High Stress Responsivity Predicts Later Blood Pressure Only in Combination With Positive Family History and High Life Stress

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Abstract—High cardiovascular responsivity to stressors has not consistently improved prediction of later blood pressure increases beyond the predictive effects of baseline pressure. Animal models suggest that genetic susceptibility to hypertension and frequent stress exposure are important modulating factors in stress-related hypertension. Thus in 103 men originally tested at age 18 to 22 years and reassessed 10 years later, interactive effects of genetic susceptibility (defined as 1 or more hypertensive parents) with high stress responsivity (defined as top 25% on the basis of blood pressure and cardiac responses during both reaction time and cold pressor tasks) were examined in relation to follow-up systolic and diastolic levels and to change in blood pressure status from normal (diastolic<80 mm Hg) to marginally elevated (diastolic 85 to 95 mm Hg). Men with the combination of high stress response and hypertensive parents demonstrated higher systolic (P<0.05) and diastolic levels (P<0.05) at follow-up, and they showed a 7-fold increase (7.5, 95% confidence intervals 2.3, 24.3; P<0.001) in relative risk of change in blood pressure status versus men with no family history and a 3-fold increase (3.8, confidence intervals 1.5, 9.6; P<0.004) versus less stress-responsive men who also had hypertensive parents. In 65 men who also provided ratings of daily stress, family history×stress responsivity×daily stress interactions were significant in predicting follow-up systolic and diastolic levels (P<0.006 and 0.03, respectively), with highest pressure levels seen when high life stress was reported by high stress responders and/or men with hypertensive parents. In conclusion, results suggest that stress responsivity as a long-term predictor is modulated by both genetic and environmental factors. (Hypertension. 1999;33:1458-1464.)

Key Words: stress ■ genes ■ reactivity ■ family history ■ hypertension, essential

The issue of whether high cardiovascular responses to laboratory stressors in normotensive individuals may be predictive of later hypertension development is still unresolved.1–3 The strongest support for this hypothesis derives from prospective research in which blood pressure and heart rate responses to 1 or more stressors were related to increased blood pressure (BP) at follow-up intervals ranging from 1 year to 28 years later. Hyperreactivity of systolic BP (SBP) to the cold pressor test was related to increased development of hypertension after an average of 24 and 28 years of follow-up.4,5 High cardiovascular responses to active coping mental stressors have also predicted greater BP increases at follow-up.6–13 The largest of these latter studies was based on 3300 black and white young adults from the longitudinal CARDIA Investigation.13 Their results were mixed, however, indicating that after 5 years of follow-up, high systolic reactivity to the active coping video game but not to the passive cold pressor was predictive of greater blood pressure rises and increased incidence of hypertension in men but not in women. Other studies have failed to obtain a predictive relation between cardiovascular stress responses and later hypertension development.1,14 A key example is the recent Whitehall II Study14 in which prestress resting BP was a significant predictor of BP levels after nearly 5 years of follow-up in 1003 middle-aged men, but including a second predictor based on BP increases to a mental stressor, the Ravens Matrices, did not further improve the predictive model. These inconsistent findings have led some experts to conclude that high reactivity to laboratory stressors is a less useful factor than information about chronic life stress exposure and average daily load on the cardiovascular system, assessed with 24-hour ambulatory BP monitoring (eg, high job strain in men).15–18 Studies in animal models have provided direct confirmation that stress exposure plays a causal role in the pathogenesis of hypertension. Three key examples are (1) the modified social environments that enhance confrontations regarding dominance in mice, rats, and monkeys,19–25 (2) the model of

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1458
daily exposure to shock avoidance conflict in the borderline hypertensive rat (BHR),26–30 and (3) the model of combined daily shock avoidance plus saline infusion in the dog.31–33 Each of the models demonstrates that stress exposure can be a critical factor leading directly to hypertension but also that hypertension will only occur in those animals with high susceptibility due to genetic and/or environmental factors. Recent extensions of Henry’s work has shown that hypertension with his model develops in only the most susceptible rat strains, and then only in the aggressive dominant or just subordinate males.23–25 Similarly, the BHR model is highly susceptible to either salt-induced or stress-induced hypertension because of genetic influences from its 1 spontaneously hypertensive rat (SHR) parent,30 and the dog model is susceptible because of excessive salt intake combined with potassium deficiency.32 As Harshfield and Grim34 recently summarized, the lesson that these animal models are examples of the “wrong” genes combined with the “wrong” environments needs to be extended to our research in human models of stress-related hypertension.

