Clinical Investigation and Reports

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

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Background Exaggerated cardiovascular reactivity to mental stress is hypothesized to increase atherosclerotic risk. We examined this hypothesis using cross-sectional data from the Kuopio Ischemic Heart Disease study, a population-based epidemiological sample.

Methods and Results 901 Eastern Finnish men from four age cohorts (age, 42 to 60 years) were administered a standardized testing battery to assess cardiovascular reactivity to mental stress. Ultrasound measures of intima-medial thickness (IMT) and plaque height from the common carotid arteries were used as noninvasive markers of atherosclerosis. Diastolic blood pressure (DBP) responses to mental stress were significantly associated with mean IMT ($b=.021$, $P=.006$), maximum IMT ($b=.026$, $P=.013$), and mean plaque height ($b=.017$, $P=.041$). Significant associations were also shown between stress-related systolic blood pressure (SBP) reactivity and mean IMT ($b=.0151$, $P=.042$). When examined separately by age, associations with IMT were significant only in the youngest half of the sample (age, 46 and 52 years, n=433; for mean IMT, DBP $b=.033$, $P=.0002$, SBP $b=.0266$, $P=.003$; for maximum IMT, DBP $b=.039$, $P=.002$, SBP $b=.032$, $P=.011$). Results remained significant in the younger subjects after adjustment for smoking, lipid profiles, fasting glucose, and resting blood pressure ($b=.024$, $P=.011$); results also remained significant in a subgroup of unmedicated younger subjects without symptomatic cardiovascular disease (n=135; for SBP reactivity, $b=.031$, $P=.036$; for DBP, $b=.037$, $P=.007$).

Conclusions The tendency to show exaggerated pressor responses to mental stress is a significant independent correlate of atherosclerosis in this population sample of Finnish men. The effect does not appear to be accounted for by the confounding influence of other risk factors or preexisting clinical disease. (*Circulation.* 1997;96:3842-3848.)

Key Words • atherosclerosis • cardiovascular diseases • carotid arteries • risk factors • stress

The tendency to show exaggerated cardiovascular responses to mental stress ("cardiovascular reactivity") is hypothesized to be a potential risk factor for the development of atherosclerosis and coronary heart disease.[1-3] Nonhuman primate studies are consistent with this "reactivity hypothesis": cynomolgus macaques showing the most pronounced HR responses during a fear-eliciting stimulus have been found to exhibit more extensive atherosclerosis than their less reactive counterparts.[4,5] Stress-related SNS activation has been linked with a number of atherogenic processes; for example, prolonged exposure to aversive stimuli enhances artery wall endothelial injury and dysfunction in experimental rat and monkey models, and these changes have been shown to be mediated by SNS responding.[6-9] Exaggerated cardiovascular reactors are assumed to be more susceptible to this type of stress-related SNS activation and, thus, at greater risk for atherosclerotic disease.

Although most of the evidence supporting the association between cardiovascular reactivity and atherosclerosis is derived from animal models, recent evidence is emerging consistent with this hypothesis from studies of human volunteers as well.[10-12] The recent development of standardized assessment strategies for the laboratory assessment of cardiovascular reactivity has enhanced the ability to assess this characteristic in a reliable manner.[13] To date, there are no population-based studies with standardized assessments that examine the association between reactivity and atherosclerosis in humans. The purpose of the present study was to examine the link between exaggerated stress-related reactivity and atherosclerosis in an epidemiological sample and to explore

