

Stress-Induced Blood Pressure Reactivity and Incident Stroke in Middle-Aged Men

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Background and Purpose—Exaggerated blood pressure reactivity to stress is associated with atherosclerosis and hypertension, which are known stroke risk factors, but its relation to stroke is unknown. Previous work also indicates that the association between reactivity and cardiovascular diseases may be influenced by socioeconomic status.

Methods—The impact of blood pressure reactivity and socioeconomic status on incident stroke was examined in 2303 men (mean age, 52.8±5.1 years) from a population-based, longitudinal study of risk factors for ischemic heart disease in eastern Finland. Reactivity was calculated as the difference between blood pressure measured during the anticipatory phase of an exercise tolerance test (before exercise) and resting blood pressure, measured 1 week earlier. Mean systolic reactivity was 20 mm Hg (±15.9), and mean diastolic reactivity was 8.6 mm Hg (±8.5). Socioeconomic status was assessed as years of education. One hundred thirteen incident strokes (90 ischemic) occurred in 11.2 (±1.6) years of follow-up.

Results—Men with exaggerated systolic reactivity (≥20 mm Hg) had 72% greater risk of any stroke (relative hazard ratio [RH], 1.72; 95% CI, 1.17 to 2.54) and 87% greater risk of ischemic stroke (RH, 1.87; 95% CI, 1.20 to 2.89) relative to less reactive men. Moreover, men who were high reactors and poorly educated were nearly 3 times more likely to suffer a stroke than better educated, less reactive men (RH, 2.90; 95% CI, 1.66 to 5.08). Adjustment for stroke risk factors had little impact on these associations. Diastolic reactivity was unrelated to stroke risk.

Conclusions—Excessive sympathetic reactivity to stress may be etiologically important in stroke, especially ischemic strokes, and low socioeconomic status confers added risk. (*Stroke*. 2001;32:1263-1270.)

Key Words: ischemia ■ reactivity ■ social class ■ stress ■ stroke

Cardiovascular reactivity reflects underlying sympathetic nervous system activation and has been shown to vary according to individual characteristics (eg, personality factors, emotions), environmental exposures (eg, job stress, socioeconomic adversity), interpersonal and social contexts and interactions, and genetic predispositions to disease (eg, positive family history of hypertension or heart disease).¹⁻⁵ Typically, this sympathetic hyperreactivity is manifest as excessive blood pressure (BP) or heart rate responses to psychological or behavioral stressors or stressful situations.⁵ Several human and animal studies support the hypothesis that exaggerated hemodynamic or cardiovascular reactivity to stress contributes to elevations in BP, carotid atherosclerosis, and coronary artery disease.⁶⁻¹³ Findings are not entirely consistent,^{14,15} however, with some evidence that the clinical significance of the association between reactivity and disease may be limited.¹⁶ Others have suggested that pathological

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consequences of reactivity may occur only in the presence of chronically stressful social environments.¹⁷

There are several recognized stroke risk factors, including hypertension, atherosclerosis, and atrial fibrillation. These risk factors are most strongly related to nonhemorrhagic stroke, and each involves arousal or activation of the autonomic nervous system, which suggests that sympathetic activation plays a role in stroke and particularly ischemic stroke. Thus, it stands to reason that stress-induced cardiovascular reactivity also may contribute to increased risk of stroke and especially stroke resulting from ischemia or ischemic mechanisms. To our knowledge, no prior population study has tested this hypothesis.

Stroke incidence and mortality are known to vary inversely with socioeconomic position.¹⁸⁻²⁰ Similarly, as noted above,

