect for the cold pressor task was apparent for women and for whites in race- and gender-specific models, whereas the diastolic BP effect for the video game was apparent for men.

Conclusions—Young adults who show a large BP response to psychological stress may be at risk for hypertension as they approach midlife. (Circulation. 2004;110:74-78.)

Key Words: hypertension ■ risk factors ■ stress

A longstanding hypothesis is that individuals who are prone to frequent, large increases in blood pressure (BP) during psychological stress are at risk for developing essential hypertension.1 However, after many years of investigation, a clear understanding of the etiologic role of stress responses has not emerged. Most prospective studies have used the cold pressor test as an analog of stress. This test may be less than optimal because it is a thermal pain test and does not elicit a β-adrenergically mediated myocardial response thought to be important to early neurogenic hypertension.2 Of the 7 large-scale studies using the cold pressor test, results of 4 supported the hypothesis,3–6 whereas the results of 3 did not.7–9 Of interest, though, is that in the same study cohort, a survival analytic approach that assessed length of time to the occurrence of hypertension showed a strong positive effect of systolic BP (SBP) response to the cold pressor, whereas a more conventional analysis based on the occurrence of hypertension at final evaluation did not.3

Studies using other analog tests of psychological stressors, eg, video games or mental arithmetic, have yielded more promising results than those that used the cold pressor test. Several studies of young and middle-aged adults found associations between the magnitude of BP changes during such stressors and subsequent rises in resting BP over 1 to 10 years later.10–13 In Finnish middle-aged men, BP reactivity to anticipation of an exercise test predicted the development of hypertension 4 years later,14 and in English male civil servants, BP reactivity to a nonverbal cognitive task predicted the development of hypertension 10 years later.15 Stressors do not have the same meaning for all gender and ethnic groups. An extensive body of literature has documented that relative to women, men have greater BP increases to challenging achievement tasks such as video games16 and that relative to whites, blacks have greater BP responses to tasks that typically yield an α-adrenergic response such as cold pressor or star tracing tasks.17 Perhaps the effects of stress-induced BP responses on risk for hypertension vary by gender and ethnic groups.

We examined the association between BP responses to 3 tasks (cold pressor test, star tracing, and video game) and incident hypertension in the subsequent 13 years among black and white men and women enrolled in CARDIA. A prior CARDIA report10 showed that the magnitude of SBP responses during the video game predicted increases in resting BP 5 years later, an association observed primarily in men. In the present study, we used survival analysis to examine the association of stress responses and hypertension during a 13-year interval after reactivity testing and to test whether the strength of the association varied by race or ethnicity.
Methods
The CARDIA study is an ongoing prospective, multicenter study of the natural history of cardiovascular risk development in young adulthood. In 1985 to 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, white), sex, education (high school degree or less, more than high school), and age (18 to 24 years, 25 to 30 years). More detailed descriptions of the sampling plan and initial cohort characteristics are available elsewhere.18

Participants were reexamined in years 2, 5, 7, 10, and 15 years after baseline, with reexamination rates among surviving cohort members of 91%, 86%, 81%, 79%, and 74%, respectively. Of the 4624 participants who attended the year 2 examination, 4202 completed all or partial stress testing. No stress testing was available for 422 participants; 414 of those participants also were missing the covariate data. Because of the analytic strategy (see below), this report is based on all individuals who participated in at least a portion of the stress examination conducted in year 2, were normotensive at the time of the stress examination, and had at least 1 follow-up examination with measures of resting BP, use of medications, and relevant covariates at that time.

Data Collection and Study Variables
BP was measured at each examination on the right arm with a Hawksley random-zero sphygmomanometer (WA Balm Co) with the participant seated and after a 5-minute rest. Three measurements were taken at 1-minute intervals; the last 2 were averaged. SBP and diastolic BP (DBP) were recorded as phase I and V Korotkoff sounds. Standardized questionnaires were used to collect self-report data on diagnosis and treatment of hypertension and other chronic conditions. Participants were considered normotensive at each assessment if they did not report having or being treated for hypertension and other chronic conditions. Participants were considered hypertensive if they were taking antihypertensive medication or had an examination SBP \( \geq 140 \text{ mm Hg} \) and DBP \( \geq 90 \text{ mm Hg} \). Standardized questionnaires were used to assess age, race, sex, and years of education at stress testing examination. Body weight in light clothing was measured to the nearest 0.5 lb with a beam balance scale. Height without shoes was measured to the nearest 0.5 cm with a vertically mounted centimeter ruler and a metal carpenter’s square. Body mass index (BMI) was calculated as weight (in kilograms) divided by height squared (meters squared).