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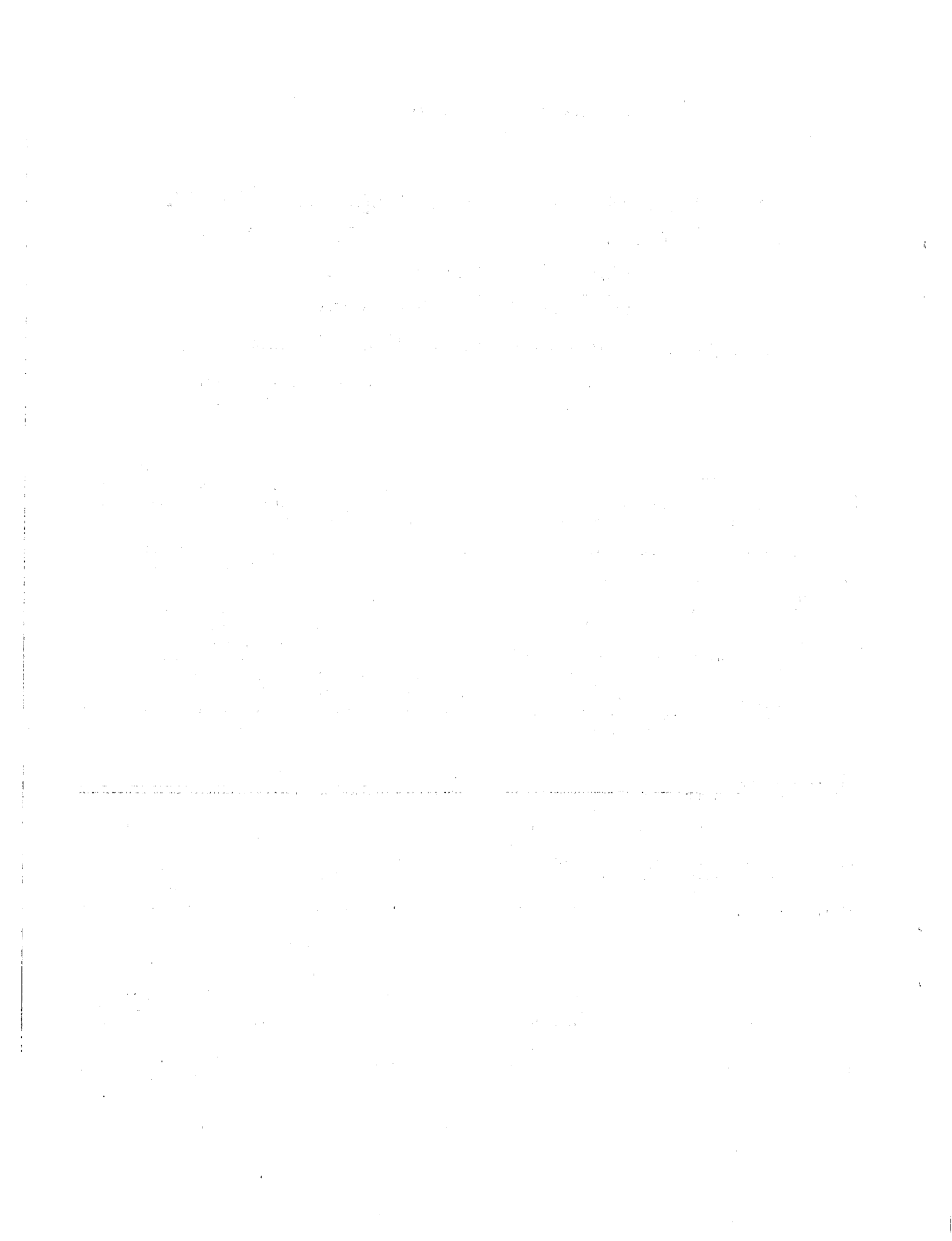
some possible pathways that account for this proposed association.

Standard risk factors for symptomatic coronary heart disease, including smoking, hypertension, cholesterol and triglycerides, and diabetes, are also significantly associated with indices of carotid atherosclerosis.[14-18] If exaggerated cardiovascular reactivity promotes atherosclerosis in humans, the extent to which this enhanced risk may be accounted for, in part, by these established risk factor concomitants remains to be explored. These factors are examined in this report.

Data presented here are from the KIHD, an ongoing epidemiological study of risk factors for atherosclerotic vascular disease and other outcomes in a population sample of Eastern Finnish men.[19,20] Important features of this study, for the purpose of this report, include the assessment of noninvasive markers of the extent of carotid atherosclerosis (ultrasound measures of IMT), the use of an extensive testing battery for measuring cardiovascular reactivity, and the availability of multiple measures of cardiovascular risk in the sample. We examined the concurrent association between reactivity and disease in this group; we examined age differences in the extent of this association; we explored the role of preexisting disease in contributing to our findings; and we investigated the effects of established risk factors in accounting for these results.

