

Toward a Causal Model of Cardiovascular Responses to Stress and the Development of Cardiovascular Disease

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Objective: Cardiovascular reactivity is hypothesized to mediate the relationship between stress and cardiovascular disease. We describe three considerations that are crucial for a causal model of cardiovascular responses to stress: the need for laboratory-life generalizability, the role of interactions between environmental exposures and individual response predispositions, and the importance of the duration of both stressor exposure and cardiovascular responding. **Methods:** We illustrate current understanding of stress-cardiovascular disease relationships with examples from the human and animal psychophysiology, epidemiology, and genetics literature. **Results:** In a causal model of reactivity, the usefulness of laboratory assessment rests on the assumption that laboratory-based cardiovascular reactivity predicts responses in the natural environment. We find only limited generalizability and suggest that cardiovascular responses to stress can be better understood when examined in the natural environment. The interaction of individual response predispositions and stressor exposures contributes to the development and progression of cardiovascular disease; stress-disease relationships could therefore be better understood if predispositions and exposures were assessed simultaneously in interactive models. Cardiovascular responses to stress are likely to be most deleterious when responses are prolonged. Responses may vary in their magnitude, frequency, and duration; however, reactivity captures only response magnitude. The assessment of anticipatory and recovery measures, with response magnitude, may therefore lead to a more useful model of the stress-disease relationship. **Conclusions:** A causal model of cardiovascular responses to stress should generalize to the real world, assess interactions between individual predispositions and environmental exposures, and focus on sustained pathogenic exposures and responses. **Key words:** cardiovascular reactivity, blood pressure, stress, hypertension, coronary artery disease.

ABP = ambulatory blood pressure; ACE = angiotensin-converting enzyme; ADH3 = alcohol dehydrogenase type 3; BHR = borderline hypertensive rat; BMI = body mass index; BP = blood pressure; CAA = coronary artery atherosclerosis; CAD = coronary artery disease; CPT = cold pressor test; CVD = cardiovascular disease; CVR = cardiovascular reactivity; DBP = diastolic blood pressure; EF = endothelial function; ER- α = estrogen receptor alpha; HR = heart rate; HRT = hormone replacement therapy; HRV = heart rate variability; HT = hypertensive; HTN = hypertension; LV = left ventricle; MA = mental arithmetic; MI = myocardial infarction; NO = nitric oxide; NT = normotensive; PNS = parasympathetic nervous system; SBP = systolic blood pressure; SES = socioeconomic status; SHR = spontaneously hypertensive rat; SNS = sympathetic nervous system; WKY = Wistar-Kyoto (rat); 5HT-TLPR = serotonin transporter gene.

INTRODUCTION

Large stress-induced blood pressure (BP) and heart rate (HR) elevations are hypothesized to lead, over time, to elevation of the tonic BP level and the development of coronary artery disease (CAD). Investigation

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Received for publication June 5, 2001; revision received July 12, 2002.

DOI: 10.1097/01.PSY.0000046075.79922.61

of cardiovascular responses to stress most often occurs in the laboratory through assessment of cardiovascular reactivity (CVR): BP and HR elevations occurring during the presentation of a discrete stressor. Early reactivity models did not postulate a causal role for reactivity in the genesis of hypertension (HTN) or CAD; rather, CVR was conceived of as a marker of risk for future HTN (1).

Over the past few decades, CVR has come to be viewed as a causal factor in the development of both HTN and CAD (1). This view has stimulated a great deal of research assessing properties of the reactivity construct, leading to a burgeoning literature investigating CVR moderators, including gender; race; socioeconomic status (SES); personality measures, such as Type A and hostility; psychological disorders, including depression, anxiety, and panic; menstrual cycle phase; and social support (1).

This review focuses on implications that arise in considering CVR to be a cause, rather than simply a marker, of CVD. We suggest that the evidence does not support such a role and that the emphasis placed on CVR during the past several decades is not justified by the published literature. This is not intended as a comprehensive review of the CVR literature; instead we focus on three properties that we think are necessary for a causal model of the stress-CVD relationship and are neglected by the current CVR paradigm:

1. *Generalizability.* A key assumption underlying CVR as a causal factor in CVD is that cardiovascular responses observed in the laboratory predict BP and HR responses occurring in the real world. We find little evidence for the generalizability of CVR. If laboratory CVR does not gener-

alize to real-world cardiovascular responses, then CVR studied in the laboratory cannot provide information about the role of stress or other psychosocial factors in CVD.

2. *The need to focus on interactions.* HTN and CAD are slowly progressive diseases that result from multiple environmental and individual difference factors, acting additively and interactively. However, the traditional CVR model emphasizes main effects. Thus, our second focus is the role of interactions between physiological or psychological predispositions and environmental exposures in predicting disease risk.
3. *Duration of stressor exposure and cardiovascular response.* BP and HR elevations in response to stress are hypothesized to lead to disease. Thus, pathogenicity should increase as the cumulative duration of cardiovascular response increases. Prolonged cardiovascular responses may occur with exposure to chronic or repeated stressors or as a result of cognitive or emotional processes that sustain cardiovascular arousal. However, laboratory CVR does not discriminate between isolated transient responses and frequent prolonged responses. Thus, our third focus is on the importance of duration of exposure and cardiovascular response to a causal model of stressor effects on CVD.

We attempt to illustrate the current understanding of CVD pathogenesis with examples from the human and animal literature in a variety of disciplines, including psychophysiology, epidemiology, and genetics. However, the relevant literature is far too great to be cited in a single review. For reviews of other facets of the CVR-disease relationship and alternate perspectives, we refer the reader to Treiber et al. (2), Kamarck and Lovallo (3), Lovallo and Gerin (4), and Pickering and Gerin (5).

GENERALIZABILITY OF LABORATORY REACTIVITY TO THE NATURAL ENVIRONMENT

In a causal model of CVR, the usefulness of laboratory assessment rests on the assumption that CVR measured in the laboratory will serve as a proxy for stress-induced cardiovascular responses occurring in the natural environment. Several reviews have examined the degree to which CVR to laboratory stressors predicts the response to stressors in the natural environment and the mean level or variability of BP or HR during daily life. Two reviews published in 1990 (5, 6) noted quantitative and methodological limitations of existing studies. Pickering and Gerin (5) examined a

dozen studies, finding little evidence of generalizability and concluding that “the data are insufficient to give a definitive answer, but are so far unimpressive.” Manuck et al. (6) noted that the generalizability of laboratory CVR was limited by the variability among stressors encountered by subjects during ambulatory monitoring (and daily life) and by the limited reliability of reactivity testing. They suggested that error variance could be reduced by performing multiple reactivity assessments and multi-day ambulatory assessments. Four years later, Turner et al. (7) identified 32 relevant studies that they thought presented moderate evidence for laboratory-life generalizability. They noted strong relationships between laboratory and field BP levels but less consistent evidence for associations between laboratory and field CVR and between laboratory CVR and field BP levels. Linden et al. (8), in 1998, assessed five studies that both compared CVR to several tasks in the laboratory with ambulatory BP (ABP) levels and tested whether the addition of CVR measures improved the prediction of ABP over that found using laboratory resting levels. They suggested that aggregation of scores across all laboratory periods (ie, baseline, adaptation, reactivity, and recovery) tended to improve predictor models, whereas reactivity tended to add little to baseline measures. They also noted that interpersonal tasks tended to show greater predictive ability than other tasks. Kamarck and Lovallo (3), in this issue, review the current generalizability literature, finding modest results and that results, when present, “are inconsistent across tasks and parameters.” Like previous authors, they suggest that the failure to find generalizability may be due to limitations of the traditional laboratory CVR methodology.

Person-by-Situation Effects Limit Generalizability

CVR is highly vulnerable to situation and person-by-situation effects, both inside and outside the laboratory (9). For example, Gerin et al. (10) examined the effect of minor variations in setting on generalizability. Female college students performed a mental arithmetic (MA) task on four occasions; all procedures except for the setting (task, equipment, experimenter, etc.) were identical during each performance of the task. The task was performed twice in the laboratory, once in a classroom, and once in the living rooms of the students' dormitories. The test-retest correlations for reactivity change scores between the two sessions conducted in the laboratory were moderately reliable for BP, with r values of 0.68, 0.62, and 0.09 for systolic BP (SBP), diastolic BP (DBP), and HR, respectively. The correlations *across settings*, however, were sub-

stantially smaller, with average correlations of 0.45, 0.35, and 0.12 for SBP, DBP, and HR, respectively. This suggests that even when identical tasks are used, CVR observed in the laboratory is at best only moderately generalizable to nonlaboratory situations.

