Vascular Medicine

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

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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 $\geq$140/90 mm Hg. After adjustment for race, gender, covariates (education, body mass index, age, and resting pressure), and their significant interactions, the larger the BP responses were to each of the 3 tasks, the earlier hypertension occurred ($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 games[16] 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 report[10] 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 if they had examination SBP <140 mm Hg and DBP <90 mm Hg. Participants were considered hypertensive if they reported being treated for hypertension with medication or had an examination SBP ≥140 mm Hg or DBP ≥90 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 during the last 4 minutes of the baseline period and once during each minute of the video games and star-tracing tasks. Because of the short duration of the cold pressor test, only 1 measure of BP was taken during the test with a mercury sphygmomanometer by trained and certified technicians. Otherwise, BP and pulse rate were recorded with an automated BP monitor (2600B Vita-Stat Spacelabs Medical Inc) throughout. Standardization of the stress protocol was accomplished by centralized training of technicians, quality assurance site visits, and use of audiotaped instructions to participants. Automated BP monitors were calibrated weekly.

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 χ^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.

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 women, men had larger increases in DBP during the cold pressor and star tracing tasks and larger increases in SBP during the video game and star tracing tasks, especially among whites. Across groups, BP changes between the video game and star tracing tasks correlated more highly ($r=0.64$ and 0.61 for SBP and DBP, respectively) than those between either the video game ($r=0.23$ and 0.19 for SBP and DBP) or the star tracing ($r=0.27$ and 0.25 for SBP and DBP) task and the cold pressor task.

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

TABLE 1.   Sample Characteristics of Normotensive Participants in Reactivity Testing

	Black Men		Black Women		White Men		White Women	
Variable	n	Mean (SD)	n	Mean (SD)	n	Mean (SD)	n	Mean (SD)
Hypertension by year 15	104		146		71		31	
Age, y†	965	26.8 (3.7)	1264	26.9 (3.8)	1087	28.0 (3.3)	1226	28.0 (3.4)
BMI, kg/m²†‡	958	25.3 (4.6)	1248	26.6 (6.8)	1087	24.9 (3.8)	1219	23.7 (4.7)
Education, y*†‡	956	13.2 (2.0)	1244	13.5 (1.9)	1081	14.9 (2.6)	1219	14.9 (2.3)
BP, mm Hg								
Resting SBP*†	884	119.1 (10.2)	1146	108.7 (9.5)	1034	116.0 (9.3)	1145	105.2 (9.1)
Resting DBP*†‡	884	64.9 (11.8)	1146	64.7 (10.6)	1035	64.8 (10.3)	1145	62.7 (9.2)
Cold pressor, mm Hg								
SBP change	759	22.4 (12.9)	814	23.5 (13.5)	980	22.5 (11.8)	1005	23.0 (12.6)
DBP change*†	731	33.9 (16.0)	788	27.4 (14.6)	965	30.3 (13.3)	983	25.6 (13.5)
Star tracing								
SBP change*†‡	854	10.3 (8.5)	1100	9.5 (8.2)	1012	13.7 (8.5)	1114	11.2 (7.7)
DBP change*	856	11.2 (8.6)	1111	10.2 (7.8)	1020	11.3 (7.5)	1128	10.4 (6.9)
Video game, mm Hg								
SBP change*‡	867	10.0 (7.9)	1105	9.3 (8.3)	1010	10.7 (7.6)	1125	8.6 (7.2)
DBP change†	871	9.4 (8.1)	1115	9.7 (7.5)	1013	8.3 (7.1)	1130	8.2 (6.5)

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.

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

	SBP Reactivity Scores During Tasks					
	Cold Pressor (n=3553)		Star Tracing (n=4075)		Video Game (n=4100)	
Effects	Parameter Estimate	SE	Parameter Estimate	SE	Parameter Estimate	SE
Intercept	4.18*	0.110	4.22*	0.105	4.21*	0.104
Reactivity score	−0.120†	0.033	−0.111†	0.031	−0.098†	0.029
Race	−0.275*	0.043	−0.287*	0.041	−0.286*	0.041
Sex	0.138‡	0.045	0.142‡	0.045	0.125‡	0.044
Race×sex	0.138†	0.040	0.104‡	0.038	0.112‡	0.038
Age	−0.297*	0.041	−0.269*	0.038	−0.272*	0.037
BMI	−0.163*	0.027	−0.158*	0.027	−0.164*	0.027
Education	0.085§	0.037	0.135†	0.038	0.120†	0.036
Resting SBP	−0.518*	0.047	−0.547*	0.045	−0.533*	0.044
Sex×BMI	−0.070‡	0.026	−0.072‡	0.025	−0.068‡	0.025
Race×education	−0.086§	0.037	−0.112‡	0.037	−0.082§	0.036
Sex×education	NS	NS	−0.083§	0.037	−0.075§	0.035
Reactivity score×sex	0.068§	0.031	NS	NS	NS	NS
Reactivity score×race	0.072§	0.033	NS	NS	NS	NS