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stress-induced reactivity varies by environmental exposures^{4,5} and socioeconomic position, although the evidence linking stress-induced reactivity and socioeconomic position is mixed. Carroll and colleagues²¹ reported that systolic BP (SBP) reactions to a psychological task (Raven's matrices) were positively related to occupational grade in a sample of British male civil servants, whereas Gump et al²² found that BP reactivity to 2 α -adrenergic tasks (mirror tracing, cold pressor) was greater in children and adolescents from socioeconomically disadvantaged families (determined by the parents' education and occupations). The nature of the tasks used in these 2 studies may account for the discrepancies in their results. Tasks that require greater psychological engagement in order to perform well, such as Raven's matrices, which is a test of nonverbal intelligence, or computer-oriented tasks, which may be intimidating to those without computer experience, may elicit stronger cardiovascular reactions among those who become differentially engaged in the task.²¹ It is plausible that such engagement could vary by educational level. On the other hand, it has been hypothesized that the more adverse circumstances and chronic stress typically experienced by those in lower socioeconomic strata may contribute to exaggerated cardiovascular response to stress.²³ We previously have reported that the effect of reactivity on progression of intimal-medial thickening (IMT) is potentiated in men of lower socioeconomic status (SES),²⁴ which supports the hypothesis that the impact of reactivity on disease depends in part on one's social environment and associated stressors.¹⁷ Thus, it may be that the relation of stress-induced reactivity to stroke also varies by SES.

The present study investigated the relation between stress-induced BP reactivity and subsequent 11-year risk of stroke in a population sample of >2300 middle-aged men. Using data from the Kuopio Ischemic Heart Disease (KIHD) Risk Factor Study, an ongoing study of biopsychosocial risk factors for cardiovascular disease, we were able to examine the independent effects of reactivity on stroke risk, after taking into consideration known risk factors for stroke. Secondly, we examined joint effects of reactivity and SES on stroke risk.

Subjects and Methods

Study Population

The KIHD Study is a comprehensive, population-based study of biological, socioeconomic, and psychosocial risk factors for atherosclerosis, heart disease, mortality, and other outcomes²⁵ among middle-aged men from Kuopio, Finland, and surrounding rural communities in eastern Finland. Participants included 2682 men (82.9% of eligible), aged 42, 48, 54, or 60 years, who were enrolled between March 1984 and December 1989 (see details on the study protocol below). Subjects were excluded from the present analyses if they had a history of stroke ($n=60$), missing information on the measure of BP reactivity ($n=255$), or missing data on covariates ($n=64$), leaving a total of 2303 men eligible for the present study. (In regard to missing information on the measure of BP reactivity, because of scheduling conflicts, 255 participants were unable to participate in the bicycle ergometer stress test at the baseline examination. These men tended to be older and less educated ($P<0.01$), were more likely to be current smokers and to be taking antihypertensive medications at baseline ($P<0.04$), and had marginally higher resting SBP ($P<0.07$) than the 2303 participants included in the analyses.) Nonparticipants were older, less educated, and more

TABLE 1. Mean Values or Prevalence of Baseline Subject Characteristics

| | n | 2303 |
|---------------------------------|---|--------------|
| Age, y | | 52.8 (5.1) |
| BMI, kg/m ² | | 26.8 (3.4) |
| $\dot{V}O_2$ max, mL/(kg · min) | | 30.9 (8.9) |
| SBP, mm Hg | | 130.3 (17.1) |
| DBP, mm Hg | | 88.2 (10.8) |
| LDL cholesterol, mmol/L | | 4.0 (1.0) |
| HDL cholesterol, mmol/L | | 1.3 (0.3) |
| Fibrinogen, g/L | | 3.0 (0.5) |
| Alcohol consumption, g/wk* | | 86.6 (143.5) |
| Education | | |
| ≤ 6 years of school | | 29.3% |
| 7–8 years of school | | 35.3% |
| ≥ 9 years of school | | 35.4% |
| Smoking status | | |
| Never | | 27.3% |
| Former | | 39.5% |
| Current† | | 33.2% |
| Diabetes | | 5.1% |
| Medication use | | |
| Antihypertensive | | 20.4% |
| Cholesterol-lowering | | 0.5% |

Values in parentheses are SD.

*Excludes 291 nondrinkers; 1 drink has approximately 13 g of alcohol.

†Among current smokers, mean (SD) pack-years were 26.3 (18.7).

likely to be current smokers and to take medications for hypertension and hypercholesterolemia ($P<0.03$) but did not differ from participants in terms of resting BP, fibrinogen, body mass index (BMI), alcohol consumption, LDL or HDL cholesterol, or prevalence of diabetes at baseline. Baseline subject characteristics are shown in Table 1.

