Exaggerated Blood Pressure Responses During Mental Stress Are Prospectively Related to Enhanced Carotid Atherosclerosis in Middle-Aged Finnish Men

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Background—Hemodynamic reactions to mental stress may contribute to atherosclerosis. We previously observed cross-sectional relationships between blood pressure reactions to a standardized stress battery and carotid intima-media thickness (IMT) in the Kuopio Ischemic Heart Disease (KIHD) study. These are the first prospective results on this relationship.

Methods and Results—Men from 4 age cohorts (42 to 60 years old at study onset) were challenged with a standardized mental stress battery, and heart rate and blood pressure reactions were assessed. Ultrasound measures of common carotid IMT were collected at this time and 7 years later as noninvasive markers of atherosclerosis. Data were collected from a sample of 756 men at both times. Systolic blood pressure reactions to mental stress at study onset were positively related to mean carotid IMT 7 years later (β=0.035, P=0.001, by blood pressure quartile, IMT=0.91, 0.93, 0.96, 1.00 mm) and to the progression of IMT (β=0.020, P=0.006, by blood pressure quartile, ΔIMT=0.08, 0.09, 0.11, 0.11 mm). Similar significant relations were shown for maximal IMT and plaque height. Diastolic blood pressure responses were less strongly related to carotid IMT than were systolic responses. Heart-rate responses were unrelated. Adjustment for standard risk factors did not substantially reduce the relation between systolic blood pressure reactivity and the progression of mean carotid IMT (standardized β=0.059, P=0.026), maximal carotid IMT (standardized β=0.084, P=0.006), or plaque height (standardized β=0.093, P=0.008).

Conclusions—The degree of systolic blood pressure reactivity to mental challenge is prospectively related to carotid IMT in middle-aged and older men, independent of known risk factors. **(*Circulation*. 2004;110:2198-2203.)**

Key Words: atherosclerosis ■ cardiovascular diseases ■ carotid arteries ■ risk factors ■ stress

The amplitude of cardiovascular reactions to laboratory stress/challenge tasks has been related to a number of cardiovascular diseases assessed concurrently with the reactions to stress (ie, cross-sectionally).[1,2] Less is known about whether cardiovascular reactions to stress relate to the development over time of cardiovascular diseases (ie, prospective relationships).[3] For coronary heart disease (CHD), "preclinical"[4] indexes that document cardiovascular disease before overt events, such as myocardial infarction, provide appropriate evidence. The use of such indexes is possible in widespread community samples, permits the assessment of the temporal development of disease, and in our case, lessens the interpretive problem of the impact of CHD on the capability of the heart and vasculature to respond to stress/challenge. Cross-sectional studies suggest that hemodynamic responsivity to stress relates to preclinical CHD indexes. In the present study, we question whether stress responsivity assessed in healthy participants predicts the subsequent incidence and progression of preclinical disease.

Carotid intima-media thickness (IMT) is an important preclinical measure of atherosclerotic vascular disease that has been strongly associated with CHD. Carotid artery wall thickness is correlated to the degree of systemic atherosclerosis[5,6] and angiographically determined coronary atherosclerosis,[7] and is further correlated with incidence and prevalence of myocardial infarction and stroke.[8–10]

We reported a cross-sectional association between the degree of blood pressure reactivity to laboratory challenges and carotid IMT in the population-based Kuopio Ischemic Heart Disease (KIHD) study.[11] Controlling for other risk factors and preexisting disease states, we found that blood-pressure responses to mental stress were significantly associated with mean and maximum IMT as well as plaque height.

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In the present study, we examine the 7-year progression of carotid artery atherosclerosis in the KIHD sample. This sample is larger and the follow-up period longer than important previous longitudinal examinations of the relationship of cardiovascular reactivity to subsequent carotid IMT.[12,13] Two reports from the same KIHD sample[14,15] demonstrated that high reactivity in combination with either low social class or high job demands related to carotid IMT changed within 4 years. Here, we report a direct influence of reactivity on carotid IMT with a standardized stress battery to elicit cardiovascular reactions; the previous reports used a single measure, blood pressure response in anticipation of bicycle exercise. The unique value of the hemodynamic reactions to the standardized stress battery is their established reproducibility across multiple samples.[2,16,17]