Methods

Subjects

The KIHD is a population-based epidemiological investigation of risk factors for ischemic heart disease, atherosclerotic vascular disease, and other outcomes in Eastern Finnish men. The subjects involved in the reactivity testing were drawn from four cohorts of men ages 42, 48, 54, and 60 years at time of initial testing who were born in the city and region of Kuopio, Finland. A total of 2682 men were enrolled and participated in baseline assessments between March 1984 and December 1989. A 4-year follow-up examination was conducted between 1991 and 1993 on the men (n=1229) who had undergone carotid ultrasound assessments at baseline. Of those, 52 had died, had severe illness, or had migrated away from the region, and 139 could not be contacted or refused to participate. Thus, a total of 1038 volunteers (88.2% of those eligible) participated in the 4-year follow-up testing. Due to subject availability and scheduling constraints, only 901of the 1038 men participated in the cardiovascular reactivity testing as part of this 4-year follow-up examination: 433 subjects in the youngest two age cohorts (age 46 and 52 at the time of follow-up testing) and 468 subjects in the oldest two cohorts (age 58 and 64 at the time of testing). It should be noted that the tested sample (n=901) was somewhat younger and better educated and showed somewhat less disease at the 4-year follow-up than the subjects (n=137) who were not available for reactivity testing (age difference *t* [1036], 3.34, *P*<.001; mean age of tested subjects, 51.14 years; mean age of untested subjects, 53.17 years; education difference [four category] χ^2=13.10, *P*<.01, 7% of participants and 13% of

nonparticipants had not completed elementary school; prevalence of symptomatic coronary heart disease,[2] χ^2=2.88, *P*<.10; 21% of participants and 28% of nonparticipants had a diagnosis of coronary heart disease). Because these differences were relatively small in absolute terms, we do not expect the sample characteristics to affect the generalizability of the results.

Procedures

Examinations for the 4-year follow-up point were carried out over 2 days, 1 week apart, and consisted of a variety of biochemical, physiological, anthropometrical, and psychosocial measures. All subjects gave their informed consent to the testing, and the study protocol was reviewed and approved by the Institutional Ethical Committee of the University of Kuopio.

Measures

Measurement of Carotid Atherosclerosis

The extent of carotid atherosclerosis was assessed by high-resolution B-mode ultrasonography of the right and left CCAs in a 1.0- to 1.5-cm section at the distal end of the CCA, proximal to the carotid bulb. Images were focused on the posterior wall of the right and left CCAs and recorded on videotape for later analysis. Ultrasound examinations were conducted by one of four trained sonographers and were performed with the subject in a supine position after a 15-minute rest.

At the 4-year follow-up, images were obtained with a Biosound Phase 2 scanner equipped with a 10-MHz annular array probe.[21] Wedge phantom studies of this system, calibrated against an RMI 414B tissue phantom, have demonstrated measurement precision of ±0.03 mm.[21,22] Four-year follow-up scans were taken concurrently with the reactivity assessments and are used in all of the analyses described below; all carotid measures were statistically adjusted for sonographer (multiple sonographers were used for the 4-year assessments).

IMT measurements were made via computerized analysis of the videotaped ultrasound images using Prosound software (University of Southern California, Los Angeles, Calif). This software uses an edge-detection algorithm, specifically designed for use with ultrasound imaging,[23,24] that allows automatic detection, tracking, and recording of the intima/lumen and media/adventitia interfaces. IMT, calculated as the mean distance between these interfaces, was estimated at ≈100 points in both the right and left CCAs.

For the present study, three measures of IMT were used: (1) mean IMT, calculated as the mean of all IMT estimates from the right and left CCAs and considered an overall measure of the atherosclerotic process in the carotid arteries; (2) maximum IMT, the average of the points of maximum thickness from the right and left CCAs and indicative of the depth of intrusion of atherosclerotic thickening into the lumen in this part of the CCA; and (3) plaque height, the average of right and left CCA measurements of plaque height, calculated as the difference between maximum and minimum thickness, and an assessment of how steeply atherosclerotic lesions protruded into the lumen.

Growing evidence supports the use of carotid ultrasound measures as valid noninvasive markers of atherosclerosis. Ultrasound carotid assessments are associated with pathological and histological measures of atherosclerosis in autopsy samples,[25] appear to reliably discriminate between patients with and without coronary artery stenosis by angiography,[26,27] and have been shown to be prospectively associated with the risk for coronary events (eg, myocardial infarction, sudden cardiac death), even among initially asymptomatic individuals.[15,28-30] Because carotid measures can be used to assess preclinical manifestations of vascular disease, they are well suited for investigation of possible antecedents of atherosclerosis in a population sample.