Study Protocol

The baseline study consisted of 2 examination days, separated by 1 week. Participants provided information on health habits, including diet, smoking, and alcohol consumption, family and personal history of disease, medications, SES, social support and social networks, and various psychological characteristics. Participants also underwent a medical examination, including measurement of height, weight, percent body fat, and BP (see details below), ultrasonographic assessment of carotid atherosclerosis, and a bicycle ergometer maximal exercise tolerance test. Lipids, hemostatic factors, and plasma glucose and insulin, among other biochemical substrates, were determined from venous blood samples obtained on the first examination day, after overnight fasting and abstinence from smoking (12 hours), alcohol (3 days), and analgesics (7 days). Blood was drawn without tourniquet after a 30-minute supine rest, with the use of Terumo Venoject VT-100 PZ, vacuum tubes, and cooled immediately on ice (4°C).

Complete details of the KIHD Study protocol and recruitment procedures have been reported previously.²⁵ The KIHD Study was approved by the University of Kuopio Research Ethics Committee and conducted according to their established guidelines for human research participants and data confidentiality.

Measurement of BP and Reactivity

The measurement protocol for assessing SBP and diastolic BP (DBP) included a 15-minute supine rest with BP measured 3 times at

5-minute intervals, a standing rest with 1 BP reading taken after 1 minute, and a 10-minute seated rest with BP measured twice at 5-minute intervals. Resting BP was measured on the first examination day. The average of the 2 seated BP readings was considered baseline resting BP. On the second examination day, 1 week later, a second measure of sitting BP was obtained after the participant had been seated on the bicycle ergometer for 5 minutes but before the exercise test protocol was begun. Measurements on both examination days occurred in the mornings. All BP readings were obtained with a random zero sphygmomanometer by a trained observer.

SBP and DBP reactivity were defined as the change in SBP and DBP in anticipation of the maximal exercise bicycle ergometer test relative to the average resting baseline BP obtained 1 week earlier. Research indicates that physiological, behavioral, and emotional arousal occurs in anticipation of exercise and its impending challenge.²⁶ Consequently, elevations in BP during this anticipation phase are considered a measure of cardiovascular activation in response to psychological and behavioral stress, ie, cardiovascular reactivity.

Measurement of SES

Self-reported number of years of completed education was used as the measure of SES. Because of the known association between SES and stroke risk,¹⁸⁻²⁰ we also included education as a covariate in the risk factor-adjusted model (modeled continuously) assessing the impact of reactivity on stroke risk.

Ascertainment of Strokes

Stroke ascertainment was completed through December 31, 1997. Incident strokes that occurred during 1984-1992 were ascertained through the FINMONICA stroke register²⁷ for this area and classified according to the *International Classification of Diseases, Ninth Revision* codes 430 to 438. Data on strokes that occurred after 1992 were obtained from the national hospital discharge registry via computerized linkage. A neurologist (J. Sivenius) used these data to classify incident strokes, using the same diagnostic criteria as FINMONICA. Average follow-up time was 11.2 ± 1.6 years.

Data Analyses

A series of Cox proportional hazards models²⁸ was used to assess the relation between stress-induced BP reactivity and incident stroke. Reactivity was modeled continuously and categorically (based on a median split) in separate models. All models were adjusted for age and resting SBP (resting DBP in models with DBP reactivity as the predictor). Additional multivariate models included a number of covariates representing known stroke risk factors, including BMI, alcohol consumption, smoking, HDL and LDL cholesterol, fibrinogen, SES, prevalence of diabetes, and use of medication for hypertension or hypercholesterolemia, as described below. LOGISTIC and GLM procedures from SAS, version 6.12 (SAS Institute), were used for analyses.

Assessment of Baseline Covariates

Age was modeled categorically with the use of dummy-coded variables for ages 48, 54, and 60, with 42-year-olds as the referent group. BMI was calculated as weight (kilograms) divided by height (meters) squared and modeled continuously. Maximum oxygen uptake ($\dot{V}O_2\text{max}$), an indicator of fitness, was defined as the highest value of oxygen uptake as measured by breath-by-breath respiratory gas exchange; $\dot{V}O_2\text{max}$ was modeled continuously. Resting SBP and DBP were calculated as the average of 2 seated BP measurements (described above) and modeled continuously. Cigarette smoking was determined by self-report and modeled with a dummy-coded variable representing former smokers and a continuous variable representing pack-years for current smokers, with never smokers as the reference group. Alcohol consumption was assessed by a questionnaire on drinking behavior over the last 12 months and a 4-day dietary record and modeled continuously as grams of ethanol per week. HDL and LDL cholesterol levels were measured in millimoles per liter and modeled continuously. Fibrinogen was measured in grams per liter