Methods

Participants

Participants were drawn from 4 cohorts of men 42, 48, 54, and 60 years old at initial testing. The men participated in KIHD, an epidemiological investigation sampling the community of Kuopio, Finland, and focusing on risk factors for cardiovascular disease in a relatively high-risk geographic region. Between 1984 and 1989, 2682 men were enrolled in KIHD. Details of this study have been reported previously.[18] The present report focuses on results from the standardized reactivity battery obtained at a 4-year follow-up examination conducted between 1991 and 1993 on 1038 participants who had undergone repeat carotid ultrasound assessments. Because of subject availability and scheduling constraints at the 4-year follow-up, only 901 of the 1038 men participated in the cardiovascular reactivity testing battery. This sample was somewhat younger and better educated and showed less disease at year 4 than did the subjects (n=137) who were not tested.[11] Between 1999 and 2001, 756 of these men participated in an 11-year follow-up, which included a carotid artery ultrasound examination. Loss between years 4 and 11 was accounted for by death or serious illness in 10% of the sample, refusal to participate further in 2.5%, and loss of contact with a remaining 3%. We compared selected demographic and health characteristics recorded in year 4 and found that participants in the 11-year follow-up were relatively younger, better educated, and healthier (ie, lower resting blood pressure, less smoking, higher LDL, and less reporting of disease) than were their counterparts who did not participate in the 11-year follow-up. Follow-up examinations were carried out during 2 days, 1 week apart, and consisted of a variety of biochemical, physiological, anthropometric, and psychosocial measures. Participants provided informed consent, and the Institutional Ethical Committee of the University of Kuopio approved the study protocol.

Carotid Atherosclerosis

The extent of carotid atherosclerosis was assessed by high-resolution B-mode ultrasonography of the right and left common carotid arteries (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. Ultrasound examinations were conducted by 1 of 4 trained sonographers and were performed with the subject lying supine after a 15-min rest period. Both assessments were obtained with a Biosound Phase 2 scanner (BiosoundEsaote) that was equipped with a 10-MHz annular array probe.[19] Details of the scanning procedures, reliability, and precision of measurement have been reported elsewhere.[19,20] Computerized analysis of videotaped ultrasound images via Prosound software (University of Southern California) was conducted with an edge-detection algorithm[21] permitting 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 right and left CCAs.

In the present study, we used 3 measures of IMT: mean IMT, the mean of all of the IMT estimates from the right and left CCAs; maximum IMT, the mean of the points of maximum thickness from the right and left CCAs; and plaque height, the average of right and left CCA measurements of plaque height, calculated as the difference between maximum and minimum thicknesses.

Standard Risk Factors

Blood samples were drawn from subjects after fasting and abstaining from smoking for 12 hours, abstaining from consuming alcohol for 3 days, and abstaining from taking analgesic medications for 7 days. Participants rested supine for 30 min, after which blood was drawn from them without the use of a tourniquet with 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 by both ultracentrifugation and precipitation. The cholesterol content of all lipoprotein fractions and serum triglycerides was measured enzymatically (ie, 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 precipitating the proteins with trichloric acetic acid. Smoking status was measured by self-report.

Cardiovascular Reactivity Testing

Individual differences in cardiovascular reactivity were assessed with an automated test battery comprising 4 standardized computer-based tasks, each 9 min long. These tasks required the use of a range of cognitive and psychomotor skills (memory task, reaction time task, tracing task) and a computerized version of the Stroop Color-Word Task.[2,22] Each task was preceded by a 9-min baseline (rest and recovery) period. The difficulty level of each task was adjusted after each trial to maintain a performance level of ≈60% success, which ensured a continuous and optimal level of challenge. This battery yielded stable estimates of individual differences in acute task-induced reactivity in a variety of US samples[16,17] and in a subsample of the KIHD sample that was retested 8 to 12 months after the initial assessment.[2]

Physiological measures included a 2-lead ECG, automated blood pressure (Dinamap Vital Signs Monitor, General Electric) from the dominant arm, cardiac output and peripheral resistance from Minnesota Impedance Cardiograph Model 304B (Surcom, Inc), and a photoelectric peripheral vascular pulse. Blood pressure measurements were taken every 90 seconds during the baseline and task periods. Impedance cardiography and pulse wave measurements were not substantially related to carotid IMT. The scoring and measurement systems associated with this task battery were described previously.[23]

Assessments for each cardiovascular parameter (ie, heart rate, systolic blood pressure, and diastolic blood pressure) were averaged separately across each 9-min rest period and each 9-min task period. The 4 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 to remove the slight linear relationships ($r<0.13$) between the response to each task and the level of performance (average difficulty level for each trial) achieved by the subject on the task. The resulting adjusted reactivity measures were standardized within each task and were averaged across tasks, which yielded a single performance-adjusted score for each subject for each cardiovascular parameter.