Stress testing included an 8-minute baseline period followed by the presentation of a video game (Atari Breakout) and star tracing task (with a mirror image) in randomized order for 3 minutes each. The cold pressor test consisted of 45 seconds of hand immersion in an ice-water tank. BP was measured at 1-minute intervals; the last 2 were averaged. SBP and DBP were recorded as phase I and V Korotkoff sounds. Standardized questionnaires were used to collect self-report data on diagnosis and treatment of hypertension and other chronic conditions. Participants were considered normotensive at each assessment if they did not report having or being treated for hypertension and other chronic conditions. Participants were considered hypertensive if they were taking antihypertensive medication or had an examination SBP \( \geq 140 \text{ mm Hg} \) and DBP \( \geq 90 \text{ mm Hg} \).

A large number of individuals did not complete the last task, the cold pressor task, although they completed 1 or both of the other tasks (n=635). Recall that only 1 BP measure was taken during this task. There were no significant differences in mean BMI, age, resting SBP, or resting DBP between those who did or did not complete the cold pressor task within each of the 4 gender-ethnic groups.

Compared with whites, blacks had greater increases in DBP during the video game and cold pressor tasks and smaller increases in SBP during the star tracing task. Compared with men, women were less educated, but had greater increases in DBP during the cold pressor task. Compared with whites, men were more likely to complete the cold pressor task.

Statistical Analysis
BP reactivity scores were determined by subtracting the average of the final 3 baseline readings from the average levels measured during each task. The analysis was conducted to assess the association between BP reactivity in relation to the first examination in the subsequent 13 years of follow-up that participants met the criteria for hypertension with adjustments for the covariates of age, education, BMI, resting BP (either SBP or DBP as appropriate to the measure of reactivity) at the time of stress testing, and all 2- and 3-way interactions among the predictor variables. Backward elimination of nonsignificant 2- and 3-way interaction terms was conducted to yield the final models. (Smoking status and alcohol consumption were not included because they were not statistically significant or added nothing to model fit.) Because some participants did not attend all examinations and the examinations were not equally spaced, the usual sort of actual event time used in survival analysis was not appropriate. SAS PROC LIFEREG with the assumption of a Weibull survival distribution (increasing hazard with time) was used. Survival distributions in the class of the generalized gamma family were considered. This family includes the exponential and the Weibull as subclasses. Sequential likelihood ratio tests showed no statistical improvement from the Weibull distribution to the generalized gamma model. For this reason, the Weibull distribution was selected as the most parsimonious model. To facilitate the interpretation of the parameter estimates, all covariates were standardized with 0 mean and SD of 1 before the model parameters were estimated. The algebraic signs of the coefficients reflect their role in describing survival times. Coefficients that describe the log of the hazard function are minus a constant times these values. Thus, a negative coefficient reflects an increasing hazard. Significant interactions of reactivity scores and race or sex were further evaluated by \( \chi^2 \) Wald tests within race or sex groups. Values of \( P<0.05 \) were considered statistically significant.

Results
Characteristics of normotensive participants in the stress reactivity examination are given in Table 1. Participants were on average 27 years of age, with whites slightly older than blacks. On average, participants had some college education, with blacks having less education than whites. BMI was higher for blacks than whites, especially among females. Resting SBP and DBP levels were higher for blacks than whites and for men than women. Over the course of the 13 years of follow-up, 352 participants became hypertensive, with proportionately more blacks becoming hypertensive.

Consistent with previous reports from CARDIA,19,20 risk of early hypertension was greater among participants who were older, were less educated, and had a higher BMI and higher resting SBP or DBP at the time of stress testing (Tables 2 and 3). In addition, the effect of higher BMI was greater among men compared with women (BMI-by-sex interaction), whereas the effect of low education was greater among whites or women compared with blacks or men (education-by-race or -sex interaction). Parameter estimates
vary in size because of differing sample size and predictor variables in the models.

The greater the SBP changes were during all 3 tasks (reactivity score), the earlier the occurrence of hypertension was. The effect of SBP change during the cold pressor task varied somewhat by sex and race (reactivity-by-race or -sex interaction). In separate models conducted for women and men and for whites and blacks, the effect of cold pressor reactivity was apparent among women (estimate, 0.18; \( P=0.001 \)) and whites (estimate, 0.20; \( P=0.001 \)) and not among men (estimate, -0.05; \( P=0.23 \)) or blacks (estimate, -0.05; \( P=0.25 \)).

The greater the DBP changes were during all 3 tasks, the earlier the occurrence of hypertension was. The effect of DBP change during the video game varied by sex, and separate models showed that the effect was apparent among men.