Aggregation as a Strategy for Improving Generalizability

Kamarck et al. (3, 11) hypothesized that the lack of evidence for the generalizability of laboratory CVR may be due to the failure to sample an adequate number of laboratory tasks and sessions. Aggregation across multiple tasks and sessions might allow greater generalizability for two reasons. First, each measurement contains random error not due to systematic influences (ie, person or situation effects); the use of multiple measurements will increase reliability and reduce the contribution of random error variance. Second, aggregation is likely to increase the diversity of sampled situations so that they may better represent those encountered in the real world.

Studies using aggregation as a technique to improve generalizability have shown mixed results (11–13). The most successful study was done by Kamarck et al. (11), who measured anticipatory responses and CVR to giving two classroom speeches. Laboratory tasks were each performed at two sessions and consisted of four computer-based active coping tasks and two other tasks, silently preparing a speech and delivering the speech. Correlations between the response to the individual laboratory tasks and the classroom stressor were quite modest (mean r values = 0.13, 0.17, and 0.16 for SBP, DBP, and HR, respectively) and were not significantly different from zero.

The authors performed generalizability analyses aggregating across the laboratory tasks, aggregating across the two testing sessions, and aggregating across both tasks and sessions. Average correlations between CVR aggregated across sessions in the laboratory and in the classroom were small and nonsignificant. For average task-aggregated CVR, the relationship to classroom reactivity was significant for DBP ($r = 0.31$) only. When aggregating across both task and session, correlations with the classroom measures were significant, with r values of 0.26, 0.40, and 0.30 for SBP, DBP, and HR, respectively. We note, however, that even under this “best-case scenario,” laboratory CVR accounted for only 7% to 16% of the variance in response to a discrete real-world stressor, a classroom speech. However, if the utility of aggregation stems from the ability to represent the average response to a diverse array of situations, that utility will be obscured when only one real-life stressor has been sampled as the outcome.

Use of Tasks With Low Ecological Validity May Limit Generalizability

The ecological validity of many commonly used laboratory tasks is questionable. Many laboratory studies use stressors that are relatively easy to administer yet have no compelling rationale for their use. Stressors associated with the development of CVD or overall mortality include job strain (14, 15), marital stress (16), caregiving strain (17), and low SES (18). The commonality between the emotional, cognitive, and physiological responses to these real-world stressors and the response to laboratory tasks such as star mirror tracing, the cold pressor test (CPT), and MA has not been demonstrated. Animal studies of the stress-CVD relationship, in contrast, generally involve potent and chronic stressors, such as unstable social living situations or daily threat of bodily harm, lasting months to years (eg, Refs. 19 and 20).

As noted by Linden et al. (8), several studies (21–24) have shown greater generalizability for tasks such as social competence or Type A interviews, discussing an anger-provoking event, and listening to a competitor’s speech than for traditional laboratory stressors. This suggests that social tasks may be more representative of daily life stressors than are the cognitive and physical tasks historically used in assessing CVR.

Addition of Anticipatory and Recovery Responses May Allow Greater Generalizability to Daily Life

The focus, in the laboratory, on cardiovascular responses that occur *during* exposure to a stressor may neglect clinically important aspects of the psychological and physiological response to stress; cardiovascular responses to stress vary not only in their magnitude but also in the extent to which they anticipate the stressor and continue after the stressor has passed as well as the degree to which they recur. These dimensions may not be tapped by laboratory reactivity, potentially limiting generalizability to daily life BP.

The lack of evidence that CVR generalizes to the real world undermines the putative role of CVR, as it is currently conceptualized and assessed, as a causal pathway in the development of CVD. However, it is important to note that lack of support for the laboratory CVR model does not imply that BP and HR elevations occurring in response to stress in the real world cannot lead to the development of CVD.

There are several modifications to laboratory CVR protocols that may improve generalizability. The use of social stressors (or other more ecologically valid tasks), aggregation across tasks to account for person-by-situation effects, and the addition of anticipatory

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and recovery responses may allow better prediction of variability in real-life responding. However, in light of the limited generalizability of the laboratory CVR model, the understanding of the cardiovascular response to stress is likely to benefit from greater emphasis on assessing responses occurring in the natural environment.

A noteworthy parallel occurs with regard to the diagnosis of HTN, which has traditionally been based on readings obtained in the physician's office. The rationale for office measurement is similar to that underlying the study of laboratory CVR: measurement in the physician's office is considered useful because it is thought to reflect the "true" BP. However, the relationship between the office BP and BP in daily life is quite weak for many persons who have white coat HTN (25), or masked HTN (26). Indeed, ABP levels are more useful predictors of cardiovascular morbidity than is office BP (27, 28), likely because ambulatory measurements sample BP during the self-selected, broad array of situations persons encounter in their lives. Thus, to know a person's BP as it occurs in the real world, measurements must be taken in the real world. We suggest that the same is true for CVR.

INTERACTIONS AMONG ENVIRONMENTAL, INDIVIDUAL DIFFERENCE, AND GENETIC FACTORS

Development of CVD and its risk factors, including HTN and atherosclerosis, is multifactorial, determined by a broad array of genetic, environmental, and behavioral factors (29). It is important to note that genetic and nongenetic factors *do not act merely in parallel* but in an *interactive* fashion. Thus, the effect of many genes will depend on the environment in which they are expressed. Likewise, there is great interindividual variability in response to environmental factors, with the impact of a given factor often dependent on the individual's genetic predisposition (30). We review several individual predispositions and environmental exposures that have been found to interact in predicting CVD development.

When Macaque monkeys consume diets that induce moderate hypercholesterolemia, they develop atherosclerotic lesions that are similar to those seen in human beings. Macaque monkeys exhibit complex social interactions: social groups are characterized by status hierarchies in which dominant animals reliably defeat subordinates. The presence of unfamiliar monkeys increases confrontation among the group members as individuals attempt to reestablish affiliate and hierarchic relationships (31).

Kaplan et al. (19) performed an experiment in which

male cynomolgus macaques were fed an atherogenic diet similar to that consumed by typical North Americans. The monkeys were housed in five-member groups and assigned to one of two social conditions. In the unstable condition, group memberships were altered periodically, and a female was placed into the groups on a regular basis to provide an additional stimulus for competition. In the stable condition, initial group memberships were maintained without disruption for the 22 months of the experiment. Behavioral observation allowed classification of monkeys as either dominant or subordinate. At the conclusion of the experiment, necropsy examination of coronary arteries showed an interaction between social environment and social status on the development of atherosclerosis. Dominant monkeys in the unstable social condition showed significantly more coronary artery atherosclerosis (CAA) than dominant monkeys in stable social groups or subordinate animals in either condition. Thus, social dominance was associated with severity of CAA in male macaques, but only when they were exposed to social conditions that provided recurrent behavioral challenges.

Female monkeys showed a different pattern of responses. In a similar experiment (32), premenopausal female cynomolgus macaques consumed an atherogenic diet while housed in five-member stable or unstable social groups. Males eating the same diet were housed in five-member stable social groups. Dominant females showed less atherosclerosis than the males. However, this protection did not extend to subordinate females, who showed atherosclerosis of similar severity to that seen in males. In females, no effect of social stability was seen, with animals showing comparable CAA whether housed in stable or unstable social groups.

The macaque model offers an example of a behavioral predisposition (dominance or subordination) interacting with exposure to a social stressor (instability) and gender in predicting CAA development. Rat models of BP regulation exhibit similar relationships, with genetic predisposition interacting with stressor or salt exposure to predict HTN. Lawler et al. (33) developed the borderline hypertensive rat (BHR) model of environmentally induced HTN. BHRs are the product of mating the spontaneously hypertensive rat (SHR) and the Wistar-Kyoto (WKY) rat. The SHR has a progressive rise in BP with age and inevitably develops HTN; the WKY rat is a normotensive control (20). BHRs inherit a genetic predisposition from their hypertensive parent. But unlike the SHR, they ordinarily have a "borderline" resting SBP of 140 to 160 mm Hg at 4 months of age and do not display increasing BP with age. However, when BHRs are exposed to chronic

stress or a high-salt diet, they quickly develop frank HTN, a response that is not seen in the genetically nonsusceptible WKY rat, which remains normotensive (20).

Similarly, persons differ in their predisposition to develop disease as a result of stress and other environmental exposures. In addition, the effect of a given predisposition will vary on the basis of the environment in which it is expressed. Thus, if the environment tends to be characterized by little social conflict and other sources of stress, or stress is buffered by, for example, social support or constructive coping behaviors, stress-induced CVD is unlikely to develop even in those who may have a physiological susceptibility.