Analyses

The regression of blood pressure and heart rate responses on IMT was assessed by covarying only age and educational level (factors

TABLE 1. Mean Carotid IMT (SD) for KIHD Participants Completing Cardiovascular Reactivity Test Battery and Remaining in Follow-Up

Carotid Measure	Year 1	Year 4	Year 11
Mean IMT, mm	0.746 (0.154)	0.858 (0.182)	0.954 (0.229)
Maximum IMT, mm	1.007 (0.268)	1.290 (0.358)	1.387 (0.476)
Plaque height index difference, mm	0.370 (0.165)	0.640 (0.182)	0.563 (0.250)

n=756.

known to influence cardiovascular responses). This regression was then repeated adding IMT from the 4-year assessment as a covariate. The above analyses were repeated adding standard risk factors (ie, smoking status, LDL, HDL, serum triglyceride, fasting serum glucose, and resting systolic and diastolic blood pressures) as covariates. Finally, participants reporting no cardiovascular disease or cardiovascular medication use at the 4-year assessment were selected and the analyses were repeated.

Results

Carotid IMT

Mean and maximum carotid IMT and plaque height increased as would be expected between study onset and the 11-year follow-up. Table 1 presents mean carotid IMT measurements at intake and years 4 and 11 for participants with cardiovascular reactivity and carotid measurements at all 3 time points. All means are significantly different from one another between years of assessment as evaluated by dependent *t* test, including the unanticipated decrease in the carotid plaque height index between years 4 and 11.

Seven-Year Prospective Relations Between Reactivity and Carotid Measures

Enhanced blood pressure reactions to mental stress at year 4 related both to greater atherosclerosis at year 11 and to increase in atherosclerosis between years 4 and 11. Table 2 presents the results for all of the IMT measures. The columns on the left show the prediction of carotid indexes from the year 4 reactivity measures to the year 11 carotid measures without taking into account the carotid indexes at year 4. The year 4 carotid indexes are entered into the prediction equation (ie, examining progression by removing the influence of year 4 IMT values) in the columns on the right.

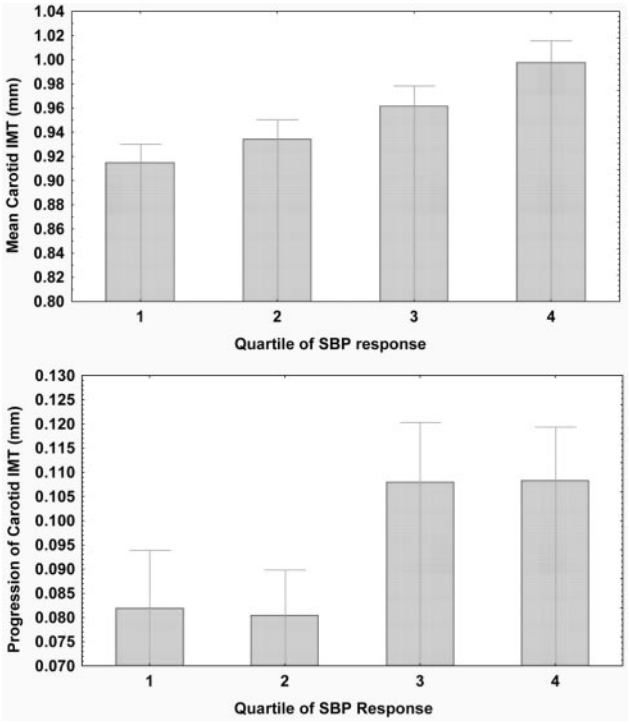
Both systolic and diastolic reactivity to challenge are prospectively related to mean and maximal carotid IMT and plaque height after adjusting for age and education. Heart-rate reactivity is not related to carotid measures. Blood pressure reactivity continued to be significantly related to all carotid measures when the measures taken at year 4 were covaried. Thus, the progression in the carotid measures is related to systolic and diastolic blood pressure reactivity. The exception to this summary is the marginally significant relationship ($P=0.081$) between diastolic blood pressure and mean carotid IMT with the year 4 IMT covaried. The Figure illustrates the results for the mean IMT at year 11 and the increase in mean IMT since year 4. Systolic blood pressure reactivity is split into quartiles and the mean or progression of carotid IMT value for each quartile is plotted.