Assessment of Standard Risk Factors

Blood samples were drawn after fasting and abstinence from smoking for 12 hours, abstinence from alcohol for 3 days, and abstinence from analgesic medications for 7 days. Subjects rested supine for 30 minutes, after which blood was drawn without the use of a tourniquet by using Terumo Venoject VT-100 PZ vacuum tubes (Terumo Corp). Lipoproteins were separated from unfrozen plasma within 3 days of sampling. The HDL and LDL fractions were separated from fresh plasma through the use of both ultracentrifugation and precipitation. The cholesterol content of all lipoprotein fractions and serum triglycerides was measured enzymatically (CHOD-PAP method for lipoproteins and GPO-PAP method for triglycerides; Boehringer-Mannheim Biochemica) on the day after the last spin. Blood glucose was measured according to the glucose dehydrogenase method after precipitation of the proteins with trichloric acetic acid. Resting blood pressure assessments were obtained by a trained observer using a random-zero muddler sphygmomanometer (Hawksley) at minutes 5 and 10 during a seated rest period; the two readings were averaged. Medical history and medication use were recorded during a medical examination at the baseline and follow-up assessments. Smoking status was measured by self-report.

Cardiovascular Reactivity Testing

A recently developed automated test battery for the assessment of individual differences in cardiovascular reactivity was used in this study. The version of the battery used here involved four standardized computer-based tasks, each 9 minutes long, that required a range of cognitive and psychomotor skills (memory task, reaction time task, tracing task, and computerized version of the Stroop Color Word Task[20,31]). Each task was designed to simulate a state of mild mental stress or challenge and was preceded by a 9-minute baseline (rest and recovery) period.[32] The difficulty level of each task was adjusted after each trial to maintain a performance level of ≈60% success, ensuring a continuous and optimal level of challenge for each subject. These tasks have been shown to elicit significant acute changes in cardiovascular activity (changes from baseline in HR, blood pressure, and other cardiovascular functions), and this multiple-task battery has been shown to yield stable estimates of individual differences in reactivity in a variety of US samples.[13,33,34] Reliable measures of reactivity were also obtained from this battery in a subsample from the KIHD study retested 8 to 12 months after the initial assessment.[20] With instrumentation and instructions, the entire reactivity assessment protocol lasted ≈2 hours for each participant.

In preparation for reactivity testing, each subject was instrumented with a two-lead ECG across the chest, an automated blood pressure device (Dinamap Vital Signs Monitor) on the dominant arm, impedance cardiograph electrodes (Minnesota Impedance Cardiograph model 304B[35]) on the neck and thorax, and a peripheral vascular pulse transducer[36] on the thumbnail of the nondominant arm. Blood pressure measurements were taken every 90 seconds during the baseline and task periods; ECG measures were ensemble-averaged across each consecutive 30-second interval throughout the assessment period. Additional impedance cardiography and pulse wave measurements were collected but are not reported here. These additional measures were not consistently associated with indices of atherosclerosis in the sample; some, however, were affected by the health status of the participants.[20] The scoring and measurement systems associated with this task battery have been previously described.[37] Because of occasional arm movement or equipment failure, there was some data loss on ≈5% of the sample for the blood pressure and HR measurements, so we report the sample size separately for each of the analyses described below.

Assessments for each cardiovascular parameter (HR, SBP, and DBP) were averaged separately across the 9-minute period for each rest period and each task. The four resulting rest period values were averaged and subtracted from each averaged task score to derive estimates of cardiovascular reactivity. Each of these reactivity scores was performance-adjusted by removing any linear relationship between the response to each task and the level of performance (average difficulty level for each trial) achieved by the subject on the task. This correction was introduced to reduce the small but significant association between task performance and cardiovascular responsiveness (r=≤.13) shown in this sample. Resulting adjusted reactivity measures were standardized within each task and averaged across tasks, yielding a single performance-adjusted score for each subject for each cardiovascular parameter.*

Data Analysis

Measures of carotid IMT were regressed on measures of HR and blood pressure reactivity using a general linear models procedure (PROC GLM[38]). Associations were explored separately in subjects above and below the median age of the sample (55 years) at the time of testing. Because of their previously observed effects on cardiovascular responsiveness,[33,39] educational level and remaining variations in age were used as covariates in all models. To reduce the possible confounding effects of concurrent disease on reactivity as a plausible causal explanation for the results, we repeated our significant analyses in the subgroup of subjects who were free of symptomatic cardiovascular disease and cardioactive medication. Finally, in our initial model, we entered established cardiovascular risk factors as additional covariates to assess their contribution to the results.