### Table 1. Sample Characteristics of Normotensive Participants in Reactivity Testing

<table>
<thead>
<tr>
<th>Variable</th>
<th>Black Men</th>
<th>Black Women</th>
<th>White Men</th>
<th>White Women</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypertension by year</td>
<td>15</td>
<td>104</td>
<td>71</td>
<td>31</td>
</tr>
<tr>
<td>Age, y†</td>
<td>965</td>
<td>26.8 (3.7)</td>
<td>1264</td>
<td>26.9 (3.8)</td>
</tr>
<tr>
<td>BMI, kg/m²†‡</td>
<td>958</td>
<td>25.3 (4.6)</td>
<td>1248</td>
<td>26.6 (6.8)</td>
</tr>
<tr>
<td>Education, y†‡</td>
<td>956</td>
<td>13.2 (2.0)</td>
<td>1244</td>
<td>13.5 (1.9)</td>
</tr>
<tr>
<td>Resting SBP**†</td>
<td>884</td>
<td>119.1 (10.2)</td>
<td>1146</td>
<td>108.7 (9.5)</td>
</tr>
<tr>
<td>Resting DBP**†‡</td>
<td>884</td>
<td>64.9 (11.8)</td>
<td>1146</td>
<td>64.7 (10.6)</td>
</tr>
<tr>
<td>Cold pressor, mm Hg</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SBP change</td>
<td>759</td>
<td>22.4 (12.9)</td>
<td>814</td>
<td>23.5 (13.5)</td>
</tr>
<tr>
<td>DBP change*†</td>
<td>731</td>
<td>33.9 (16.0)</td>
<td>788</td>
<td>27.4 (14.6)</td>
</tr>
<tr>
<td>Star tracing</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SBP change**†‡</td>
<td>854</td>
<td>10.3 (8.5)</td>
<td>1100</td>
<td>9.5 (8.2)</td>
</tr>
<tr>
<td>DBP change*†</td>
<td>856</td>
<td>11.2 (8.6)</td>
<td>1111</td>
<td>10.2 (7.8)</td>
</tr>
<tr>
<td>Video game, mm Hg</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SBP change*‡</td>
<td>867</td>
<td>10.0 (7.9)</td>
<td>1105</td>
<td>9.3 (8.3)</td>
</tr>
<tr>
<td>DBP change†</td>
<td>871</td>
<td>9.4 (8.1)</td>
<td>1115</td>
<td>9.7 (7.5)</td>
</tr>
</tbody>
</table>

From 2 (sex)-by-2 (race) ANOVA, *\( P<0.05 \) for sex main effect; †\( P<0.05 \) for race main effect; ‡\( P<0.05 \) for sex-by-race interaction.

### Table 2. Standardized Parameter Estimates From Survival Analyses of SBP Reactivity Predicting Time to Occurrence of Hypertension

<table>
<thead>
<tr>
<th>SBP Reactivity Scores During Tasks</th>
<th>Cold Pressor (n=3553)</th>
<th>Star Tracing (n=4075)</th>
<th>Video Game (n=4100)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Effects</td>
<td>Parameter Estimate</td>
<td>SE</td>
<td>Parameter Estimate</td>
</tr>
<tr>
<td>Intercept</td>
<td>4.18*</td>
<td>0.110</td>
<td>4.22*</td>
</tr>
<tr>
<td>Reactivity score</td>
<td>-0.120†</td>
<td>0.033</td>
<td>-0.111†</td>
</tr>
<tr>
<td>Race</td>
<td>-0.275*</td>
<td>0.043</td>
<td>-0.287*</td>
</tr>
<tr>
<td>Sex</td>
<td>0.138‡</td>
<td>0.045</td>
<td>0.142‡</td>
</tr>
<tr>
<td>Race×sex</td>
<td>0.138†</td>
<td>0.040</td>
<td>0.104‡</td>
</tr>
<tr>
<td>Age</td>
<td>-0.297*</td>
<td>0.041</td>
<td>-0.269*</td>
</tr>
<tr>
<td>BMI</td>
<td>-0.163*</td>
<td>0.027</td>
<td>-0.158*</td>
</tr>
<tr>
<td>Education</td>
<td>0.085§</td>
<td>0.037</td>
<td>0.135†</td>
</tr>
<tr>
<td>Resting SBP</td>
<td>-0.518*</td>
<td>0.047</td>
<td>-0.547*</td>
</tr>
<tr>
<td>Sex×BMI</td>
<td>-0.070†</td>
<td>0.026</td>
<td>-0.072‡</td>
</tr>
<tr>
<td>Race×education</td>
<td>-0.086§</td>
<td>0.037</td>
<td>-0.112‡</td>
</tr>
<tr>
<td>Sex×education</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>Reactivity score×race</td>
<td>0.072§</td>
<td>0.033</td>
<td>NS</td>
</tr>
</tbody>
</table>

*\( P<0.0001 \), †\( P<0.01 \), ‡\( P<0.05 \), §\( P<0.05 \). NS not in final model.