Covarying known risk factors did not significantly modify the positive relationship between systolic blood pressure reactions to mental stress and carotid IMT or its progression. Table 3 shows the results of this analysis. As noted previously,[2] blood pressure reactivity is only modestly related to standard cardiovascular risk factors. Given this relationship, the independent prediction of carotid IMT from systolic blood pressure reactivity is reasonable. Diastolic blood pressure relationships were eliminated when risk factors were covaried; results only for systolic blood pressure responses are included in Table 3. The heart rate responses remained unrelated to the carotid measures.

TABLE 2. Cardiovascular Reactivity to Mental Stress at 4-y Evaluation Related to 11-y Carotid Atherosclerosis With and Without Covariate of 4-y Carotid Atherosclerosis (Age and Education Covaried)

	Basic Regression			Regression With 4-y Covaried		
	β	SE of β	*P*	β	SE of β	*P*
SBP reactivity, n=726						
Mean IMT	0.035	0.010	0.001	0.020	0.007	0.006
Max IMT	0.071	0.021	0.001	0.058	0.017	0.001
Plaque height	0.040	0.011	0.000	0.036	0.010	0.001
DBP reactivity, n=720						
Mean IMT	0.027	0.010	0.008	0.013	0.007	NS (0.081)
Max IMT	0.051	0.022	0.018	0.035	0.017	0.042
Plaque height	0.026	0.012	0.023	0.023	0.010	0.027
HR reactivity, n=727						
Mean IMT	−0.008	0.010	NS	...	...	...
Max IMT	−0.024	0.021	NS	...	...	...
Plaque height	−0.007	0.011	NS	...	...	...

β indicates unstandardized beta weight; SE, standard error of β; and *P*, probability β weight of this magnitude would occur by chance. No. of patients (n) reduced from 758 because of data missing in cardiovascular assessments.



Mean carotid IMT (SEM) at year 11 (top) and 7-y progression (bottom) plotted as function of quartile of systolic blood pressure reactivity at year 4.

Standardized β values are presented in Table 3 to permit direct comparison of the strength of the relationship between risk factors.

Interaction terms were added to both sets of analyses to determine whether blood pressure reactivity was relatively more predictive of carotid IMT within particular age cohorts in current or former smokers or in both current and former smokers. Repeating regression analyses with this term added, however, failed to show any significant influence for these interactions. The risk conferred by systolic blood pressure reactivity was not notably different between age cohorts or smokers relative to former smokers or nonsmokers.

TABLE 3. Prediction of Mean/Maximum Carotid IMT and Plaque Scores From SBP Reactivity

	Mean IMT		Maximum IMT		Plaque Score	
Source Variable	β	*P*	β	*P*	β	*P*
Age	0.056	0.047	0.077	0.016	0.085	0.020
Education	−0.041	0.103	−0.042	0.158	−0.059	0.085
Triglycerides	−0.047	0.099	−0.023	0.474	−0.004	0.916
Fasting glucose	0.025	0.344	0.016	0.598	0.015	0.671
LDL cholesterol	0.032	0.211	0.037	0.211	0.069	0.041
HDL cholesterol	−0.025	0.377	−0.038	0.232	−0.056	0.127
Resting SBP	0.024	0.511	0.056	0.189	0.090	0.066
Resting DBP	0.041	0.070	0.050	0.226	0.046	0.334
Smoking status	0.087	0.001	0.104	<0.001	0.139	<0.001
Previous carotid measure	0.699	<0.001	0.586	<0.001	0.384	<0.001
SBP reactivity	0.059	0.026	0.084	0.006	0.093	0.008
Total *df*	12 675	...	12 675	...	12 675	...
R^2 for model	0.583	...	0.453	...	0.268	...

Shows adjustment for cardiovascular risk factors and carotid measures taken 7 y earlier.

*Standardized β values.