Race=1 for blacks, −1 for whites; sex=1 for men, −1 for women.
*$P\leq0.0001$; †$P\leq0.001$; ‡$P\leq0.01$; §$P\leq0.05$. NS not in final model.

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

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

Race=1 for blacks, −1 for whites; sex=1 for men, −1 for women.
*$P \leq 0.0001$; †$P \leq 0.001$; ‡$P \leq 0.01$; §$P \leq 0.05$. NS not in final model.

(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
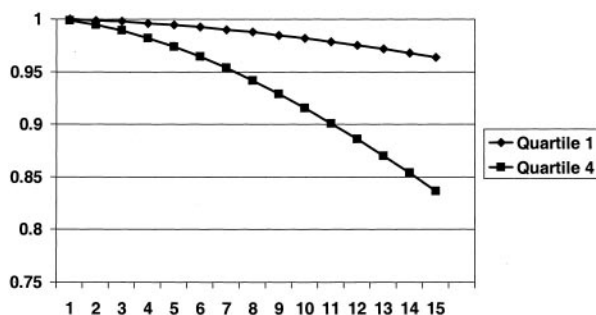
Figure 1. Probability of remaining normotensive in 2 participants with similar covariates but in top and bottom quartiles of DBP reactivity to cold pressor test.
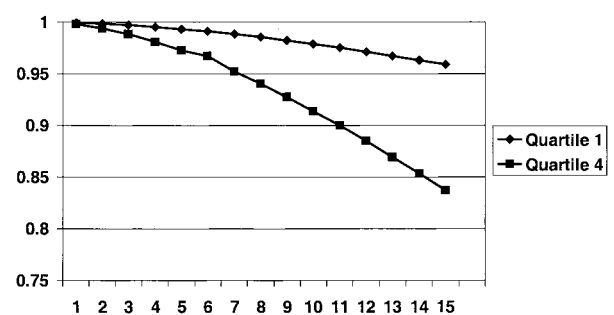

Figure 2. Probability of remaining normotensive in 2 participants with similar covariates but in top and bottom quartiles of DBP reactivity to star tracing task.
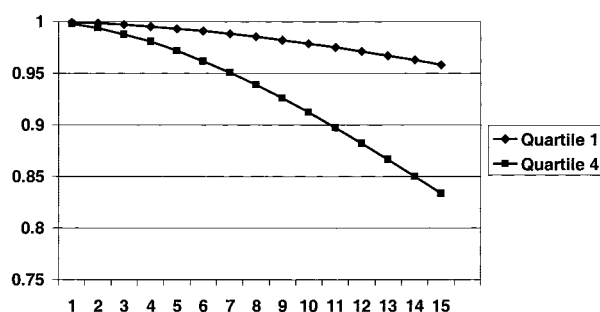
Figure 3. Probability of remaining normotensive in 2 participants with similar covariates but in top and bottom quartiles of DBP reactivity to video game.

the cold pressor task obtained in some prior studies of white men is consistent with the stronger results obtained in the present study for women. It is also likely that the present findings are more definitive than prior studies because of the analytic approach. It assumed an accelerating risk of hypertension as opposed to a constant risk, evaluated time remaining free of hypertension as opposed to hypertension at the end of the follow-up period, and allowed for left-, right-, and interval-censored observations and for multiple covariates.

The utility of the present findings rests on BP reactivity being a reliable characteristic of the prehypertensive individual and not an immediate consequence of hypertension. Numerous studies show that BP reactivity is a reliable characteristic of normotensive adults, with correlations for aggregated task BP change scores ranging from 0.71 to 0.81 across 5 studies with intervals of 1 week to 1 month.[22] BP reactivity is related to ambulatory BP elevations in response to everyday stressful circumstances.[23,24]

Although our data confirm a longstanding psychosomatic hypothesis, they do not elucidate the nature of that association.[25–27] One can posit direct effects of frequent BP changes on the vasculature, leading to damage and impairing arterial compliance. 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 vasoconstrictive 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 midlife, 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.

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