Results

Blood pressure reactivity to the testing battery was significantly and positively associated with ultrasound measures of carotid atherosclerosis in this sample, with the results being largest for the measure of DBP response. Reported results include the unstandardized partial regression coefficients describing the change in carotid wall or plaque thickness (in mm) for each average mm Hg change in blood pressure response after adjustment for age and education and associated P values for each parameter: DBP reactivity showed significant associations with all three measures of carotid morphology (n=859; for mean IMT, b=.021, P=.006; for maximum IMT, b=.026, P=.013; and for mean plaque height, b=.017, P=.041). Significant effects were shown for SBP reactivity on average IMT (n=867; mean IMT, b=.0151, P=.042), and SBP reactivity was marginally related to maximal IMT as well (maximum IMT b=.0187, P=.078, n=867). HR reactivity showed a marginally significant inverse association with mean IMT (b=−.014, P=.054, n=868) and maximum IMT (b=−.019, P=.071, n=868).

When results were examined separately by age group, we found that the association between blood pressure reactivity and carotid atherosclerosis was accounted for

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*Because of a computer software error, some blood pressure data (the last five readings from each baseline measurement and the last four readings from each task period collected during the protocol) was lost for 136 subjects. These subjects were equally divided among the four age cohorts. For these missing-data subjects, reactivity scores were derived on the basis of the remaining readings available for each (one remaining reading for each of the four tasks and four baseline periods) with the aid of regression weights derived from the rest of the sample. To ensure that results were not an artifact of these data imputation strategies in some manner, we reran the analyses and omitted data for the subjects for whom these data were estimated. The results were virtually identical. Therefore, all data in the present report included the subjects with the estimated blood pressure values.

A

Younger Subjects (n=420)

B

Older Subjects (n=439)

C
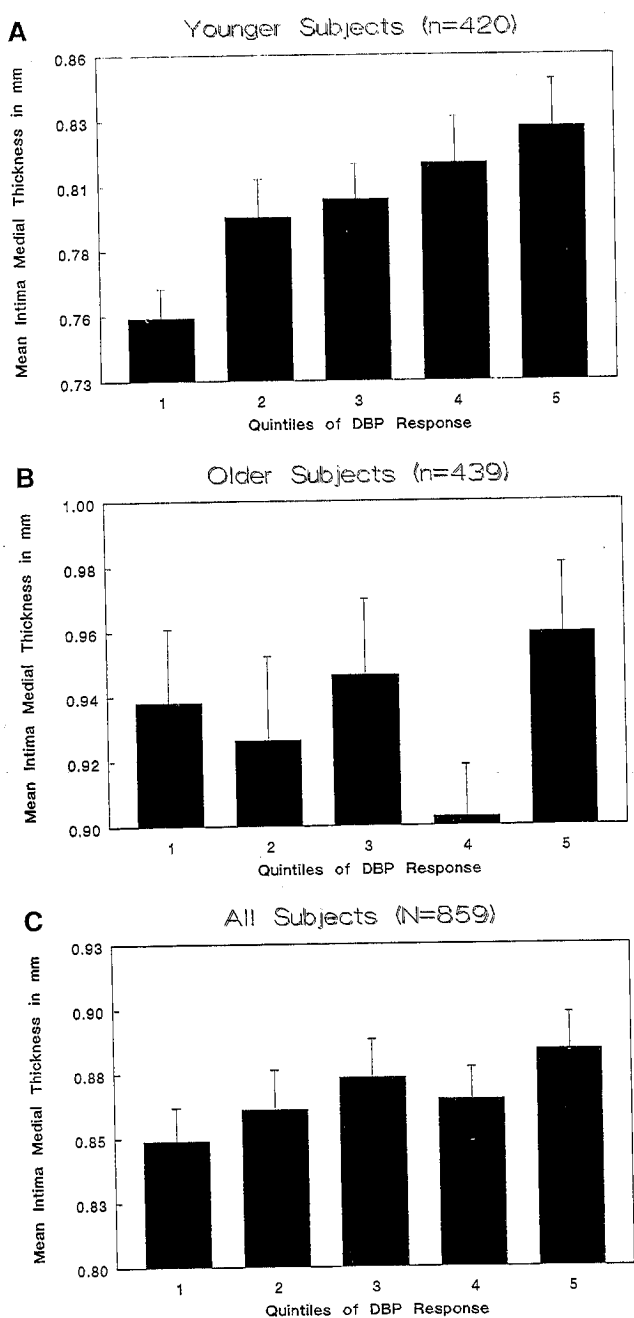
All Subjects (N=859)