*Race=1 for blacks, −1 for whites; sex=1 for men, −1 for women.

The greater the DBP changes were during all 3 tasks, the earlier the occurrence of hypertension was. The effect of DBP change during the video game varied by sex, and separate models showed that the effect was apparent among men.
(estimate, −0.27; \( P<0.0001 \)) and not among women (estimate, −0.01; \( P=0.88 \)). DBP changes during the tasks had similar effects in both blacks and whites.

To illustrate the effects of reactivity on risk for hypertension, Figures 1 through 3 show the survival curves of 2 women who had the most similar levels of the covariates (race, age, BMI, education, and resting DBP but not reactivity) but were in the top (long survivors) and bottom (short survivors) quartiles of survival from hypertension (or probability of remaining normotensive). Their reactivity scores were in the lowest quartile of reactivity for the long survivors and the highest quartile of reactivity for the short survivors.

Secondary analyses examined whether a change in pulse rate during star tracing and video game was a significant predictor of time to hypertension. It was not (data not shown), although elevated resting heart rate was a predictor of early hypertension risk, as reported in elsewhere\(^21\) (\( P<0.01 \)).

### Discussion

This study tested a longstanding hypothesis that normotensive individuals who show large responses to mental and physical challenges are at risk for hypertension. In a large sample of black and white normotensive adults in their 20s and 30s, the magnitude of the BP response to cold pressor, star tracing, and video game tasks predicted the likelihood of hypertension during the subsequent 13 years of the study. Furthermore, the relationship was obtained when statistical adjustments were made for the major predictors of hypertension, including age, race, gender, BMI, education, resting pressure, and their significant interactions.

We explored whether the relationship varied in magnitude by race or gender, given that reactivity scores varied by race and gender in the present study and other studies. Indeed, for the video game task, DBP changes were a more important predictor for men, and for the cold pressor test, SBP changes were a more important predictor for women and whites. The null results for

### Table 3. Standardized Parameter Estimates From Survival Analyses of DBP Reactivity Predicting Time to Occurrence of Hypertension

<table>
<thead>
<tr>
<th>Effects</th>
<th>Cold Pressor (n=3463) Parameter Estimate</th>
<th>SE</th>
<th>Star Tracing (n=4108) Parameter Estimate</th>
<th>SE</th>
<th>Video Game (n=4122) Parameter Estimate</th>
<th>SE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intercept</td>
<td>4.14*</td>
<td>0.110</td>
<td>4.19*</td>
<td>0.104</td>
<td>4.20*</td>
<td>0.104</td>
</tr>
<tr>
<td>Reactivity score</td>
<td>−0.115†</td>
<td>0.040</td>
<td>−0.158*</td>
<td>0.035</td>
<td>−0.176*</td>
<td>0.034</td>
</tr>
<tr>
<td>Race</td>
<td>−0.280*</td>
<td>0.043</td>
<td>−0.304*</td>
<td>0.042</td>
<td>−0.307*</td>
<td>0.042</td>
</tr>
<tr>
<td>Sex</td>
<td>−0.101†</td>
<td>0.049</td>
<td>−0.140†</td>
<td>0.047</td>
<td>−0.093§</td>
<td>0.041</td>
</tr>
<tr>
<td>Race×sex</td>
<td>0.106†</td>
<td>0.040</td>
<td>0.112†</td>
<td>0.039</td>
<td>0.119†</td>
<td>0.039</td>
</tr>
<tr>
<td>Age</td>
<td>−0.212*</td>
<td>0.040</td>
<td>−0.182*</td>
<td>0.036</td>
<td>−0.202*</td>
<td>0.036</td>
</tr>
<tr>
<td>BMI</td>
<td>−0.125*</td>
<td>0.029</td>
<td>−0.107*</td>
<td>0.028</td>
<td>−0.115*</td>
<td>0.028</td>
</tr>
<tr>
<td>Education</td>
<td>0.135†</td>
<td>0.040</td>
<td>0.158*</td>
<td>0.038</td>
<td>0.143*</td>
<td>0.037</td>
</tr>
<tr>
<td>Resting DBP</td>
<td>−0.450†</td>
<td>0.049</td>
<td>−0.475*</td>
<td>0.044</td>
<td>−0.465§</td>
<td>0.042</td>
</tr>
<tr>
<td>Sex×BMI</td>
<td>−0.086†</td>
<td>0.029</td>
<td>−0.073†</td>
<td>0.027</td>
<td>−0.063§</td>
<td>0.026</td>
</tr>
<tr>
<td>Race×education</td>
<td>−0.106†</td>
<td>0.038</td>
<td>−0.106†</td>
<td>0.038</td>
<td>−0.090§</td>
<td>0.037</td>
</tr>
<tr>
<td>Sex×education</td>
<td>−0.081§</td>
<td>0.039</td>
<td>−0.083§</td>
<td>0.037</td>
<td>−0.078§</td>
<td>0.036</td>
</tr>
<tr>
<td>Sex×DBP</td>
<td>0.089§</td>
<td>0.038</td>
<td>0.078§</td>
<td>0.035</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>Reactivity score×sex</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>−0.010†</td>
<td>0.032</td>
</tr>
</tbody>
</table>