Thus, although BP tends to rise with age in many populations, in some environments this tendency is not expressed. An example is provided by a group of Italian nuns living in secluded orders (34). At baseline, the age, BP, body mass index (BMI), and family history of HTN did not differ between the nuns and a group of lay women living in the same area. Although 19% of the nuns had a family history of HTN, over a 30-year follow-up period, none developed a DBP greater than 90 mm Hg. In contrast, SBP and DBP increased with age in the lay women. These differences were not explained by differences in physical activity, diet, childbearing, or changes in BMI.

Several epidemiological studies have compared the BPs of rural villagers with their counterparts who have migrated to urban areas. In populations as diverse as the Kenyan Luo, the Oromos of Ethiopia, northwest Iranians, and the Pacific island population of Tokelau, migration from a rural to urban environment is associated with the development of higher BP and increased incidence of HTN (35–38). This change has been variously attributed to exposure to the psychosocial stress of urban life or to an “industrial” diet, including high sodium intake.

Migration does not result in a universal rise in BP in the affected population; rather it is likely that those who possess a genetic or behavioral susceptibility show elevated BP, leading to an overall increase in the population BP level and HTN prevalence. Similarly, as has been suggested previously (39), the tendency toward large cardiovascular responses to stress is likely to lead to disease only when hyperreactive persons are exposed frequently to stress or possess other predispositions.

Indeed, recent studies have demonstrated that stress exposure and cardiovascular responses to stress may interact to predict the development of HTN and atherosclerosis (40–42). Light et al. (40) exposed male college students to CPT and shock threat reactivity testing; BP was reassessed 10 years later. Men who

exhibited high reactivity *and* who had a positive family history of HTN showed higher clinic BP at follow-up. In those with a negative family history of HTN, however, no evidence of differences in follow-up BP based on reactivity group were found. In addition, high reactors with high self-reported daily stress had higher BP levels at follow-up compared with high reactors with low daily stress exposure. Thus, an effect of individual differences in CVR on the development of elevated BP was seen only in those who reported high levels of stress exposure or were likely to possess a genetic predisposition to develop HTN.

Everson et al. (41) and Lynch et al. (42) investigated predictors of the 4-year progression of carotid artery atherosclerosis in a population-based sample of Finnish men. They assessed workplace demands and SES, and BP response in anticipation of an exercise stress test. Significant interactions between workplace demands and anticipatory cardiovascular responses were seen: men who showed a ≥ 20 mm Hg SBP increase before the exercise stress test *and* who reported high job demands showed the greatest atherosclerotic progression at follow-up. There was also some evidence of an interaction between SES and anticipatory SBP response: men who showed an SBP increase of ≥ 30 mm Hg *and* were of low SES also showed greater atherosclerotic progression, although many of the SES interaction terms were marginally significant.

Demanding work environments and socioeconomic hardship could both be circumstances that might provide physiologically or temperamentally susceptible individuals with frequent occasions for exaggerated cardiovascular responses. In the foregoing studies, the predisposition to hyperreactivity was associated with pathology when highly reactive persons were exposed to chronically stressful conditions or were likely to possess a genetic predisposition to develop disease. Thus, cardiovascular responses to stress should be studied in interaction with stress exposure and genetic susceptibility. We suggest that investigations in individuals' usual environments are likely to be most fruitful.

Perhaps the most well-developed literature addressing specific gene-environment interactions on CVD in humans assesses pharmacogenetic effects, genetically determined variations in the response to medication. Thus, two recent studies (43, 44) suggest that variation in the genes for estrogen receptor α (*ER- α*) and prothrombin (a coagulation protein) may affect the cardiovascular response to the use of hormone replacement therapy (HRT). Behaviors that have been found to interact with genetic predispositions include exercise and tobacco and alcohol use. Hines et al. (45) investigated the relationship between alcohol use and alcohol

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dehydrogenase type 3 (*ADH3*) genotype on the risk of MI in males. Moderate alcohol consumption is associated with a decreased risk of MI (45). A polymorphism in the gene for *ADH3* alters the rate of alcohol metabolism; the γ_1 allele is associated with a faster rate of metabolism than the γ_2 allele (46). A significant interaction between alcohol use and *ADH3* genotype was seen; men who consumed at least one drink per day and were homozygous for (had two copies of) the γ_2 allele had the greatest reduction in risk of MI, suggesting that slower clearance maximizes the beneficial effect of alcohol on cardiovascular risk. Montgomery et al. (47) investigated the relationship between exercise and angiotensin-converting enzyme (*ACE*) genotype on left ventricular (LV) mass. The *D* allele of the *ACE* gene is associated with higher *ACE* levels than the *I* allele. *ACE* is responsible for the degradation of growth-inhibitory kinins and the formation of angiotensin II, which has several effects, including the promotion of cardiac hypertrophy. LV mass was compared at the start and end of 10 weeks of intensive physical training. Pretraining LV mass was similar across genotypes, but those with the *D/D* genotype experienced an increase in LV mass with training, whereas those with the *I/I* genotype did not. The *D/D* *ACE* genotype may be associated with a small elevation in risk of MI (48). The different responses of those with the *D/D* and *I/I* genotypes to an "exercise stressor" suggest that it is possible that the *ACE* gene interacts with other hypertrophic stimuli, such as the presence of HTN or chronic stress, to promote CVD. Two other genes that might interact with stressor exposure in the development of CVD are the serotonin transporter gene, *5HTTLPR*, and the β_2 -adrenergic receptor gene. A common polymorphism affects transcription of the *5HTTLPR* gene, with activity of the *l* allele greater than that of the *s* allele (49). Williams et al. (50) exposed subjects to several laboratory stressors, including anger and sadness recall tasks and neutral reading. They found no differences in baseline BP among the three genotypes (*l/l*, *l/s*, and *s/s*); however, those with at least one copy of the *l* allele showed greater BP reactivity to the (aggregated) stressors.

Stimulation of the β_2 -adrenergic receptor by epinephrine leads to vasodilation, which may blunt the pressor effects of sympathetic nervous system (SNS) stimulation. β_2 -adrenergic receptor polymorphisms include Arg16/Gly16 and Gln27/Glu27. Dishy et al. (51) found that subjects homozygous for the Glu27 allele showed the greatest maximal response to a β_2 -adrenergic agonist. Those homozygous for the Arg16 allele (particularly if they were also homozygous for Gln27) showed desensitization of the response to the β_2 agonist so that venodilation was not maintained over a

2-hour treatment period. It is possible that long-term exposure to SNS activity (eg, due to chronic stress) might lead to tonically elevated BP in those with a predisposition to β_2 -adrenergic desensitization. Li et al. (52) investigated the relationship between these polymorphisms and BP measured at baseline and during a 3-minute MA task and 2-minute CPT. They found that Arg16 was associated with baseline and task SBP and DBP levels and with DBP reactivity. BP during prolonged tasks or an extended recovery period (to allow for differential desensitization to occur) was not assessed. Conflicting studies (ie, Refs. 53 and 54) have assessed the relationship between β_2 -adrenergic receptor polymorphisms and BP level or HTN status. Ambulatory BP regulation in those with the β_2 -adrenergic receptor (or *5HTTLPR*) polymorphisms is not yet well characterized, and interactions with real-world stressor exposure have not yet been assessed.

The traditional model of cardiovascular responses to stress has emphasized main effects. However, CVD results both from the additive effects of genetic and environmental factors and from their interaction. We have illustrated interactions among environmental factors (ie, social stress, workplace demands, SES), genetic variation (ie, salt sensitivity, alcohol metabolism), behaviors (ie, alcohol use, exercise, diet), and personality traits (ie, dominance). Those mentioned are only a few of the many factors that may act interactively as predispositions or exposures. Others include psychosocial factors such as depression and personality traits such as hostility, defensiveness, and neuroticism. Furthermore, many of the categorizations we have used are somewhat simplistic. Behaviors and personality traits have complex genetic and environmental origins and may act both as exposures and predispositions.

CVD cannot be fully understood by examining single factors in isolation. Environmental, behavioral, and genetic risk factors must be assessed simultaneously. Doing so has the potential to elucidate disease pathways, lead to identification of persons at risk for disease, and allow interventions to be tailored to individuals' predispositions and exposures.

IMPORTANCE OF THE DURATION OF EXPOSURE AND RESPONSE TO STRESS

If cardiovascular responses to stress are pathogenic, the most deleterious effects would be expected when such responses occur over a prolonged period of time. This can occur when people are exposed to *chronic or repeated stressors*. Indeed, most stressors associated with the development of CVD or overall mortality are chronic. For example, job strain is associated with the

development of HTN (14) and with the risk of cardiovascular-related death in men (15). Marital stress predicts the development of recurrent cardiovascular events in women (16). Spousal caregivers who report associated emotional or mental strain show higher rates of all-cause mortality than noncaregivers (17). Low SES is associated with increased risk of CVD and death (18). Such chronic exposures may be poorly represented by brief laboratory stressors.