This vision of stress-induced hypertension as requiring the wrong genes and the wrong environment offers a parsimonious explanation for inconsistencies in previous longitudinal investigations in humans. The prior studies of predictive relations of stress responsivity, including those by our research group, did not control for or examine effects of this predictor in combination with high versus low genetic risk of hypertension or with environmental factors influencing susceptibility or stress exposure. The goal of this report is to provide a preliminary test of whether the relation of cardiovascular stress responses in predicting long-term increases in blood pressure in males may be dependent on, first, genetic susceptibility, as reflected in family history of hypertension, and second, environmental factors reflecting individual differences in stress exposure (perceived daily stress level). A corollary of this hypothesis is that a high stress responder will rarely show substantial blood pressure elevations over time if his genetic susceptibility to hypertension is low. Also, a high stress responder will rarely show pressure elevations if his environment is low in stress exposure, since this will minimize his cardiovascular responses in daily life despite the individual’s tendency to exaggerated responsivity. In the present report, the interactive effects of high cardiovascular responsivity to stress with positive versus negative family history of hypertension and with subjective ratings of daily stress levels predicted BP levels in young men after 10 years of follow-up.

**Methods**

**Subjects**

Participants were recruited from the 183 male volunteers who had participated in a study of cardiovascular responses to laboratory stressors in 1982 to 1983, when undergraduates were 18 to 22 years of age at the University of North Carolina (UNC).35 This initial testing provided the cardiovascular baseline and stress responses used as predictors in the present analyses. The follow-up data collection occurred 10 years later, in 1992 to 1993. Three of the 183 men had died in the decade after initial testing (none from cardiovascular causes), and 17 had moved without giving a forwarding address. Of the 163 still living for whom addresses were available, 103 (63%) provided informed consent for further participation, which involved completion of questionnaire data on job stress, personality and behavioral patterns, and social support, as well as clinical assessment of BP status based on a single clinical visit, with 5 BP readings obtained at that visit. Of these 103 volunteers, 65 of the 80 subjects who currently lived within 435 km of Chapel Hill also agreed to have a research assistant visit them at home before work on a typical weekday to be instrumented with an ambulatory BP monitor and to wear the monitor for 24 hours. At the end of this day, these 65 men rated their perceived stress exposure by completing the Daily Stress Inventory, a 60-item scale on which the subject indicates whether he experienced any of these common hassles and stresses during this day and rates the severity of his perceived stress reaction to any which he experienced.36 Of these 65 men, 59 also agreed to undergo a repetition of their initial laboratory testing in an effort to document the 10-year stability of their laboratory stress responses. The findings confirming satisfactory test-retest stability for SBP, heart rate (HR), and prejection period (PEP) but not for diastolic BP (DBP) responses to the stressors have been previously reported37 and will not be detailed here, nor will the ambulatory BP data. However, the total stress scores from the Daily Stress Inventory were used in secondary analyses of prediction of clinic SBP and DBP levels to evaluate the hypothesized interaction of family history × stress responsivity × daily stress exposure.

The representativeness of the 103 subjects who participated in the follow-up study was assessed by comparing their cardiovascular responses at initial testing to those 80 subjects who could not be retested due to death, inability to contact, or unwillingness to be retested. The 2 groups were statistically similar in terms of age, ethnic composition (90% white, 10% black/Hispanic/other), and baseline, prestress and stress BP, and HR levels at time 1 (all P>NS).

**Physiological Recording**

**1982 to 1983 Initial Testing**

Details of initial testing have been described by Sherwood et al.37 To summarize briefly, all subjects were tested during 2 stressors in an order counterbalanced across subjects: (1) a 90-second foot cold pressor test, and (2) a 5-minute reaction time task involving threat of shock, but no shocks were actually delivered. BP determinations were performed with a BP cuff with a Korotkoff sound microphone over the brachial artery that permitted pressure and sounds to be depicted on a chart recorder; BP at onset and marked attenuation of Korotkoff sounds (phase I and phase IV) were used to define SBP and DBP levels, respectively, a method previously validated against invasively monitored brachial arterial BP. HR was obtained from the ECG and PEP was derived by subtracting left ventricular ejection time from total electromechanical systole as previously described.37 After instrumentation but before the stressors, a 15-minute rest period ensued, with data obtained during the last 3 minutes used as prestress resting levels. Subjects also returned to the laboratory on 2 subsequent days, underwent similar instrumentation, and simply rested for 15 minutes on each visit, with responses from the last 3 minutes of both sessions averaged as baseline levels.