and modeled continuously. Use of medications for hypertension or hypercholesterolemia, confirmed during the medical examination, was modeled with dummy-coded variables. Prevalent diabetes, confirmed if a participant reported currently using diet or medication to control diabetes or if his fasting blood glucose level was ≥ 6.7 mmol/L (120 mg/dL) was modeled with a dummy-coded variable. (Self-reported history of and/or use of medication for atrial fibrillation also was obtained at the baseline examination. However, only 10 participants had a history of atrial fibrillation, and none of these had a stroke during the follow-up. Consequently, we did not include a covariate representing this risk factor in our multivariate models.)

Results

A total of 113 first strokes was identified during the 11 years of follow-up, with 90 of them determined to be ischemic or thrombotic, 21 determined to be hemorrhagic, and 2 undifferentiated. The average change in SBP in anticipation of exercise was 20 mm Hg (SD, 15.9; median, 19). The corresponding change in DBP was 8.6 mm Hg (SD, 8.5; median, 8). On average, participants reported 8.7 years (SD, 3.5) of education. Education was significantly, inversely related to both SBP ($b, -0.49; t, -5.18; P < 0.0001$) and DBP changes ($b, -0.15; t, -3.04; P < 0.003$) in anticipation of exercise.

All Strokes

A Cox proportional hazards model, with covariates for age and resting SBP, found that each 1-mm increase in SBP in anticipation of exercise corresponded to a significant 1-point increase in risk of stroke (relative hazard ratio [RH], 1.01; 95% CI, 1.00 to 1.02). Dichotomizing respondents into high (greater than the median) and low reactors (equal to or less than the median) showed that men whose SBP rose > 19 mm Hg in anticipation of exercise had a 72% greater risk of stroke over the subsequent 11 years than men who were less reactive ($P < 0.006$) (Table 2). This association was modified only slightly and remained significant after adjustments for age, resting SBP, SES, smoking, alcohol consumption, BMI, $\dot{V}O_2\text{max}$, LDL and HDL cholesterol, fibrinogen, history of diabetes, and use of medication for hypertension or hypercholesterolemia. Anticipatory diastolic response was not related to increased stroke risk.

Reactivity and Stroke Risk by Type of Stroke

The majority (79.6%) of incident strokes that occurred in our population were due to ischemia or thromboembolism. Analyses that limited the outcome to these nonhemorrhagic strokes produced results similar to, albeit slightly stronger than, those seen for all strokes combined. Each 1-mm increase in the anticipatory SBP response corresponded to a significant 1.5% increased risk of ischemic stroke (RH, 1.015; 95% CI, 1.00 to 1.03), with adjustment for age and resting SBP. Modeling SBP reactivity categorically showed that high reactors had 87% greater risk relative to men who were less reactive in anticipation of exercise ($P < 0.005$) (Table 2). Inclusion of covariates representing known stroke risk factors modified this association only slightly, with high reactors demonstrating a significant 74% excess risk of ischemic stroke in the fully adjusted model. DBP reactivity was unrelated to ischemic strokes.

TABLE 2. SBP Reactivity to Exercise and Risk of Stroke

| | Model 1 | | Model 2 | |
|-------------------------|---------|-----------|---------|-----------|
| | RH | 95% CI | RH | 95% CI |
| All strokes (n=113) | | | | |
| SBP>19 mm Hg | 1.72 | 1.17–2.54 | 1.58 | 1.07–2.33 |
| SBP≤19 mm Hg | 1.0 | Referent | 1.0 | Referent |
| DBP>8 mm Hg | 1.02 | 0.70–1.50 | 0.95 | 0.65–1.39 |
| DBP≤8 mm Hg | 1.0 | Referent | 1.0 | Referent |
| Ischemic strokes (n=90) | | | | |
| SBP>19 mm Hg | 1.87 | 1.20–2.89 | 1.74 | 1.12–2.70 |
| SBP≤19 mm Hg | 1.0 | Referent | 1.0 | Referent |
| DBP>8 mm Hg | 1.13 | 0.74–1.73 | 1.05 | 0.68–1.60 |
| DBP≤8 mm Hg | 1.0 | Referent | 1.0 | Referent |