In addition to reflecting chronic stressful *exposures*, prolonged cardiovascular *responding* can occur when people use cognitive or emotional processes that sustain arousal. Stress-related thoughts and emotions are, of course, not limited to those occasions when a stressor is physically present. For most people, little time is actually spent “in the heat of the moment.” However, the greater portion of a lifetime can be spent in anticipation of future stressors and recovery from past stressors, including their repeated cognitive representation. Posttraumatic stress disorder may be considered an extreme example of such prolonged cognitive activation.

Indeed, the relationship between the duration of the physiological stress response and the development of disease has been a critical element of both early and recent concepts of stress pathology. In 1936 Selye (55) described the stress response as a process involving three phases: activation, resistance, and exhaustion. He suggested that the body responds initially to challenge with physiological activation of defense systems; a resistance phase follows, during which stress is to be resolved, and if unsuccessful, the body may experience exhaustion. Activation that endures beyond the resistance stage is hypothesized to cause disease. Selye’s model of the stress response presaged more modern conceptions of allostatic systems (those that respond to stressors through the dynamic regulation of physiological states). Allostatic load often involves frequent or prolonged responding. Such sustained arousal may be due to recurring stress, poor adaptation to repeated stressors, or the inability to inactivate allostatic responses after a stressor ends (56).

CVR captures only the *magnitude* of the stress response and assesses only the response that occurs at the time the stressor is present; thus it is poorly suited to assessing prolonged cardiovascular arousal. This approach neglects assessment of the *frequency* of the response as well as its *duration*: the speed and degree of recovery in the period following the stressor and the extent to which the cardiovascular response occurs in anticipation of stressors that may yet occur. Thus, laboratory reactivity may be inherently limited in its ability to model the multidimensional nature of real-life responding. It is possible that the cumulative load

from moderate but prolonged anticipatory and recovery BP elevations may far exceed that caused by reactivity spikes. Sustained BP elevations predict the development of end-organ damage, whereas the role that brief BP peaks may play remains uncertain (57).

Hines and Brown, who published the first report comparing cardiovascular responses to the CPT in HTs and NTs (58), considered measurement of recovery to be a standard element of the test and noted that hypertensive patients show both delayed recovery and greater CVR than normotensive subjects. Poorer recovery in hypertensive subjects than in normotensive subjects has been found in many studies using a wide array of stressors (59). Haynes et al. (60) assessed 65 studies in which CVR and recovery data were collected. Among 81 analyses indicating nonsignificant effects of a variable (ie, condition or group) during the reactivity period, significant effects on recovery were found in 74% of cases. Conversely, of 74 analyses that indicated significant effects on reactivity, 42% showed nonsignificant effects on recovery. This suggests that reactivity and recovery capture substantively different information and points to the potential utility of measuring recovery. However, it is as yet unclear whether current laboratory methods of assessing the duration of BP and HR elevation in response to stress (ie, the use of anticipatory or recovery measures assessed immediately before or after stressor presentation) will prove useful for modeling cardiovascular responding as it occurs in the real world.

There is presently no universally accepted method for measuring recovery; change scores (from baseline or reactivity) and “time to recovery” indices are commonly used. Christenfeld et al. (61) compared the 1-week test-retest reliability of four measures of recovery: time to achieve complete recovery, recovery change score at a fixed time after the end of the stressor, recovery change score across a 20-minute recovery period, and a curve-fitting method using a three-parameter (amount, speed, and level of recovery) logistic function. Recovery was measured in students after walking in place, MA, and a speech task. They found only modest reliability for the three traditional measures of recovery. However, each of the three parameters of the curve-fitting measure showed acceptable reliability, with average *r* values of 0.56 to 0.65. Thus, curve-fitting methods may prove to be superior predictors of outcomes than other measures of recovery; however, they are as yet infrequently utilized.

Few studies have investigated the generalizability of recovery measures to the natural environment. Rutledge et al. (62) examined BP at baseline, reactivity, and recovery for MA, handgrip, and speech tasks, among normotensive adults in whom workday ABP

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was assessed. They found that both reactivity and recovery scores contributed to the prediction of ABP levels, above that predicted by baseline BP. Recovery residualized change scores added 3% to the prediction of ambulatory SBP and DBP, above that predicted by regression models including both baseline and reactivity values. When baseline, reactivity, and recovery scores were each entered into the equations, only baseline and recovery scores remained reliable predictors, with reactivity not explaining any additional variance.

To date three studies have prospectively investigated the relationship between delayed BP recovery from psychological stressors in the laboratory and the development of HTN. Borghi et al. (63) assessed 44 borderline HT adults 5 years after the performance of a MA task. They noted that poor DBP recovery from the task (defined as a recovery period BP level 6% greater than at baseline) was a sensitive and specific predictor of the development of frank HTN and had greater predictive power than BP reactivity. Stewart and France (64) measured CVR and recovery in response to MA, CPT, tourniquet ischemia, cycle exercise, and step exercise in 73 young adults. They found that after accounting for initial BP and other traditional predictors, SBP recovery from CPT, tourniquet ischemia, and step exercise accounted for 4%, 4%, and 8%, respectively, of the additional variance in resting SBP at 3-year follow-up. HR reactivity to MA also accounted for 4% of the variance in follow-up SBP beyond that explained by the control variables. Neither reactivity nor recovery measures added significantly to the prediction of follow-up DBP. Treiber et al. (65) evaluated 385 normotensive adolescents with a family history of CVD. Subjects performed four laboratory tasks: postural change, video game, social competence interview, and parent-child conflict discussion. Resting BP was measured during each of the following 4 years. SBP recovery averaged across tasks predicted resting SBP in year 4; DBP recovery predicted resting DBP in year 1. BP reactivity, but not recovery, was included in the most generalizable models predicting resting BP; however, the measure of recovery used (the lowest BP measured during the 5-minute period following the stressor) likely has poor reliability (61). These studies provide only weak evidence for the predictive power of cardiovascular recovery. However, all used very short follow-up times, over which there was often little change in BP level; none used a "curve-fitting" measure of recovery. There are as yet no data regarding prediction of CAD development. Laboratory recovery has intuitive appeal as a means of assessing duration of cardiovascular activation; however, it has obviously not yet fulfilled the criteria of reliability, generalizability, and predictive ability, which are necessary to be

considered a useful model of cardiovascular responses to stress.

Many of the thoughts and emotions associated with a stressor may occur in anticipation of occurrence (66). Anticipation has been associated with BP elevations before events such as a thesis defense (67), school examinations (68), and dental procedures (69). In the laboratory, BP elevations have been observed while subjects anticipated performing tasks such as difficult math problems (70) and the CPT (71). However, BP elevations are not always seen during anticipation of laboratory tasks (72, 73). It is as yet unclear how best to model anticipation in the laboratory. There has been little study of the reliability and generalizability of laboratory measures of anticipation. In two studies in which anticipation of laboratory tasks was compared with anticipation of a musical performance jury (74) and a thesis defense (12), results were mixed or negative. One prospective study (75) has found that the BP change from resting levels during anticipation of physical exercise predicts the development of HTN at 4-year follow-up. As noted earlier, in this population anticipation of physical exercise has also been shown to interact with job demands and SES to predict 4-year progression of carotid atherosclerosis (41, 42).

Cognitive and Affective Underpinnings of Cardiovascular Recovery and Sustained BP Elevation

Stress-related thoughts, emotions, and physiological activation may precede a stressor, occur during the stressor, and persist after the stressor has ended. In addition, these psychological and physiological responses can recur over minutes, days, and even years. Glynn et al. (76) harassed participants during a MA task; after the conclusion of the session, participants returned to the laboratory after either 20 minutes or 1 week. On return, participants were asked to recall the stressful task, imagining it as vividly as possible. Both groups showed substantial BP elevations with no significant effect of amount of time elapsed. These results suggest that recall of an emotional stressor can recreate BP elevations and that the potential for recall-provoked activation may be sustained over significant periods of time. As an example of the potency of recalled stressors, the recall of an anger-provoking event has been demonstrated to increase the difficulty of terminating ventricular tachycardia in arrhythmia-prone patients (77) and to acutely decrease LV ejection fraction in subjects with CVD (78).