**1992 to 1993 Testing**

All subjects visited either UNC Medical School or their own personal physician or agreed to have our research assistants visit them in their homes for determination of SBP and DBP by clinical auscultation with an arm cuff and stethoscopic determinations of onset and marked attenuation of Korotkoff sounds, obtained by use of a carefully standardized method. The BP recording method, which had to be confirmed by a signed statement by the physician, physician’s assistant, or nurse if not obtained by our staff, involved at least 5 minutes of seated rest followed by 5 sequential BP determinations, allowing at least 1 minute of recovery between each reading and the next. The first reading was dropped, and the 4 remaining readings were used to define current BP status. If the DBP level during those readings included 1 or more readings of 85 to 89 mm Hg, the individual was identified as having high normal BP.
and if they included 1 or more readings of 90 to 95 mm Hg, the individual was identified as having borderline to stage 1 hypertension. At follow-up, all subjects completed a questionnaire on demographic and medical history information, including information on history of hypertension and/or heart disease in each of the subject’s parents. If the subject reported that one or both parents had hypertension, he was identified as having a positive family history, whereas if neither parent had hypertension he was identified as having negative family history.

Data Analyses
First, high, moderate and low Cardiovascular (CV) Stress Responder groups were identified with the use of z-scores, based on their relative SBP, DBP, HR, and PEP response levels during both the reaction time and the cold pressor challenges at original (time 1) testing, with more increased BP and HR and more decreased PEP combined to index greater CV stress responsivity. Multiple measures were combined in an effort to identify those men who showed evidence across 2 differing stressors of substantial pressor responses associated with high cardiac sympathetic activity (high BP responses with high HR and decreased PEP responses). (Preliminary analyses indicated that individual measures [SBP response alone, PEP alone, etc] were less successful than the composite z-score measure in demonstrating relationships to follow-up clinic SBP and DBP. Therefore, the composite measure alone was retained in final analyses. Note that because PEP during the cold pressor did not show reliable changes from baseline to stress, this measure was not included.)

Those subjects falling into the top quartile of the original sample of 183 subjects based on relative responses averaged across these multiple measures were defined as high stress responders, those in the middle 2 quartiles were defined as moderate stress responders, and those in the bottom quartile were defined as the low stress responders. Of the 103 men providing follow-up BP data, 27 were high stress responders, 50 were moderate stress responders, and 26 were low stress responders, in close proportion to expectations based on the original group. Change in BP status over time (development of clinic DBP levels ≥85 mm Hg vs continued DBP <85 mm Hg) of subjects in these 3 stress responder groups 10 year later was compared within the positive and negative family history of hypertension subgroups with χ² analysis, using the PROC FREQ program of the SAS analysis systems (SAS Institutes, Cary, NC), and computation of relative risk (RR) ratios. All subjects evaluated for change in BP status showed normal DBP at time 1, defined as both baseline and prestress rest DBP levels ≤80 mm Hg.

Second, the 2-way interaction of family history and CV stress response level was examined as a potential predictor of the average clinic levels of SBP and DBP, with the use of the SAS General Linear Models program. Two traditional predictors, body mass index (BMI) and time 1 baseline BP levels, were entered as permanent first-line predictors (covariates) in these models, and effects of the hypothesized interactions were examined as additions to the base models. (Model evolution indicated that first-line predictors [covariates] BMI and time 1 baseline BP yielded significant models for both follow-up SBP and DBP: \( P < 0.006, R^2 = 0.139 \), and \( R^2 = 0.144 \), respectively. The addition of main effects for CV stress responder group to the models was not significant, whereas the addition of main effects for family history were originally significant (\( P < 0.03 \)), but its independent contribution became nonsignificant (\( P = 0.80 \)) for both SBP and DBP prediction after addition of the interaction of these 2 factors. Thus in the final models, the 2 main effects were deleted, and the significant interactions [\( P < 0.015 \) and \( P < 0.004 \); final, \( R^2 = 0.191 \) and \( R^2 = 0.251 \)] plus the first-line predictors were retained.)