Covariate-adjusted common carotid mean IMT (in mm) by quintiles DBP reactivity in the KIHD. A, Younger subjects (n=420). B, Older subjects (n=439). C, All subjects (N=859).

entirely by the youngest half of the sample (age, 46 and 52 years; n=433). Again, all models included covariates for the remaining variance in age and education. In these younger age cohorts, both SBP and DBP reactivity were significantly associated with mean and maximum IMT (for mean IMT, DBP $b=.033$, $P=.0002$, n=420, SBP $b=.0266$, $P=.003$, n=422; for maximum IMT, DBP $b=.039$, $P=.002$, n=420, SBP $b=.032$, $P=.011$, n=422) (see Table 1). For the older half of the sample (age, 58 and 64 years; n=469), these associations were not significant (blood pressure $b=.005$ to .017, $P>.18$ for SBP and DBP responses). There were no marginal or significant associations involving HR reactivity in either the

older or the younger half of the sample. Fig 1 illustrates the association between DBP reactivity and mean carotid IMT (carotid IMT scores adjusted for age and education) across each of the five quintiles for DBP response separately in the younger and older groups and across the entire sample. Although the pattern of associations between blood pressure reactivity and IMT appeared quite different in the younger and older groups, the interactions between age and reactivity were not significant (for DBP reactivity, $P=.124$ to .944).

To reduce the possible confounding effects of preexisting disease on cardiovascular reactivity, we selected a subsample of healthy and unmedicated subjects by excluding the following groups: (1) all subjects with a reported history of symptomatic coronary disease, stroke, hypertension, or diabetes at baseline or the 4-year follow-up; (2) all subjects with resting blood pressure in the hypertensive range (SBP >140 or DBP >90) at the follow-up; and (3) all subjects who indicated that they were taking cardiac medications, including any antihypertensive medications or antiarrhythmic drugs, at either baseline or follow-up. After selection of a healthy and unmedicated subgroup, we reexamined the data from the youngest half of the sample (135 subjects met all of the criteria). Significant effects of reactivity were retained for the mean IMT measure among these healthy subjects (for SBP reactivity, $b=.031$, $P=.036$, n=132; for DBP reactivity, $b=.037$, $P=.007$, n=132). In this healthy subgroup, there were no significant effects of reactivity on maximum IMT and no significant effects of HR reactivity on any of the carotid measures.*

In the two younger age cohorts, we also examined the relationship between measures of blood pressure reactivity and seven standard measures of cardiovascular risk that have been implicated in the development of carotid atherosclerosis (smoking status; LDL and HDL cholesterol, serum triglycerides, and fasting serum glucose; and SBP and DBP at rest). Each of these risk factor measures was collected at the 4-year follow up, along with the reactivity assessments. As shown in Table 2, blood pressure reactivity measures showed small but significant associations with each of the seven measures of cardiovascular risk. Hierarchical regression analyses (PROC GLM; Type III sums of squares[38]) in the younger half of the sample were used to regress each carotid thickness measure on reactivity after these standard risk factors were controlled, along with age and education. The adjusted effect associated with reactivity was somewhat smaller in the model with these nine covariates compared with the two-covariate model described above, suggesting that shared variance with these other risk factors accounts for some portion of the association between reactivity and carotid disease. The association between DBP reactivity and mean IMT remained statistically significant, however, after these risk adjustments ($b=.024$, $P=.011$ in the model with risk factor covariates versus $b=.033$, $P=.0002$ in the original model, as de-

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*The significant associations between blood pressure responsiveness and carotid disease measurements in the younger subjects were maintained, for the most part, when comparable baseline carotid ultrasound measures taken 4 years earlier were used as covariates in each model. Along with the analyses in the healthy subgroup, these results are consistent with the hypothesis that preexisting disease cannot entirely account for the association between reactivity and IMT in this sample.

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TABLE 1. Associations Between Cardiovascular Reactivity to Mental Stress and 4-Year Carotid Atherosclerosis, by Ultrasound, in 46- and 52-Year-Old Men With Age and Education as Covariates

	b*	CI†	P
DBP reactivity (n=420)‡			
Mean IMT	.033	.023 to .043	.000
Max IMT	.039	.024 to .053	.002
Plaque height	.016	.005 to .028	.107
SBP reactivity (n=422)			
Mean IMT	.027	.017 to .037	.003
Max IMT	.032	.018 to .047	.011
Plaque height	.016	.005 to .028	.110
HR reactivity (n=419)			
Mean IMT	−.010	−.019 to −.001	.225
Max IMT	−.015	−.028 to −.002	.188
Plaque height	−.008	−.018 to −.002	.380

*Covariate-adjusted unstandardized regression coefficients.
†Represent 75% confidence intervals for regression coefficients.
‡Missing data account for differences in sample size.