\( *P<0.0001; †P<0.001; ‡P<0.01; §P<0.05. \) NS not in final model.
inability of the endothelium to counteract adequately the vaso-
may be a measure of poor endothelial dysfunction or the
leading to increased risk for hypertension. Finally, BP reactivity
general hyperadrenergic state, with elevations in neurohormones
improvement. Another possibility is that BP reactivity reflects a more
the vasculature, leading to damage and impairing arterial com-
pressor test was based on 1 BP measure and the loss to follow-up
participants from young adulthood into midlife, when the risk for
protocol using well-characterized laboratory stressors; a large
response to acute stressors predict incident hypertension.
Numerous studies show that BP reactivity is a reliable
characteristic of normotensive adults, with correlations for
reactivity to video game.

Although our data confirm a longstanding psychosomatic
hypothesis, they do not elucidate the nature of that associa-
tion.25–27 One can posit direct effects of frequent BP changes on
the vasculature, leading to damage and impairing arterial compli-
cance. Another possibility is that BP reactivity reflects a more
general hyperadrenergic state, with elevations in neurohormones
leading to increased risk for hypertension. Finally, BP reactivity
may be a measure of poor endothelial dysfunction or the
inability of the endothelium to counteract adequately the vaso-
constrictive forces induced by sympathetic stimuli.

In conclusion, our data show that large BP changes in
response to acute stressors predict incident hypertension.
Strengths of this study include state-of-the-art methods for
measuring cardiovascular 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, when the risk for
hypertension accelerates; and a sophisticated analytic approach.
Limitations include that the reactivity measure for the cold
pressor test was based on 1 BP measure and the loss to follow-up
of CARDIA participants. Assessment of BP changes in response
to stress may be a useful additional tool for the assessment of
future risk of hypertension.

Acknowledgments
This research was supported by contracts N01-HC-48047, N01-HC-
48048, N01-HC-48049, N01-HC-48050, and N01-HC-95095 from
the National Heart, Lung and Blood Institute and by the Pittsburgh
Mind-Body Center (HL 65111 and HL 65112).

References
1. Matthews KA, Weiss TM, Dote T, et al. Handbook of Stress, Reactivity, and
2. Julius S, Weder AB, Egan BM. Pathophysiology of early hypertension:
implication for epidemiologic research. In: Gross F, Strasser T, eds. Mild
3. Menkes MS, Matthews KA, Krantz DS, et al. Cardiovascular reactivity to
the cold pressor test as a predictor of hypertension. Hypertension. 1989;
14:524–530.
5. Kasagi F, Masazumi A, Shimaoa K. Relation between cold pressor test
and development of hypertension based on 28-year follow-up. Hyper-
at the cold pressor test and the prediction of future blood pressure status:
7. Harlan WR Jr, Osborne RK, Graybiel A. Prognostic value of the cold
pressor test and the basal blood pressure based on an eighteen year
8. Armstrong HR, Rafferty JA. Cold pressor test follow-up study for seven
to(video) game predicts subsequent blood pressure increases in young
11. Matthews KA, Woodall KL, Allen MT. Cardiovascular reactivity to stress
12. Murphy JK, Alpert BS, Walker SS. Ethnicity, pressor reactivity, and
functioning in youth with family histories of essential hypertension: a
response to exercise predicts future high blood pressure in middle-aged
the cold pressor test as a predictor of hypertension. Hypertension.
17. Esler MD, Julius S, Zwindler A, et al. Mild high-renin essential hypertension:
18. Goldstein D. Plasma catecholamines and essential hypertension: an