Third, in those 65 subjects who provided ratings of current life stress levels at follow-up based on Daily Stress Inventory total scores, the 3-way interactions of this measure with family history and CV stress response level was substituted for the 2-way interaction in predictive models of follow-up clinic SBP and DBP levels. In all primary analyses, \( \alpha \) level was set at 0.05 for 2-tailed comparisons. In examining the simple effects of interactions related to the expected increase in BP related to the combination of positive family history, high stress responsivity, and high daily stress, directional a priori hypotheses permitted use of 1-tailed tests for final analyses.

Results

Prediction of Change in Blood Pressure Status by Family History and CV Stress Response
Of the 103 men participating in the follow-up study, 18 (17.5%) men whose time 1 baseline and prestress resting DBP levels were originally <80 mm Hg demonstrated a change in BP status over the 10-year period, showing development of high normal DBP to stage 1 hypertension (defined as follow-up clinic DBP levels of 85 to 95 mm Hg). Initial \( \chi^2 \) analyses indicated (as expected) that subjects with a positive family history were at increased risk of development of high normal or elevated DBP; only 3 of the 45 negative family history subjects versus 15 of the 58 positive family history subjects showed this change in BP status (\( \chi^2=6.28, P<0.012 \)). Because of the low frequency of change in BP status among negative family history subjects, no effect of CV stress responder group could be detected within those subjects. Within the positive family history group, change in BP status was found to be directly related to increasing CV stress response at time 1, with elevated DBP at follow-up evident in 0% of low stress responders, 17.9% (5 cases) of moderate stress responders, and 50.0% (10 cases) of high stress responders (\( \chi^2=10.5, P<0.005 \)). Thus the RR of a change in BP status was substantially increased only in the subjects with both a positive family history and high CV stress responsivity (RR = 1 for all negative family history subjects vs RR = 1.9, confidence intervals [CI] 0.5, 7.7, \( P = \text{NS} \) for positive family history subjects who were low and moderate stress responders vs RR = 7.5, CI = 2.3, 24.3, \( P<0.001 \) for positive family history subjects who were high stress responders). Furthermore, if only men with a positive family history were included, those who were high stress responders still showed a significant increase in risk compared with the low and moderate responders (RR = 3.8; CI = 1.5, 9.6; \( P<0.004 \)).

Prediction of Follow-Up Clinic SBP and DBP Levels by Family History and CV Stress Response Groups
High CV stress responsivity was also found to predict actual clinic levels of both SBP and DBP 10 years later, interacting with and potentiating effects of a positive family history of hypertension. For follow-up SBP levels, the model based on BMI, initial baseline SBP, and the interaction of family history by CV stress response level was significant: \( F(3,98) = 7.69, P<0.0001 \). The interaction effect was itself a significant addition to the model: \( F(1,98) = 6.21, P<0.015 \); parameter estimate = 1.84; SE, 0.74. Simple effects analyses indicated that CV Stress Responder Group did not differentiate follow-up clinic SBP levels among the negative family history subjects (\( P=\text{NS} \)), but higher stress responder status was related to progressively higher follow-up SBP among the positive family history subjects (\( P<0.05 \); see Figure 1). Subsequent comparisons among means revealed that positive family history subjects who were high stress responders at
time 1 had significantly higher SBP at follow-up compared with all negative family history subgroups regardless of stress responder status \((P<0.05)\). In contrast, those positive family history subjects who were low stress responders showed no greater SBP level at follow-up than negative family history groups, and those who were moderate stress responders showed only a nonsignificant trend toward higher SBP \((P>0.09)\).

In predicting follow-up clinic DBP levels, the model based on BMI, baseline DBP, and the interaction of family history by CV stress response level was likewise significant: \(F(3,98)=10.79, P<0.0001\). The interaction was a significant addition to the model: \(F(1,98)=13.66, P<0.004\); parameter estimate, 2.09; SE, 0.56. As with prediction of later SBP, there was no evidence of any difference in follow-up DBP among stress responder groups with negative family history \((P=NS)\), but higher follow-up DBP was related to higher stress response in the positive family history group (see Figure 1). Subsequent mean comparisons showed that the positive family history subjects who were high CV stress responders had higher DBP at follow-up than any of the negative family history groups \((P<0.05)\), whereas the positive family history subjects who were low or moderate stress responders showed only a nonsignificant trend toward higher DBP levels than those with negative family history \((P>0.10)\). Thus in prediction of levels of both clinic SBP and DBP 10 years later, high CV stress response was an important factor, but only when present together with genetic susceptibility, that is, with a positive family history of hypertension.