A final analysis selected only those participants who did not report any cardiovascular disease (including hypertension), who did not take any cardiac medication, and whose blood pressure measures were in the reference range. Within this subsample of 195 participants, we found that systolic blood pressure responses at year 4 remained predictive of mean carotid IMT (unstandardized β 0.040, SE 0.016, $P<0.015$). By covarying year 4 carotid IMT, however, we reduced the significance of this relationship to $P<0.10$ (unstandardized β 0.020, SE 0.012).

Discussion

We have shown that systolic blood pressure reactivity to mental stress is positively and prospectively related to carotid IMT measures taken 7 years later. This relationship has never been demonstrated in a community sample with a standardized stress challenge with known test-retest reliability. We found that mean carotid IMT was 0.035-mm thicker for each standardized unit of mental stress–induced change of systolic blood pressure ($\approx$7 mm Hg of change in blood pressure). This prospective relationship remained significant when preexisting carotid artery values and recognized risk factors were taken into account. A 7-year progression of 0.02-mm thickening was associated with each standardized unit change in the systolic blood pressure response to mental stress, although as the Figure shows the progression may not be linear across the range of blood pressure reactions. Nonetheless, the degree of progression can be evaluated relative to risk estimates that were computed for the KIHD sample.[19] Each increment of 0.1 mm carotid IMT was prospectively associated with an $\approx$10% increase in risk for acute myocardial infarction across a 3-year follow-up period.[19,24] This comparison suggests that the magnitude of the association between blood pressure reactivity and carotid IMT may have public health significance, particularly when considered in conjunction with other independent risk factors.

The results of the present study add significant support to the hypothesis that cardiovascular reactivity is related to the progression of atherosclerosis. Some doubt remained after previous studies because of the size of the samples and their selection,[12,13] the absence of pre- and post-measures of IMT in 1 study,[13] and the use of a single-task estimate of reactivity.[14,15] In the KIHD sample, cardiovascular reactivity had been predictive only as it interacted with socioeconomic status or job strain.[14,15] The present results are, however, consistent with these studies in showing that blood pressure reactivity relates to carotid IMT measures. The present investigators, Everson and colleagues,[14] and Lynch and colleagues[15] used the KIHD sample of Finnish men, but Matthews and colleagues[13] studied women and Barnett and colleagues[12] used a mixed-gender sample. In short, the present evidence suggests that

blood pressure reactivity, even when assessed with different challenges, may be predictive of the progression of carotid IMT in both men and women. Future studies should evaluate the association between blood pressure reactivity and cardiovascular disease events or morbidity. None of the existing studies of these relationships has included a standardized cardiovascular reactivity battery with known reproducibility.

Blood pressure reactivity was associated with atherosclerosis independently of standard risk factors. A number of possible mechanisms could underlie the association of blood pressure reactivity and carotid IMT thickening[11,25,26] and are derived from the known influences of mental stress and the consequent effect of exaggerated hemodynamic responses to these stressors: (1) hyperdynamic circulatory changes may be injurious to the endothelial lining of coronary vessels,[27] (2) sympatheticoadrenal activation may contribute to vasospasm,[28] (3) adrenomedullary and adrenocortical responses may contribute to lipid mobilization, platelet aggregation, or both,[29,30] and (4) mental stress may induce immunologic responses that may have an impact on coronary artery plaque development.[31] A diathesis-stress model[11,26] suggests that these processes may be the most potent among individuals who not only show exaggerated reactivity but also experience chronic exposure to stress.[25]

The present study has several limitations. First, generalization is limited by geography and gender. Generalization to populations with typical risk profiles is limited because Kuopio is located in eastern Finland, an area with some of the highest cardiovascular event rates in the world.[32] We countered this possibility by showing that a subsample rated as having very good health demonstrated the same trends as the present overall sample, which suggests that our results may generalize to individuals with risk profiles that are less extreme than those that are typical of eastern Finland. The sample is composed solely of Finnish men, and the results may not generalize to women or individuals of different races, although, as noted above, Matthews and colleagues[13] found similar results in their study of healthy women. Second, these results are necessarily correlational. Factors co-occurring with individual differences in cardiovascular reactivity may play a causative role in the atherosclerotic process. We controlled for known risk factors and preexisting carotid IMT, but such statistical controls fall short of establishing causation. We can claim only that relative to our previous cross-sectional findings,[11] these prospective results provide further evidence of a role for cardiovascular reactivity in the atherosclerotic process. The 7-year progression of atherosclerotic disease was positively related to the degree of blood pressure reactivity to mental stress.

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