Rumination

Rumination may be an example of a psychological process that tends to sustain cardiovascular activation. After a stressful event, people may ruminate about the causes and consequences of their distress (79, 80). Such responses have been shown to perpetuate and worsen negative mood. In the laboratory, when depressed individuals are asked to ruminate, they show stable or increased depressed mood; similarly, rumination maintains anger after an anger-provoking stressor (79). Prospectively, depressed persons who engage in self-focused rumination show longer and more severe periods of depression than those who do not ruminate (80).

Glynn et al. (76) and others (81) have found that recovery after emotional stressors takes much longer than recovery from nonemotional stressors, even when the magnitude of CVR to the stressors is identical. This suggests that cognitions or emotions induced after the stressor perpetuate cardiovascular activation. Schwartz et al. (82) examined the effect of rumination after recall of an anger-provoking event. They found that when participants were distracted after the task, they showed more complete recovery and reported less thought-related negative affect. When distractions were not provided, participants scoring high on trait measures of rumination or reporting ruminating after the task showed poorer recovery than those who reported little rumination. Rumination may thus predict persistent BP elevations after anger.

AN EXPANSION OF THE CVR MODEL

It is beyond the scope of this article to provide an in-depth review of the pathways that may link stress with CAD or HTN. Instead we focus on one proposed mediator of this relationship, CVR. We propose an expansion of the CVR model to incorporate other processes by which stressors produce physiological responses that lead to disease. The next sections provide an overview of candidate pathways.

Models of the Stress-HTN Relationship

The reactivity literature provides compelling evidence that BP may be elevated during the experience of a stressor. Such effects are seen in the laboratory as well as during daily life, for example in the workplace (83). There is also evidence that BP may be elevated when no tangible stressor is present but an individual continues to be under cognitive load (82). However, the mechanisms by which environmental stressors might lead to tonically elevated BP, or HTN, remain poorly specified.

The control of BP results from actions of the kidneys, central and autonomic nervous systems, hypothalamic-pituitary-adrenal axis, vascular endothelium, and other pathways (57). In the development of HTN, a distinction must be made between short-term factors that initiate BP elevation, and long-term self-perpetuating mechanisms that sustain the hypertensive state. The set of factors that initially raise BP may be quite distinct from the factors that perpetuate HTN, and by the time BP is tonically elevated, the initiating factors may no longer be present (84, 85).

Acute BP elevations in response to stress are usually attributed to SNS activity. Other processes may also contribute to acute BP elevation; these may include diminished endothelial nitric oxide (NO) production (86) and vagal withdrawal (87). Long-term regulatory changes that may perpetuate HTN include vascular remodeling and endothelial dysfunction (84). Vascular remodeling involves alterations in vessel architecture, including decreased lumen diameter and rarefaction (in which the number of microvessels is reduced), both of which lead to a chronic increase in vascular resistance. Remodeling results from hemodynamic changes in blood flow and pressure and from changes in the level of vasoconstrictive and vasodilatory substances such as norepinephrine, angiotensin II, and NO. Vascular remodeling may facilitate the transition from an initial high cardiac output stage of HTN to a high total peripheral resistance state (84).

The innermost layer of blood vessels, the endothelium, contributes to regulation of vascular tone through the production of vasoconstrictive and vasodilatory substances that act on vascular smooth muscle. NO is an important endothelium-derived vasodilatory substance; its catabolism may impair endothelial function (EF), resulting in sustained HTN (84). There is evidence that acute BP elevations may impair EF, perhaps suggesting a mechanism by which short-term BP elevations could lead to HTN (88).

Guyton (89) has suggested that the kidney's regulation of sodium and water balance acts as the primary long-term determinant of the BP level; it has been proposed that both vascular remodeling and endothelial dysfunction could lead to sustained changes in the renal set-point for BP regulation (84).

Models of the Stress-CAD Relationship

Stress has effects on many pathways affecting CAD. To illustrate, we will briefly summarize the evidence regarding the relationship between stress and two hypothesized mediators of the stress-CAD relationship: endothelial dysfunction and heart rate variability (HRV).

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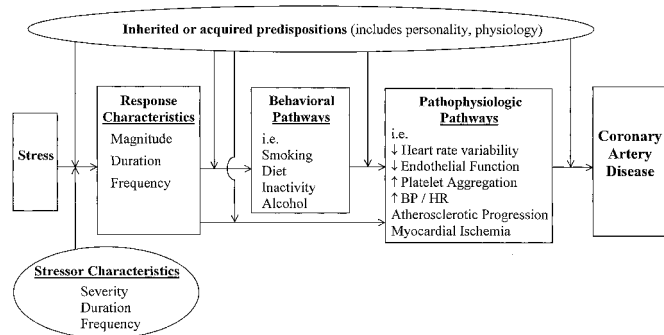
The endothelium contributes to the regulation of vascular tone, platelet aggregation, and other processes relevant to atherosclerosis. "Endothelial dysfunction" indicates abnormalities in these regulatory actions, particularly the impairment of endothelium-dependent vasodilation (90). Hypertensive and hypercholesterolemic patients exhibit abnormalities in EF, and endothelial dysfunction is thought to be an initial step in atherosclerosis (90). EF, assessed as the amount of vasodilation in response to the endothelium-dependent vasodilator acetylcholine, increased blood flow, or the CPT, is an independent predictor of the development of cardiovascular events (91). Ghiadoni et al. (92) found that healthy persons exposed to a brief mental stressor (a 5-minute speech task) showed reduced endothelium-dependent vasodilation sustained over at least 90 minutes. BP and HR elevations, however, returned to prestress levels within 2 minutes. Similarly, cynomolgus monkeys exposed to a social stressor (being housed in unstable social groups) show endothelial cell injury (93) and impaired EF (94). Of note, EF has been linked to hemodynamic patterns of response to stress, with individuals showing poorer EF exhibiting a larger systemic vascular resistance response to laboratory stressors (95). This suggests that such stress-induced hemodynamic changes may be markers for underlying EF rather than independent predictors of the development of disease.

HRV reflects autonomic nervous system input to the heart. Low HRV reflects reduced parasympathetic nervous system (PNS) or increased SNS stimulation. This loss of normal HR modulation may increase vulnerability to arrhythmia and accelerate CAD progression (96). In population studies, low HRV predicts the development of cardiovascular events (97), cardiac mortality (98), and all-cause mortality (98). Numerous studies (eg, Ref. 99) have established that low HRV is an independent risk factor for mortality in patients who have had an MI. Hostility, anxiety, and depression have been linked with low HRV, and several studies indicate that these psychological factors interact with stressor exposure to lower HRV. Sloan et al. (100) exposed healthy individuals to MA and Stroop color-word tasks as well as passive tilt. They found that participants who scored high on a trait measure of hostility showed greater reductions in HRV in response to the mental, but not physical, stressors. There is evidence that persons high in depressive symptoms also show greater HRV decreases in response to mental stress than nondepressed persons (101); however, not all studies have found this (102). Of note, HRV is significantly lower in depressed than nondepressed CAD patients (103) and is decreased in individuals with high levels of anxiety (104).

Other pathways that might link stress and CAD include adoption of unhealthy behaviors, development of HTN, increases in platelet activity mediated by alterations in serotonergic pathways, hypercortisolemia and other hypothalamic-pituitary-adrenal axis abnormalities, alterations in immune function, induction of myocardial ischemia, and changes in adrenergic receptor regulation (105).

In Figure 1, we depict proposed models of the causal pathways between stress and CAD (Fig. 1, *a*) and HTN (Fig. 1, *b*). In both models the relationship between stress exposure and cardiovascular response is moderated by stressor characteristics (severity, frequency, and duration) as well as the individual's inherited or acquired response predispositions. The response may be behavioral or physiologic and will vary in its magnitude, duration, and frequency of recurrence. In the model of CAD development (Fig. 1, *a*), the individual's responses may ultimately affect at least one of several pathophysiological pathways that can lead to CAD. These include atherosclerotic progression, decreased HRV or EF, elevated BP or HR, increased platelet activation, and myocardial ischemia. In the model of HTN development (Fig. 1, *b*), initiation of BP elevation, perhaps through the activity of the

(a) Coronary Artery Disease



(b) Hypertension

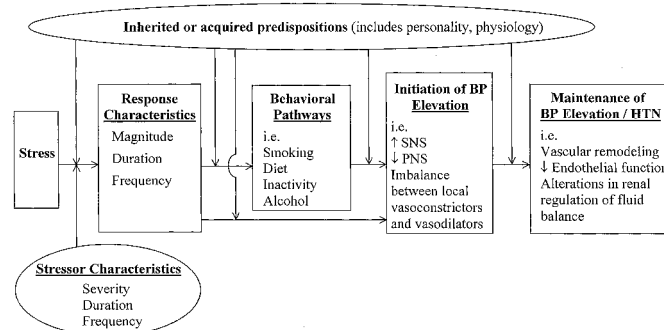


Fig. 1. Proposed models of the causal pathways between stress and CAD (*a*) and HTN (*b*).