Model 1 is adjusted for age and resting SBP (or DBP). Model 2 is adjusted for age, resting SBP (or DBP), SES, smoking, alcohol consumption, BMI, $\dot{V}_{O_2\max}$, LDL and HDL cholesterol, fibrinogen, history of diabetes, and use of medication for hypertension and hypercholesterolemia.

Neither SBP reactivity nor DBP reactivity was significantly related to risk of hemorrhagic stroke. However, relatively few strokes in our population were due to hemorrhage, and it is therefore likely that we did not have adequate power to reliably assess these associations.

SES, Reactivity, and Risk of Stroke

Because stroke incidence and mortality are typically higher in lower SES groups^{19–20} and there is some evidence that cardiovascular reactivity varies inversely with SES,²² we also sought to determine the joint effects of SBP reactivity and SES on stroke risk. Education was significantly associated with stroke risk in the multivariate model reported in Table 2, with increasing education associated with decreasing risk (RH, 0.90; 95% CI, 0.83 to 0.97). Subsequent categorical analysis using approximate tertiles of education corresponding to primary school or less (≤ 6 years of school), some vocational training or education beyond primary school but no high school (7 to 8 years of school), and some high school or more (≥ 9 years of school) showed that the least educated men were at increased risk of stroke (RH, 2.03; 95% CI, 1.22 to 3.37) relative to the best educated men, but those with 7 to 8 years of education were not (RH, 1.33; 95% CI, 0.79 to 2.23).

Consequently, to assess the joint effects of SBP reactivity and education on risk of stroke, we conducted a set of Cox proportional hazards models that included terms representing the main effects of reactivity and education as well as their interaction for all strokes combined and for ischemic strokes. Reactor status was dichotomized by a median split of SBP response in anticipation of exercise, as above, and education was dichotomized as primary school or less versus greater than primary school on the basis of the aforementioned findings for education. The interaction term was the cross product of these 2 terms.

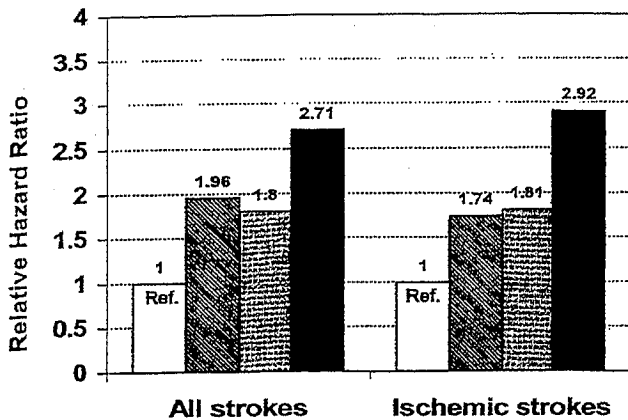
We did not observe a significant, multiplicative interaction between reactor status and education for either all strokes combined (RH, 0.75; 95% CI, 0.35 to 1.60) or ischemic strokes (RH, 0.93; 95% CI, 0.39 to 2.20). However, we did find significant main effects for both reactor status and

education (RH, 1.93; 95% CI, 1.15 to 3.26, and RH, 2.00; 95% CI, 1.09 to 3.67, respectively) with all strokes as the outcome. Moreover, contrasting men with both risk factors (high reactors with low education) with men with neither risk factor showed that reactive men with the least education had the greatest risk of stroke (RH, 2.90; 95% CI, 1.66 to 5.08) after adjustment for age and resting SBP. With ischemic strokes as the outcome, we observed a marginally significant main effect for education (RH, 1.76; 95% CI, 0.87 to 3.55) and a significant main effect for reactor status (RH, 1.90; 95% CI, 1.04 to 3.45) and again saw the greatest risk of stroke in men with both risk factors (RH, 3.11; 95% CI, 1.67 to 5.77) compared with men with neither risk factor. Risk factor adjustments produced only minor decrements in the point estimates and thus showed little effect of confounding by known stroke risk factors. For illustrative purposes, we have graphed the risk factor-adjusted results of the contrasts between the 4 groups that are identified by jointly considering reactor status and education (Figure). Although the interaction term between reactivity and education was not significant in our models, we believe that it is informative to note the combined main effects of reactor status and low education.