Conversely, the effect of positive versus negative family history in differentiating follow-up SBP and DBP levels was substantially more robust in the high CV stress responders than in low or moderate stress responders.

High Daily Life Stress Augments BP Effects of Family History and Stress Response

Among the 65 subjects who rated their current life stress levels at follow-up using the Daily Stress Inventory, additional analyses were performed in which the 3-way interaction of family history by CV stress response level by daily stress was substituted for the 2-way interactions in models predicting follow-up clinic levels of SBP and DBP. For both SBP and DBP, the 3-way interaction was significant: \(F(1,59)=8.19\) and 5.11, \(P=0.006\) and 0.0275; parameter estimates 0.05, SE 0.5 and 0.03, SE 0.01. Simple effects analyses were used to clarify the sources of these interactions. When the high CV stress responders were examined separately, a significant main effect of daily stress was obtained for SBP after adjusting for family history: \(F(1,13)=5.59, P<0.035\). As shown in Figure 2, high stress responders with high daily stress \((n=6)\) showed higher clinic SBP levels at follow-up compared with high stress responders with low daily stress exposure \((n=11)\) \((129.2\pm3.5 vs 119.2\pm2.9 \text{ mm Hg}, P<0.035)\). When the low and moderate CV stress responders were examined, those reporting high versus low daily stress did not differ overall; however, a significant interaction of family history by daily stress was obtained: \(F(1,41)=7.66, P<0.0085\). In these less stress-responsive subjects, high daily stress was associated with increased follow-up SBP levels only when combined with a
positive family history of hypertension. The subjects with both positive history and high daily stress (n=14) showed higher clinic SBP levels than those with positive history but low daily stress (n=8) (125.2±2.2 vs 116.7±2.9 mm Hg, P<0.027) and higher SBP than negative family history subjects with high or low daily stress (both n=12, SBP levels 112.3±2.4 and 117.9±2.4, P<0.0004 and 0.033, respectively).

Simple effects analyses with follow-up DBP levels yielded significant effects among high CV stress responders only. In analyses with low and moderate stress responders, all effects involving daily stress alone or in combination with family history were nonsignificant (P=NS). Among the high CV stress responders, however, Family History and Daily Stress showed independent but additive effects after adjustment for baseline DBP at time 1, F(1,12)=4.92 and 3.74, P<0.047 and 0.077. A priori 1-tailed comparisons among means indicated that high stress responders had greater follow-up DBP if their family history was positive versus negative (81.6±2.2 vs 70.9±3.9 mm Hg, P<0.023) when examined independently of stress levels. Similarly, independent of family history, high stress responders showed higher follow-up DBP if they reported high versus low stress exposure (80.0±2.9 vs 72.5±2.7, P<0.039; see Figure 2).

Discussion

In this homogeneous sample of 103 predominantly white men tested originally at ages 18 to 22 and reevaluated ~10 years later, original stress responsivity was an important predictor of higher clinic BP level and of change in BP status toward hypertension at follow-up. As a test of the so-called reactivity hypothesis, this study can be counted as another example of a supportive finding. Its unique contribution, however, is that its results may also help explain the negative studies and those studies yielding only weakly supportive relations. In the current study, the predictive importance of stress responsivity was seen only in the subgroup of men with high genetic susceptibility to hypertension, defined as having 1 or more hypertensive parents. Also, it is important to emphasize that although family history of hypertension was a meaningful predictor of change in BP status on its own, high stress responsivity greatly potentiated this increased risk of developing elevated BP. The high stress responders with a positive family history of hypertension demonstrated a ≥7-fold increase in risk relative to men with a negative family history, but they also showed a nearly 4-fold increase relative to less stress-responsive men who also had hypertensive parents. This inclusion of family history as an interactive factor, and particularly looking at risk increments among the positive family subjects who were high stress responders, was not a strategy used in prior prospective studies, although several studies did include family history as part of the base model, and 2 other studies focused exclusively on persons with a positive family history. In this study, positive family history together with high stress responsivity proved to be a critical combination.