SNS, PNS, or local vasoconstrictors, may eventually lead to a state in which BP elevation is maintained. Maintenance of BP elevation might occur through vascular remodeling, decreased EF, or alterations in renal regulation of fluid balance.

SUMMARY AND FUTURE DIRECTIONS

Generalizability

Traditionally CVR has been examined in the laboratory; few studies attempt to assess CVR in the natural environment. There is little evidence, however, that CVR assessed in the laboratory generalizes to the real world. There may be modest improvements in generalizability with methodological changes such as aggregation across multiple tasks and sessions. However, the lack of lab-to-life generalizability indicates that a laboratory model of CVR provides a poor methodology for studying cardiovascular responses to stress occurring in the real world. We therefore suggest that investigations of BP and HR responses to stress would benefit from greater focus on observations made in the natural environment.

Interactive Effects on Cardiovascular Disease

Human and animal studies demonstrate that the interaction of individual predispositions and environmental exposures contributes to the development and progression of CVD. The traditional CVR model has focused on main effects; however, CVD cannot be fully understood by examining single factors in isolation. We suggest that models of cardiovascular responses to stress would benefit from placing greater emphasis on the interaction of individual predispositions and stressor exposures in the development of CVD.

Duration of Exposure and Response to Stressors

If cardiovascular responses to stress are pathogenic, the most deleterious effects would be expected when such responses occur over a prolonged time period. This can occur when individuals are exposed to chronic or repeated stressors or when stress-related responding occurs in the absence of a tangible stressor. However, there is little evidence that acute laboratory stressors are appropriate models of pathogenic chronic stressors. Furthermore, stress-related cognitive activation and concomitant cardiovascular responses may occur in anticipation of future stressors, in the period following past stressors, or may recur long after stressor presentation. CVR captures only the magnitude of response to an acute stressor during its presentation. We suggest that future models should assess all dimen-

sions of the cardiovascular response to stress, focusing on the cumulative duration of responding.

Preparation of this review was supported by the American Heart Association, Grant 9750544N, and the National Heart, Lung, and Blood Institute, National Institutes of Health, Grants HL47540 and HL67677.

We thank Thomas Kamarck and Devon Neale for helpful comments on an earlier version of this manuscript.

REFERENCES

1. Gerin W, Pickering TG, Glynn L, Christenfeld N, Schwartz A, Carroll D, Davidson K. An historical context for behavioral models of hypertension. *J Psychosom Res* 2000;48:369–77.
2. Treiber FA, Kamarck T, Schneiderman N, Sheffield D, Kapuku G, Taylor T. Cardiovascular reactivity and development of pre-clinical and clinical disease states. *Psychosom Med* 2003;65:46–62.
3. Kamarck T, Lovallo B. Cardiovascular reactivity to psychological challenge: conceptual and measurement considerations. *Psychosom Med* 2003;65:9–21.
4. Lovallo WR, Gerin W. Psychophysiological reactivity: mechanisms and pathways to cardiovascular disease. *Psychosom Med* 2003;65:36–45.
5. Pickering TG, Gerin W. Cardiovascular reactivity in the laboratory and the role of behavioral factors in hypertension: a critical review. *Ann Behav Med* 1990;12:3–16.
6. Manuck SB, Kasprowicz AI, Muldoon MF. Behaviorally-evoked cardiovascular reactivity and hypertension: conceptual issues and potential associations. *Ann Behav Med* 1990;12:17–29.
7. Turner JR, Ward MM, Gellman MD, Johnston DW, Light KC, van Doornen LJP. The relationship between laboratory and ambulatory cardiovascular activity: current evidence and future directions. *Ann Behav Med* 1994;16:12–23.
8. Linden W, Rutledge T, Con A. A case for the usefulness of laboratory social stressors. *Ann Behav Med* 1998;20:310–6.
9. Christenfeld N, Glynn LM, Kulik JA, Gerin W. The social construction of cardiovascular reactivity. *Ann Behav Med* 1998;20:317–25.
10. Gerin W, Christenfeld N, Pieper C, DeRafael DA, Su O, Stroessner SJ, Deich J, Pickering TG. The generalizability of cardiovascular responses across settings. *J Psychosom Res* 1998;44:209–18.
11. Kamarck TW, Debski TT, Manuck SB. Enhancing the laboratory-to-life generalizability of cardiovascular reactivity using multiple occasions of measurement. *Psychophysiology* 2000;37:533–42.
12. Davig JP, Larkin KT, Goodie JL. Does cardiovascular reactivity to stress measured in the laboratory generalize to thesis and dissertation meetings among doctoral students? *Int J Behav Med* 2000;7:216–35.
13. van Doornen LJP, Knol DL, Willemsen G, de Geus EJC. The relationship between stress reactivity in the laboratory and in real-life: is reliability the limiting factor? *J Psychophysiol* 1994;8:297–304.
14. Schnall PL, Schwartz JE, Landsbergis PA, Warren K, Pickering TG. A longitudinal study of job strain and ambulatory blood pressure: results from a three-year follow-up. *Psychosom Med* 1998;60:697–706.
15. Karasek RA, Theorell T, Schwartz JE, Schnall PL, Pieper CF,