Discussion

This study provides convincing evidence that exaggerated BP responses to stress contribute to increased risk of stroke and particularly stroke due to ischemia or thromboembolism in middle-aged and older men. The association between reactivity and incident stroke was modified very little by known risk factors for stroke. These data support the growing literature on the importance of hemodynamic or cardiovascular reactivity in the development and progression of cardiovascular diseases.^{6,7,10,11} To our knowledge, this is the first study to link reactivity to excess risk of stroke.

We also found that men who had limited education were at greater risk of stroke than more educated men, which is consistent with prior research showing an inverse socioeconomic gradient for stroke incidence and mortality.¹⁸ Educa-



Relative risk of stroke by reactor status and education: KIID Study, 1984–1996. Data are adjusted for age, resting SBP, smoking, alcohol consumption, BMI, V_{O_2max} , LDL and HDL cholesterol, fibrinogen, history of diabetes, and use of medication for hypertension or hypercholesterolemia. Black bars represent men who were high reactors (greater than the median) and had only a primary school education or less (16.2%); gray bars represent men who were high reactors but had at least some secondary school education or vocational training beyond primary school (32.1%); hatched bars represent men who were low reactors (at or below the median) but had only a primary school education or less (13.2%); and white bars represent men who were low reactors and had at least some secondary school education or vocational training beyond primary school (38.6%).

tion was inversely related to reactivity in this study. Moreover, analysis of the joint effects of low SES and reactivity on risk of stroke showed that, while there was not a differential effect of reactivity among the poorly educated men (ie, we did not observe a significant statistical interaction between reactivity and education on stroke risk), men with both risk factors in our study were nearly 3 times more likely to have had a stroke during the follow-up period compared with men who had neither risk factor. These results suggest that low SES adds to the risk of stroke associated with stress-induced autonomic arousal. However, as noted and as shown in the Figure, both SES and reactivity uniquely contributed to excess stroke risk.

In this study stress-induced reactivity was conceptualized and modeled as a characteristic of the individual. Indeed, we found that the most reactive participants had the greatest risk of stroke over the intervening 11 years of follow-up. Reactivity also may be conceptualized as a mediating mechanism by which psychological or social factors increase risk of cardiovascular disease.²⁹ Our study was not designed to test this model. The fact that we found additive but not interactive effects in our analyses in which we modeled the joint effects of reactivity and low SES suggests that the characteristic of reactivity has significant, independent health effects. Moreover, demonstrating that stress-induced reactivity increases stroke risk is an important prerequisite to future studies that may seek to examine whether such reactivity mediates the relation between various psychosocial characteristics and stroke.

The inverse association between reactivity and SES observed here is consistent with the findings reported by Gump et al²² but in contrast to results reported by Carroll et al.²¹

Variations in our respective findings may very well relate to the types of tasks used, which differ in all 3 studies. For example, we have previously argued that the anticipatory period before exercise, the stressor used in the present study, can be characterized as a period of psychophysiological arousal attendant to an impending challenge⁶ and thus represents a measure of stress-induced reactivity. Differences between this reactivity measure and the type of cognitive task used in the study of Carroll et al may account for the discrepancies in our findings. It may be that tasks not dependent on scholastic achievement, in contrast to any number of verbal or nonverbal IQ tests, may yield more consistent results across studies. Additionally, as noted earlier, it is speculated that psychological engagement that influences task performance may influence the cardiovascular responses elicited and may vary by educational level. Other task characteristics, such as level of difficulty or salience to the participant, also may influence responses,^{5,30} although their relation to SES is unknown. Surprisingly few studies to date have directly examined the relation between cardiovascular reactivity and SES, and thus additional research is needed before firm conclusions can be made.