TABLE 2. Linear Correlations Between Blood Pressure Reactivity and Standard Cardiovascular Risk Factors in 46- and 52-Year-Old Men

	DBP Reactivity	SBP Reactivity
Smoking status	−.03	−.03
	(n=402)	(n=402)
LDL cholesterol	.09	.13†
	(n=424)	(n=426)
HDL cholesterol	−.10*	−.05
	(n=424)	(n=426)
Serum triglycerides	.16†	.10*
	(n=424)	(n=426)
Fasting glucose	.12*	.14†
	(n=426)	(n=428)
Resting SBP	.18‡	.23‡
	(n=426)	(n=428)
Resting DBP	.08	.16‡
	(n=426)	(n=428)

*P<.05, †P<.01, ‡P<.001.
Missing data account for differences in sample size for each analysis.

scribed above). This suggests that an important part of the reactivity-IMT association cannot be entirely accounted for by other major predictors of atherosclerosis. Table 3 presents the standardized regression coefficients associated with each of the risk factors covariates, for the purpose of comparing the relative magnitude of effect associated with each. As can be seen, DBP reactivity, smoking, and LDL cholesterol are roughly equivalent in terms of their independent associations with mean IMT in this sample. The association between DBP reactivity and maximal IMT was only marginally significant in these analyses, and none of the SBP and HR reactivity effects were significant after the introduction of the additional covariates.

Discussion

We have shown that blood pressure reactivity to mental stress is positively associated with ultrasound measures of carotid artery wall thickness, a marker of atherosclerosis, in a sample of middle-aged Finnish men. Our data suggest an additional 0.02 to 0.03 mm of carotid artery thickness for every mm Hg of stress-related blood pressure responsiveness, with reactivity carrying a level of risk of the same order of magnitude as that associated with smoking or elevated LDL cholesterol in this sample. These associations are significant in the group as a whole, but there is no significant relationship between reactivity and disease in the subjects over age 55 in the sample. Although cross-sectional, these findings may not be entirely accounted for by any effects of preexisting disease on cardiovascular dynamics: In subjects under 55, significant effects remain among those who were completely unmedicated and asymptomatic at the time of testing. In addition, the results cannot be explained in terms of established risk factors for cardiovascular disease because some of the effects remain significant after adjustment for traditional indices of disease risk.

This is the first study to examine the association between standardized measures of cardiovascular reactivity and quantitative assessment of carotid atherosclerosis in a population sample. We used an extensive testing protocol for assessing individual differences in cardiovascular reactivity in this study, a procedure that has been shown to produce reproducible results in this

as well as previous samples. The use of noninvasive measures of carotid atherosclerosis allowed us to assess the extent of disease in symptomatic as well as asymptomatic subjects. These carotid measures have been previously validated as markers of atherosclerosis[25-27] and as predictors of future cardiovascular events. Indeed, in a previous report from the KIHD sample, each incremental 0.1 mm of carotid IMT was prospectively associated with an 11% increased risk for acute myocardial infarction across a 3-year follow-up period,[15] a finding that lends plausible clinical significance to the current results.

The reactivity-atherosclerosis association shown in this sample was quite strong for subjects younger than age 55, but it was attenuated in the older two age cohorts in the sample. There are at least four possible explanations for these apparent age-related differences in the significance of reactivity-disease associations. First, given the high burden of cardiovascular disease in this population, characteristics that reduce susceptibility to disease risk may be more prevalent among older Finnish

TABLE 3. Associations Between Carotid IMT and DBP Reactivity With Cardiovascular Risk Factors as Covariates: Results of Hierarchical Regression Models in 46- and 52-Year-Old Men