CAUSAL MODEL OF CARDIOVASCULAR RESPONSES

- Michela JL. Job characteristics in relation to the prevalence of myocardial infarction in the US Health Examination Survey (HES) and the Health and Nutrition Examination Survey (HANES). *Am J Public Health* 1988;78:910–8.
16. Orth-Gomer K, Wamala SP, Horsten M, Schenck-Gustafsson K, Schneiderman N, Mittleman MA. Marital stress worsens prognosis in women with coronary heart disease: the Stockholm female coronary risk study. *JAMA* 2000;284:3008–14.
 17. Schulz R, Beach SR. Caregiving as a risk factor for mortality: the caregiver health effects study. *JAMA* 1999;282:2215–9.
 18. Kaplan GA, Keil JE. Socioeconomic factors and cardiovascular disease: a review of the literature. *Circulation* 1993;88:1973–98.
 19. Kaplan JR, Manuck SB, Clarkson TB, Lusso FM, Taub DM. Social status, environment, and atherosclerosis in cynomolgus monkeys. *Arteriosclerosis* 1982;2:359–68.
 20. Sanders BJ, Lawler JE. The borderline hypertensive rat (BHR) as a model for environmentally-induced hypertension: a review and update. *Neurosci Biobehav Rev* 1992;16:207–17.
 21. Light KC, Turner JR, Hinderliter AL, Sherwood A. Race and gender comparisons. II. Predictions of work blood pressure from laboratory baseline and cardiovascular reactivity measures. *Health Psychol* 1993;12:366–75.
 22. Ironson GH, Gellman MD, Spitzer SB, Llabre MM, De Carlo Pasin R, Weidler DJ, Schneiderman N. Predicting home and work blood pressure measurements from resting baselines and laboratory reactivity in black and white Americans. *Psychophysiology* 1989;26:174–84.
 23. Linden W, Con A. Laboratory reactivity models as predictors of ambulatory blood pressure and heart rate. *J Psychosom Res* 1994;38:217–28.
 24. Ewart CK, Kolodner KB. Predicting ambulatory blood pressure during school: effectiveness of social and nonsocial reactivity tasks in black and white adolescents. *Psychophysiology* 1993;30:30–8.
 25. Pickering TG, James GD, Boddie C, Harshfield GA, Blank S, Laragh JH. How common is white coat hypertension? *JAMA* 1988;259:225–8.
 26. Liu JE, Roman MJ, Pini R, Schwartz JE, Pickering TG, Devereux RB. Cardiac and arterial target organ damage in adults with elevated ambulatory and normal office blood pressure. *Ann Intern Med* 1999;131:564–72.
 27. Perloff D, Sokolow M, Cowan RM. The prognostic value of ambulatory blood pressures. *JAMA* 1983;249:2792–8.
 28. Verdecchia P, Porcellati C, Schillaci G, Borgiani C, Ciucci A, Battistelli M, Guerrieri M, Gatteschi C, Zampi I, Santucci A. Ambulatory blood pressure: an independent predictor of prognosis in essential hypertension. *Hypertension* 1994;24:793–801.
 29. Hamet P, Pausova Z, Adarichev V, Adaricheva K, Tremblay J. Hypertension: genes and environment. *J Hypertens* 1998;16:397–418.
 30. Pausova Z, Tremblay J, Hamet P. Gene-environment interactions in hypertension. *Curr Hypertens Rep* 1999;1:42–50.
 31. Kaplan JR, Manuck SB. Status, stress, and atherosclerosis: the role of environment and individual behavior. *Ann NY Acad Sci* 1999;896:145–61.
 32. Kaplan JR, Adams MR, Clarkson TB, Koritnik DR. Psychosocial influences on female “protection” among cynomolgus macaques. *Atherosclerosis* 1984;53:283–95.
 33. Lawler JE, Barker GF, Hubbard JW, Schaub RG. Pathophysiological changes associated with stress-induced hypertension in the borderline hypertensive rat. *Clin Sci* 1980;59(suppl 6):307–10.
 34. Timio M, Lippi G, Gentili S, Quitaliani G, Verdura C, Monarca C, Saronio P, Timio F. Blood pressure trend and cardiovascular events in nuns in a secluded order: a 30-year follow up study. *Blood Press* 1997;6:81–7.
 35. Poulter NR, Khaw KT, Hopwood BE, Mugambi M, Peart WS, Rose G, Sever PS. The Kenyan Luo migration study: observations on the initiation of a rise in blood pressure. *BMJ* 1990;300:967–72.
 36. Pauletto P, Caroli M, Pessina AC, Dal Palu C. Hypertension prevalence and age-related changes of blood-pressure in seminomadic and urban Oromos of Ethiopia. *Eur J Epidemiol* 1994;10:159–64.
 37. Nadim A, Amini H, Malek-Afzali H. Blood pressure and rural-urban migration in Iran. *Int J Epidemiol* 1978;7:131–8.
 38. Salmond CE, Prior IA, Wessen AF. Blood pressure patterns and migration: a 14-year cohort study of adult Tokelauans. *Am J Epidemiol* 1989;130:37–52.
 39. Light KC. Hypertension and the reactivity hypothesis: the next generation. *Psychosom Med* 2001;63:744–6.
 40. Light KC, Girdler SS, Sherwood A, Bragdon EE, Brownley KA, West SG, Hinderliter AL. High stress reactivity predicts later blood pressure only in combination with positive family history and high life stress. *Hypertension* 1999;33:1458–64.
 41. Everson SA, Lynch JW, Chesney MA, Kaplan GA, Goldberg DE, Shade SB, Cohen RD, Salonen R, Salonen JT. Interaction of workplace demands and cardiovascular reactivity in progression of carotid atherosclerosis: population based study. *BMJ* 1997;314:553–8.
 42. Lynch JW, Everson SA, Kaplan GA, Salonen R, Salonen JT. Does low socioeconomic status potentiate the effects of heightened cardiovascular responses to stress on the progression of carotid atherosclerosis? *Am J Public Health* 1998;88:389–94.
 43. Herrington DM, Howard TD, Hawkins GA, Reboussin DM, Xu J, Zheng SL, Brosnihan B, Meyers DA, Bleeker ER. Estrogen-receptor polymorphisms and effects of estrogen replacement on high-density lipoprotein cholesterol in women with coronary disease. *N Engl J Med* 2002;346:967–74.
 44. Psaty BM, Smith NL, Lemaitre RN, Vos HL, Heckbert SR, La-Croix AZ, Rosendaal FR. Hormone replacement therapy, prothrombotic mutations, and the risk of incident nonfatal myocardial infarction in postmenopausal women. *JAMA* 2001;285:906–13.
 45. Hines LM, Stampfer MJ, Ma J, Gaziano JM, Ridker PM, Hankinson SE, Sacks F, Rimm EB, Hunter DJ. Genetic variation in alcohol dehydrogenase and the beneficial effect of moderate alcohol consumption on myocardial infarction. *N Engl J Med* 2001;344:549–55.
 46. Bosron WF, Lumeng L, Li TK. Genetic polymorphism of enzymes of alcohol metabolism and susceptibility to alcoholic liver disease. *Mol Aspects Med* 1988;10:147–58.
 47. Montgomery HE, Clarkson P, Dollery CM, Prasad K, Losi MA, Hemingway H, Statters D, Jubb M, Girvain M, Varnava A, World M, Deanfield J, Talmud P, McEwan JR, McKenna WJ, Humphries S. Association of angiotensin-converting enzyme gene I/D polymorphism with change in left ventricular mass in response to physical training. *Circulation* 1997;96:741–7.
 48. Keavney B, McKenzie C, Parish S, Palmer A, Clark S, Youngman L, Delépine M, Lathrop M, Peto R, Collins R, for the International Studies of Infarct Survival (ISIS) Collaborators. Large-scale test of hypothesized associations between the angiotensin-converting-enzyme insertion/deletion polymorphism and myocardial infarction in about 5000 cases and 6000 controls. *Lancet* 2000;355:434–42.
 49. Lesch KP, Bengel D, Heils A, Sabol SZ, Greenberg BD, Petri S,