In the present study SBP reactivity in anticipation of exercise was related to greater stroke risk, whereas DBP reactivity was not. It is known that the sympathetic activation that occurs in the anticipatory phase before exercise is characterized by increased cardiac output without a compensatory decrease in vascular resistance.²⁶ Moreover, SBP reactivity represents an acute increase in cardiac force during systole, whereas DBP reactivity reflects increases in resistance during diastole. Presumably, the pressor response patterns seen here in anticipation of exercise are representative of the sympathetic arousal experienced by these men to other emotionally stressful stimuli. Therefore, with repeated or prolonged exposure to stress, it may be that SBP reactivity and its accompanying increase in the rate and force with which blood is pumped into the vasculature exacerbates stroke risk by increasing the probability of an embolism.

Alternatively, the exaggerated SBP reactivity observed in this study may elevate the risk of stroke through general atherogenic mechanisms. For example, sympathetic arousal contributes to injury and dysfunction of the arterial endothelium, which may lead to formation of atherosclerotic plaques.^{13,31} In addition, neuroendocrine correlates of sympathetic nervous system activation, including increases in norepinephrine, epinephrine, and cortisol, can promote lipid mobilization^{32,33} and platelet activation, contributing to aggregation of platelets and formation of thrombi.³⁴ Both of these processes also may exacerbate vascular injury and atherosclerotic plaque formation and progression.³⁵ As noted previously, a well-recognized, clinical complication of atherosclerosis is stroke.

We previously reported that the measure of stress-induced reactivity reported here is associated prospectively with increased risk of hypertension⁶ and progression of IMT⁷ in our population of middle-aged men from Finland. These certainly are plausible mechanisms by which reactivity increases risk of stroke. However, the design of our study does not make it possible to reliably test these hypotheses at this

time. The earlier reports were based on the subset of participants who completed the baseline and 4-year follow-up examinations of the KIHHD Study. Of the 2303 participants included in the present analyses, <38% completed the 4-year follow-up, and among these respondents, there have been too few incident strokes since the follow-up examination to adequately examine the importance of these stroke risk factors. Continued follow-up will enable us to better model causal pathways between stress-induced reactivity, changes in risk factors over time, and incident stroke.

A few limitations of our study need to be noted. First, the demographic makeup of the sample precludes widespread generalization of the findings. Our study sample consisted only of middle-aged white men. Research is needed in female, minority, and nonwhite populations to determine whether similar relationships exist between stress-induced reactivity and excess risk of stroke. Prior research suggests that there may be important differences in cardiovascular responses to stress according to sex and race or ethnicity.³⁶⁻³⁸ It is critical to determine whether these different patterns of response are differentially related to cardiovascular disease risk. Moreover, stroke morbidity and mortality are greater in minorities than in whites,³⁹ emphasizing the need for research on risk factors for stroke in nonwhite populations.

A second limitation is that we did not gather data on the acute versus chronic experience of stress among our participants. Such information would be valuable given that prolonged exposure to stress, resulting in frequent and intense stress responses, is thought to be importantly related to the development and progression of disease.^{5,17}

Our study also is limited by its inability to address the relation between stress-related reactivity and hemorrhagic stroke. A larger number of hemorrhagic strokes than occurred in our study population would be required to adequately assess the association between stress-induced cardiovascular reactivity and hemorrhagic strokes.

In summary, this study provides new epidemiological evidence of a link between stress-induced BP reactivity and an important clinical cerebrovascular end point in a population sample of middle-aged men. Additional research is needed to corroborate these findings in other populations, particularly in women and minorities. This is an important area of research to pursue, given the increasing prevalence of stroke in our aging population.⁴⁰ Our findings add to the literature that seeks to further our understanding of the critical role that stress plays in the development and progression of atherosclerosis and its clinical complications.