	Prediction of Mean IMT		Prediction of Maximum IMT	
Source Variable	b*	P	b*	P
Age	.0014	.000	.0016	.002
Education	−.0009	.012	−.0013	.009
Triglycerides	−.0001	.799	−.0004	.454
Fasting glucose	−.0001	.850	.0000	.973
LDL cholesterol	.0009	.012	.0009	.065
HDL cholesterol	−.0002	.679	−.0004	.425
Resting SBP	.0019	.000	.0029	.000
Resting DBP	−.0006	.285	−.0013	.079
Smoking status	.0008	.022	.0010	.058
DBP Reactivity	.0009	.011	.0010	.059
Total df	10/382		10/382	
R² for model	.15		.12	

*Standardized regression coefficients.
n=393.

men compared with their younger counterparts ("survivor" effects[40]). Second, the influence of aging (eg, reductions in β-adrenergic activity) may reduce the relative importance of reactivity on the pathogenesis of cardiovascular disease over time.[40] Third, there may be differences in the meaning or determinants of reactivity measurements with age. For example, although reactivity measures may reflect sympathetic nervous system activation in the young, alterations in vascular distensibility[41] may play an increasing role as determinants of reactivity in the elderly. It should be noted that changes in the predictive value of risk factors at this age transition have been previously observed.[42,43] Indeed, results in this current sample suggest an age-related attenuation in the predictive value of cholesterol as well as reactivity, with LDL cholesterol concentrations here being significantly associated with mean IMT only in the subjects under age 55 (in age-adjusted models, $b=.026$, $P=.002$ for the youngest half of the sample) and no significant effects of LDL cholesterol shown among older men ($b=.009$, $P=.427$ for the older half of the sample). Fourth, these age-related differences may be attributable to chance (consistent with this interpretation, the age×reactivity interaction effect was not significant in this study). Further investigation is necessary to determine the processes by which age may modify the association between cardiovascular reactivity and atherosclerosis.

Our data suggest that excessive blood pressure reactivity is associated with a number of established coronary risk factors, including high concentrations of serum triglycerides and LDL cholesterol, low HDL cholesterol, and high blood glucose. These correlated risk factors, however, do not appear to entirely account for the association between reactivity and atherosclerosis. A number of possible pathways by which excessive sympathoadrenal activation may uniquely contribute to the pathogenesis of coronary heart disease have been described previously.[1] For example, frequent and prolonged periods of hyperdynamic cardiovascular activity may promote mechanical injury to the endothelial lining of the coronary arteries,[9] a process that may foster coronary vasospasm[44] and the development of atherosclerotic plaque.[45] Alternatively, the neuroendocrine correlates of exaggerated reactivity (most notably, epinephrine, norepinephrine, and cortisol response) may contribute over time to lipid mobilization[46,47] or platelet aggregation,[48] each of which may exacerbate vascular injury or plaque development.[49]

The strongest form of the "reactivity hypothesis" implies that stressor exposure, as well as stress responsiveness, may contribute to SNS-mediated disease risk: To the extent that reactivity may play a causal role in the development of atherosclerosis, we might expect the association between reactivity and carotid disease to be strongest among those exposed to the most frequent or intense pressor episodes during daily life. Future research should be designed to evaluate this "diathesis-stress" model of disease pathogenesis[12,50] in human populations.

A number of limitations to this study should be acknowledged. First, the rates of cardiovascular events among Finnish men, the population used for this study, are among the highest in the world,[51] raising questions about the generalizability of these findings to lower-risk populations. The associations shown here were maintained, however,

within an unmedicated healthy subgroup with no obvious signs or symptoms of coronary disease. Second, the KIHD sample is entirely male and an ethnically homogeneous group; racial and gender differences in the prevalence of hypertensive and coronary heart disease[52,53] suggest that caution should be exercised in extending these results to more heterogeneous samples. Third, the limitations of the cross-sectional design used in the present report should also be acknowledged. Although measures were taken to enhance the interpretation of the results in the present report (subgroup analyses to reduce the influence of clinical disease or medication use, covariate adjustment for age to reduce the confounding influence of this factor), causal effects of reactivity on carotid disease cannot be inferred from this report. Prospective analyses adjusting for initial disease severity are required to establish the temporal precedence of reactivity differences as a risk factor or causal agent in the development of atherosclerosis.

It will also be critical to establish the independent predictive power of reactivity as a predictor of clinical end points in population samples. Data linking reactivity differences with clinical coronary disease end points have been reported,[54,55] although there have also been conflicting findings.[56] Continued follow-up data collection from the KIHD sample in the years ahead will permit us to draw more definitive conclusions about the potential role of exaggerated blood pressure reactivity to mental stress in contributing to atherosclerotic disease and the clinical implications of this association.

Acknowledgments

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