- Benjamin J, Müller R, Hamer DH, Murphy DL. Association of anxiety-related traits with a polymorphism in the serotonin transporter gene regulatory region. *Science* 1996;274:1527–31.
50. Williams RB, Marchuk DA, Gadde KM, Barefoot JC, Grichnik K, Helms MJ, Kuhn CM, Lewis JG, Schanberg SM, Stafford-Smith M, Suarez EC, Clary GL, Svenson IK, Siegler IC. Central nervous system serotonin function and cardiovascular responses to stress. *Psychosom Med* 2001;63:300–5.
 51. Dishy V, Sofowora GG, Xie HG, Kim RB, Byrne DW, Stein CM, Wood AJJ. The effect of common polymorphisms of the β_2 -adrenergic receptor on agonist-mediated vascular desensitization. *N Engl J Med* 2001;345:1030–5.
 52. Li GH, Faulhaber HD, Rosenthal M, Schuster H, Jordan J, Timmermann B, Hoehe MR, Luft FC, Busjahn A. β_2 -Adrenergic receptor gene variations and blood pressure under stress in normal twins. *Psychophysiology* 2001;38:485–9.
 53. Candy G, Samani N, Norton G, Woodiwiss A, Radevski I, Wheatley A, Cockcroft J, Hall IP. Association analysis of β_2 -adrenoreceptor polymorphisms with hypertension in a black African population. *J Hypertens* 2000;18:167–2.
 54. Kotanko P, Binder A, Tasker J, DeFreitas P, Kamdar S, Clark AJL, Skrabal F, Caulfield M. Essential hypertension in African Caribbeans associates with a variant of the β_2 -adrenoreceptor. *Hypertension* 1997;30:773–6.
 55. Selye H. A syndrome produced by diverse nocuous agents. *Nature* 1936;138:32.
 56. McEwen BS. Protective and damaging effects of stress mediators. *N Engl J Med* 1998;338:171–9.
 57. Black HR, Bakris GL, Elliott WJ. Hypertension: epidemiology, pathophysiology, diagnosis, and treatment. In: Fuster V, Alexander RW, O'Rourke RA, editors. *Hurst's the heart*. 10th ed. New York: McGraw-Hill; 2001. p. 1553–604.
 58. Hines EA Jr, Brown GE. A standard test for measuring the variability of blood pressure: its significance as an index of the prehypertensive state. *Ann Intern Med* 1933;7:209–17.
 59. Hocking Schuler JL, O'Brien WH. Cardiovascular recovery from stress and hypertension risk factors: a meta-analytic review. *Psychophysiology* 1997;34:649–59.
 60. Haynes SN, Gannon LR, Orimoto L, O'Brien WH, Brandt M. Psychophysiological assessment of poststress recovery. *Psychol Assess* 1991;3:356–65.
 61. Christenfeld N, Glynn LM, Gerin W. On the reliable assessment of cardiovascular recovery: an application of curve-fitting techniques. *Psychophysiology* 2000;37:543–50.
 62. Rutledge T, Linden W, Paul D. Cardiovascular recovery from acute laboratory stress: reliability and concurrent validity. *Psychosom Med* 2000;62:648–54.
 63. Borghi C, Costa FV, Boschi S, Mussi A, Ambrosioni E. Predictors of stable hypertension in young borderline subjects: a five-year follow-up study. *J Cardiovasc Pharmacol* 1986; 8(suppl 5):S138–41.
 64. Stewart JC, France CR. Cardiovascular recovery from stress predicts longitudinal changes in blood pressure. *Biol Psychol* 2001;58:105–20.
 65. Treiber FA, Musante L, Kapuku G, Davis C, Litaker M, Davis H. Cardiovascular (CV) responsivity and recovery to acute stress and future CV functioning in youth with family histories of CV disease: a 4-year longitudinal study. *Int J Psychophysiol* 2001; 41:65–74.
 66. Schulkin J, McEwen BS, Gold PW. Allostasis, amygdala, and anticipatory angst. *Neurosci Biobehav Rev* 1994;18:385–96.
 67. van Doornen LJP, van Blokland RW. The relationship between cardiovascular and catecholamine reactions to laboratory and real-life stress. *Psychophysiology* 1992;29:173–81.
 68. Sausen KP, Lovallo WR, Pincomb GA, Wilson MF. Cardiovascular responses to occupational stress in male medical students: a paradigm for ambulatory monitoring studies. *Health Psychol* 1992;11:55–60.
 69. Brand HS, Gortzak RA, Palmer-Bouva CC, Abraham RE, Abraham-Inpijn L. Cardiovascular and neuroendocrine responses during acute stress induced by different types of dental treatment. *Int Dent J* 1995;45:45–8.
 70. Contrada RJ, Wright RA, Glass DC. Task difficulty, type A behavior pattern, and cardiovascular response. *Psychophysiology* 1984;21:638–46.
 71. Gregg ME, James JE, Matyas TA, Thorsteinsson EB. Hemodynamic profile of stress-induced anticipation and recovery. *Int J Psychophysiol* 1999;34:147–62.
 72. Gerin W, Pieper C, Pickering TG. Anticipation and residual effects of an active coping task on pre- and post-stress baselines. *J Psychosom Res* 1994;38:139–49.
 73. Linden W, Frankish J. Expectancy and type of activity: effects on pre-stress cardiovascular adaptation. *Biol Psychol* 1988;27: 227–35.
 74. Abel JL, Larkin KT. Assessment of cardiovascular reactivity across laboratory and natural settings. *J Psychosom Res* 1991; 35:365–73.
 75. Everson SA, Kaplan GA, Goldberg DE, Salonen JT. Anticipatory blood pressure response to exercise predicts future high blood pressure in middle-aged men. *Hypertension* 1996;27: 1059–64.
 76. Glynn LM, Christenfeld N, Gerin W. The role of rumination in recovery from reactivity: cardiovascular consequences of emotional states. *Psychosom Med* 2002;64:714–26.
 77. Lampert R, Jain D, Burg MM, Batsford WP, McPherson CA. Destabilizing effects of mental stress on ventricular arrhythmias in patients with implantable cardioverter-defibrillators. *Circulation* 2000;101:158–64.
 78. Ironson G, Taylor CB, Boltwood M, Bartzokis T, Dennis C, Chesney M, Spitzer S, Segall GM. Effects of anger on left ventricular ejection fraction in coronary artery disease. *Am J Cardiol* 1992;70:281–5.
 79. Rusting CL, Nolen-Hoeksema S. Regulating responses to anger: effects of rumination and distraction on angry mood. *J Pers Soc Psychol* 1998;74:790–803.
 80. Nolen-Hoeksema S, Larson J, Grayson C. Explaining the gender difference in depressive symptoms. *J Pers Soc Psychol* 1999; 77:1061–72.
 81. Vitaliano PP, Russo J, Paulsen VM, Bailey SL. Cardiovascular recovery from laboratory stress: biopsychosocial concomitants in older adults. *J Psychosom Res* 1995;39:361–77.
 82. Schwartz AR, Gerin W, Christenfeld N, Glynn L, Davidson K, Pickering TG. Effects of an anger-recall task on poststress rumination and blood pressure recovery in men and women. *Psychophysiology* 2000;37(suppl 1):S12–3.
 83. Fauvel JP, Quelin P, Ducher M, Rakotomalala H, Laville M. Perceived job stress but not individual cardiovascular reactivity to stress is related to higher blood pressure at work. *Hypertension* 2001;38:71–5.
 84. Gibbons GH. Pathobiology of hypertension. In: Topol EJ, editor. *Comprehensive cardiovascular medicine*. Philadelphia: Lippincott-Raven Publishers; 1998. p. 2907–18.
 85. Kaplan NM. Systemic hypertension: mechanisms and diagnosis. In: Braunwald E, Zipes DP, Libby P, editors. *Heart disease: a textbook of cardiovascular medicine*. 6th ed. Philadelphia: WB Saunders Co; 2001. p. 941–71.
 86. Markovitz JH, Tucker D, Lewis CE, Sanders PW, Warnock DG. Inverse relationship of urinary cyclic GMP to blood pressure

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- reactivity in the CARDIA study: vasodilatory regulation of sympathetic vasoconstriction. *Psychosom Med* 1998;60:319–26.
87. Brosschot JF, Thayer JF. Anger inhibition, cardiovascular recovery, and vagal function: a model of the link between hostility and cardiovascular disease. *Ann Behav Med* 1998;20:326–32.
 88. Millgård J, Lind L. Acute hypertension impairs endothelium-dependent vasodilation. *Clin Sci* 1998;94:601–7.
 89. Guyton AC. Blood pressure control—special role of the kidneys and body fluids. *Science* 1991;252:1813–6.
 90. John S, Schmieder RE. Impaired endothelial function in arterial hypertension and hypercholesterolemia: potential mechanisms and differences. *J Hypertens* 2000;18:363–74.
 91. Al Suwaidi J, Hamasaki S, Higano ST, Nishimura RA, Holmes DR Jr, Lerman A. Long-term follow-up of patients with mild coronary artery disease and endothelial dysfunction. *Circulation* 2000;101:948–54.
 92. Ghiadoni L, Donald AE, Cropley M, Mullen MJ, Oakley G, Taylor M, O'Connor G, Betteridge J, Klein N, Steptoe A, Deanfield JE. Mental stress induces transient endothelial dysfunction in humans. *Circulation* 2000;102:2473–8.
 93. Skantze HB, Kaplan J, Pettersson K, Manuck S, Blomqvist N, Kyes R, Williams K, Bondjers G. Psychosocial stress causes endothelial injury in cynomolgus monkeys via β_1 -adrenoceptor activation. *Atherosclerosis* 1998;136:153–61.
 94. Williams JK, Vita JA, Manuck SB, Selwyn AP, Kaplan JR. Psychosocial factors impair vascular responses of coronary arteries. *Circulation* 1991;84:2146–53.
 95. Sherwood A, Johnson K, Blumenthal JA, Hinderliter AL. Endothelial function and hemodynamic responses during mental stress. *Psychosom Med* 1999;61:365–70.
 96. Huikuri HV, Mäkikallio T, Airaksinen KEJ, Mitrani R, Castellanos A, Myerburg RJ. Measurement of heart rate variability: a clinical tool or a research toy? *J Am Coll Cardiol* 1999;34:1878–83.
 97. Tsuji H, Larson MG, Venditti FJ Jr, Manders ES, Evans JC, Feldman CL, Levy D. Impact of reduced heart rate variability on risk for cardiac events. The Framingham Heart Study. *Circulation* 1996;94:2850–5.
 98. Dekker JM, Crow RS, Folsom AR, Hannan PJ, Liao D, Swenne CA, Schouten EG. Low heart rate variability in a 2-minute rhythm strip predicts risk of coronary heart disease and mortality from several causes. The ARIC Study. *Circulation* 2000;102:1239–44.
 99. Bigger JT Jr, Fleiss JL, Steinman RC, Rolnitzky LM, Kleiger RE, Rottman JN. Frequency domain measures of heart period variability and mortality after myocardial infarction. *Circulation* 1992;85:164–71.
 100. Sloan RP, Bagiella E, Shapiro PA, Kuhl JP, Chernikhova D, Berg J, Myers MM. Hostility, gender, and cardiac autonomic control. *Psychosom Med* 2001;63:434–40.
 101. Hughes JW, Stoney CM. Depressed mood is related to high-frequency heart rate variability during stressors. *Psychosom Med* 2000;62:796–803.
 102. Light KC, Kothandapani RV, Allen MT. Enhanced cardiovascular and plasma catecholamines responses in women with depressive symptoms. *Int J Psychophysiol* 1998;28:157–66.
 103. Carney RM, Saunders RD, Freedland KE, Stein P, Rich MW, Jaffe AS. Association of depression with reduced heart rate variability in coronary artery disease. *Am J Cardiol* 1995;76:562–4.
 104. Kawachi I, Sparrow D, Vokonas PS, Weiss ST. Decreased heart rate variability in men with phobic anxiety (data from the Normative Aging Study). *Am J Cardiol* 1995;75:882–5.
 105. Rozanski A, Blumenthal JA, Kaplan J. Impact of psychological factors on the pathogenesis of cardiovascular disease and implications for therapy. *Circulation* 1999;99:2192–217.