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References

1. Everson SA, McKey BS, Lovallo WR. The effect of trait hostility on cardiovascular responses to harassment in young men. *Int J Behav Med.* 1995;2:172-191.
2. Kamarck TW, Peterman AH, Raynor DA. The effects of the social environment on stress-related cardiovascular activation: current findings, prospects, and implications. *Ann Behav Med.* 1998;20:247-256.
3. Smith TW, Christensen AJ. Cardiovascular reactivity and interpersonal relations: psychosomatic processes in social context. *J Soc Clin Psychol.* 1992;11:279-301.
4. Steptoe A, Cropley M, Joeckes K. Job strain, blood pressure and response to uncontrollable stress. *J Hypertens.* 1999;17:193-200.
5. Turner JR, Sherwood A, Light KC. *Individual Differences in Cardiovascular Response to Stress.* New York, NY: Plenum Press; 1992.
6. 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;27:1059-1064.
7. 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. *Br Med J.* 1997;314:553-558.
8. Kamarck TW, Everson SA, Kaplan GA, Manuck SB, Jennings JR, Salonen R, Salonen JT. Exaggerated blood pressure responses during mental stress are associated with enhanced carotid atherosclerosis in middle-aged Finnish men: findings from the Kuopio Ischemic Heart Disease Study. *Circulation.* 1997;96:3842-3848.
9. Barnett PA, Spence JD, Manuck SB, Jennings JR. Psychological stress and the progression of carotid artery disease. *Hypertension.* 1997;15:49-55.
10. Markovitz JH, Raczynski JM, Wallace D, Chettur V, Chesney MA. Cardiovascular reactivity to video game predicts subsequent blood pressure increases in young men: the CARDIA Study. *Psychosom Med.* 1998;60:186-191.
11. Matthews KA, Owens JF, Kuller LH, Sutton-Tyrrell K, Lassila HC, Wolfson SK. Stress-induced pulse pressure change predicts women's carotid atherosclerosis. *Stroke.* 1998;29:1525-1530.
12. Watson SL, Shively CA, Kaplan JR, Line SW. Effects of chronic social separation on cardiovascular disease risk factors in female cynomolgus monkeys. *Atherosclerosis.* 1998;137:259-266.
13. Kaplan JR, Pettersson K, Manuck SB, Olsson G. Role of sympathoadrenal medullary activation in the initiation and progression of atherosclerosis. *Circulation.* 1991;84(suppl VI):VI-23-VI-32.
14. Carroll D, Davey Smith G, Willemsen G, Sheffield D, Sweetnam PM, Gallacher JE, Elwood PC. Blood pressure reactions to the cold pressor test and the prediction of ischaemic heart disease: data from the Caerphilly Study. *J Epidemiol Community Health.* 1998;52:528-529.
15. 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.
16. Carroll D, Smith GD, Sheffield D, Shipley MJ, Marmot MG. Pressor reactions to psychological stress and prediction of future blood pressure: data from the Whitehall II Study. *Br Med J.* 1995;310:771-776.
17. Manuck SB, Kasprovicz A, Muldoon MF. Behaviorally-evoked cardiovascular reactivity and hypertension: conceptual issues and potential associations. *Ann Behav Med.* 1990;12:17-29.
18. Modan B, Wagenser DK. Some epidemiological aspects of stroke: mortality/morbidity trends. *Stroke.* 1992;23:1230-1236.
19. Sacco RL, Benjamin EJ, Broderick JP, Dyken M, Easton JD, Feinberg WM, Goldstein LB, Gorelick PB, Howard G, Kittner SJ, Manolio TA, Whisnant JP, Wolf PA. American Heart Association Prevention Conference, IV: prevention and rehabilitation of stroke: risk factors. *Stroke.* 1997;28:1507-1517.
20. Kunst AE, del Rios M, Groenhouf F, Mackenback JP, for the European Union Working Group on Socioeconomic Inequalities in Health. Socio-economic inequalities in stroke mortality among middle-aged men. *Stroke.* 1998;29:2285-2291.
21. Carroll D, Davey Smith G, Sheffield D, Shipley MJ, Marmot MG. The relationship between socioeconomic status, hostility, and blood pressure reactions to mental stress in men: data from the Whitehall II Study. *Health Psychol.* 1997;16:131-136.
22. Gump BB, Matthews KA, Raikkonen K. Modeling relationships among socioeconomic status, hostility, cardiovascular reactivity, and left ventricular mass in African American and white children. *Health Psychol.* 1999;18:140-150.
23. Anderson NB, McNeilly M, Myers H. Autonomic reactivity and hypertension in blacks: a review and proposed model. *Ethn Dis.* 1991;1:154-170.
24. Lynch JW, Everson SA, Kaplan GA, Cohen RD, Salonen R, Salonen JT. Low socioeconomic status potentiates the effects of heightened cardio-