Exposure to a more stressful life environment, as assessed by Daily Stress Inventory ratings obtained at follow-up, proved to further augment SBP and DBP levels among the high stress responders. High daily stress exposure also enhanced the effect of a positive family history so that even among the low and moderate stress responders, clinic SBP levels were increased in men with hypertensive parents who reported high versus low daily stress scores. High cardiovascular stress response has been shown to be a stable characteristic of a substantial subgroup of the population over time, and this sample showed relatively good stability of cardiovascular stress responses over the full 10 years of follow-up. This suggests the possibility that high stress responsivity itself may have a genetic basis; however, the animal literature suggests that high adrenergic and pressor activity during acute stress occurs in some hypertension-vulnerable strains and also in some hypertension-resistant strains, implying that high stress responsivity and high hypertension susceptibility do not necessarily share a common genetic basis.

Altogether, these findings suggest that the reactivity hypothesis as it has been traditionally applied is overly simplified. We suggest that it be updated and replaced by the Gene and Environment Modulated Stress Responsivity Hypothesis, stating that high cardiovascular and/or adrenergic stress responsivity will be related to increased risk of elevated BP and of other adverse cardiovascular outcomes but that these risks are greater and may only be reliably detected if the sample has a high genetic vulnerability to develop hypertension and cardiovascular problems or has acquired high vulnerability through other interventions (surgery, disease, adverse nutrition, and so forth). Further, this effect will be greater if the individual’s daily life environment involves a sufficiently high exposure to stressors and/or lack of stress buffers. The present study itself must be considered only a preliminary test of this updated hypothesis. This is due to the relatively modest sample size (n=103), the concerns about the relatively high percentage of men unable to be retained at follow-up, and the fact that modulating effects of perceived life stress could be examined in only 65 of the subjects. The limited sample and lack of vascular resistance assessment at time 1 also precluded separate testing of high cardiac versus vascular responsivity as predictors. There is also the concern about possible lack of generalizability to older persons, to minorities, and to women because the sample was restricted to young, predominantly white men. Still, the study does provide a model for larger-scale future investigations. It is important to note that the model does not in fact require that family history and stress responsivity always demonstrate a clear interaction effect; in some samples, the statistical tests may instead express a similar relation as additive effects of the 2 factors. The critical component, however, is that the greatest risk of elevated BP or other cardiovascular problems must be seen in the group with both genetic susceptibility and high stress responsivity.

The present findings have implications for other research on stress-related hypertension development. Chronic stress exposure, such as long-term work in a high job strain environment or in a context with low social support, has been related to increased 24-hour ambulatory BP and to increased risk of hypertension and cardiac morbidity. The implication is that any adverse effects of increased life stress or
decreased stress buffers would be most evident among those individuals who are both high stress responders and who have a genetic susceptibility to hypertension and heart disease. Thus future studies examining the consequences of key sources of life stress on the causes of cardiovascular disorders may be best designed to look for both interactive and additive effects of these 3 critical factors rather than examining the environmental stress factor in isolation. One recent study by Everson et al44 indicated that among 591 men in the longitudinal Kuopio, Finland, sample, those who were both high systolic responders to stress and also were in the top quartile of the sample in self-reported workplace stress demonstrated greater progression of carotid artery atherosclerosis over 4.2 years of follow-up. Although familial and genetic susceptibility was not addressed in this report, their findings reinforce the importance of daily stress exposure in interaction with stress responsivity in prediction of cardiovascular health outcomes.

In conclusion, among a modest sample of 103 young men originally tested at ages 18 to 22 years, clinic BPs 10 years later were found to be higher, and onset of marginally elevated BP (high normal DBP to stage 1 hypertension) was more frequent among those who were high stress responders and also had at least 1 hypertensive parent. These effects were evident after adjustment for BMI and baseline pressure level at initial testing. High perceived daily stress exposure further enhanced increases in SBP and DBP among the high stress responders and was related to increased SBP among the low responders with hypertensive parents. These results encourage updating and elaboration of the Reactivity Hypothesis to clarify that stress responsivity may be most meaningful as a predictor of hypertension and other cardiovascular disorders when examined in combination with genetic susceptibility and environmental stress exposure.

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