Stress-Induced Pulse Pressure Change Predicts Women’s Carotid Atherosclerosis

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Background and Purpose—Individuals who exhibit large increases in blood pressure and heart rate during mental stress may be at risk for accelerated atherosclerosis. This report evaluates the association between stress-induced hemodynamic responses and carotid atherosclerosis in 254 healthy postmenopausal women.

Methods—The magnitude of change in blood pressure and heart rate from rest to public speaking and mirror image tracing, two stressful tasks, was measured. Average intima-media thickness (IMT) and focal plaque in the common carotid artery, bulb, and internal carotid artery were measured with the use of duplex ultrasonography on average 2.3 years later.

Results—The average IMT was 0.77 mm, with a range of 0.60 to 1.37; 52.5% had at least one plaque. Correlational analysis showed that greater IMT was associated with greater pulse pressure change during mental stress ($r=0.17$, $P<0.01$). Statistical adjustments for possible confounders (age, hormone replacement therapy use, resting pulse pressure, smoking status, and triglyceride levels) did not alter the results. The plaque index was associated with greater pulse pressure change during the mirror image tracing task (odds ratio =1.47, $P=0.01$) for women with a plaque score of $\geq 2$ versus 1 or 0, adjusted for possible confounders.

Conclusions—Mental stress–induced pulse pressure changes may influence the development of early atherosclerosis in the carotid artery of women. Widening of pulse pressure during stress, as well as at rest, may be a marker of compromised compliance in the vessel wall. (Stroke. 1998;29:1525-1530.)

Key Words: atherosclerosis ■ carotid arteries ■ risk factors ■ stress, psychological ■ women

Individuals vary widely in the magnitude of their BP and HR response to mental stress. The magnitude of the response appears to be reliable across repeated assessments and does not simply reflect an emotional reaction, nor is it correlated with the amount of chronic stress in an individual’s life. Individuals who exhibit frequent and large cardiovascular responses might be prone to accelerated coronary atherosclerosis.1 In support of this hypothesis are the results from several small studies showing that coronary patients exhibit larger responses to mental stress than do healthy control subjects, and male coronary patients who are especially reactive to mental stress are more likely to have a subsequent clinical event.2 Furthermore, a recent prospective analysis showed that coronary patients in whom myocardial ischemia can be induced by mental stress are at higher risk of a coronary event during the subsequent several years than their counterparts.3 The results from animal research in which the cynomolgus monkey was used are consistent with the proposed atherogenic effect of reactivity to mental stress. Male and female animals that exhibit the largest HR response to an experimenter approaching them with a monkey glove have the greatest amount of histologically confirmed coronary atherosclerosis.4

Atherosclerosis in the carotid arteries is a marker of generalized atherosclerosis throughout the body, including the coronary arteries.5 Carotid arteries are an easily accessible site for B-mode ultrasound measurement of IMT as well as focal plaque. IMT is thought to be an early marker of diffuse atherosclerosis6–8 but may also represent thickening specifically due to elevated BP or both. Standard risk factors for CHD, eg, age, SBP and DBP, LDL cholesterol, history of CHD, smoking, and diabetes are associated with IMT9–11 even in healthy postmenopausal women.12,13 Furthermore, several population-based studies show that high levels of IMT in asymptomatic men and women predict new clinical CHD and stroke, even when investigators controlled statistically for major cardiovascular risk factors.14–16 Thus, ultrasound measures of carotid IMT and plaque can provide a test of the association of the cardiovascular risk associated with mental stress responses.

To our knowledge, only two studies related to the mental stress hypothesis used ultrasound measures of carotid atherosclerosis. In one study,4 a smaller change in HR during mental stress was associated with greater carotid plaque in a sample composed of hospital outpatients with high levels of risk factors or symptoms of vascular disease and community

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volunteers. In a subsample of unmedicated participants, progression of atherosclerosis was more substantial among those who showed greater SBP responses to stress. A second study showed that BP increases during mental stress were correlated with mean IMT and plaque height among Finnish men aged 46 to 52 years but not among older men. Subanalyses showed that the association persisted among younger men when investigators adjusted for standard CHD risk factors and among the subgroup of 135 unmedicated younger men with no symptomatic cardiovascular disease. The objective of the present study was to test whether healthy middle-aged women who exhibit large BP and HR increases during two mental stressors were at high risk for the development for early carotid atherosclerosis. The mental stress testing took place on average 2.3 years before the ultrasound measures, and study participants were free of medications that affected the cardiovascular system at the time of mental stress testing.

Subjects and Methods

Study Overview

From 1983 to 1984, 541 premenopausal women were enrolled in a study of changes in biological and behavioral characteristics of women as they experienced the menopause. They had been contacted by letter sent to randomly selected women living within certain zip codes in Allegheny County, Pennsylvania, and were subsequently interviewed by telephone regarding the following eligibility criteria: age 42 to 50 years; menstrual bleeding within the last 3 months; no surgical menopause; DBP <100 mm Hg; and no medications known to influence biological risk factors under study, eg, lipid-lowering, insulin, thyroid, estrogen, antihypertensive, and psychotropic medications. Sixty percent of eligible women volunteered. The University of Pittsburgh Institutional Review Board approved the project protocol, and all participants gave informed consent for their participation. Participant characteristics and recruitment procedures are described in detail elsewhere.

All women completed a baseline examination and then reported their menstrual status monthly. When women reported that they had stopped menstruating and/or had taken HRT for 12 months, they were considered postmenopausal; they were reevaluated at that time and at 2.5, and 8 years after menopause. Starting in September 1993, the carotid ultrasound measures were added to the protocol for women who were evaluated at 5 or 8 years after menopause.

Participants

Starting in March 1991, women were administered the mental stress protocol. Two hundred ninety-four women who completed mental stress testing previously and who completed the fifth or eighth year examination underwent the carotid ultrasound protocol as of March 1995. An additional 98 women had mental stress testing but not carotid ultrasound protocol at that point: 1 woman died; 5 declined participation; 3 moved out of the area; and 89 women were ineligible because they were not at least 5 years past the menopause. Of the 294, 40 women were taking medications known to influence the cardiovascular system at the time of the mental stress testing (eg, β-blockers) and were excluded from analysis.

Mental Stress Protocol

Embedded in the larger clinical evaluation was the mental stress protocol. SBP, DBP, and HR were monitored with an IBS model SD-700A automated BP monitor (Industrial and Biomedical Sensors Corp) with a standard occluding cuff placed on the participant’s nondominant arm. It employs a low-frequency sensor mounted on the cuff to detect arterial wall motion and Korotkoff vibrations. Detection of Korotkoff vibrations, in addition to sounds, enables measurements of low levels of BP. The device automatically inflates and deflates at a rate that is preset from 1 to 6 mm Hg per heartbeat per second and indicates invalid readings due to factors such as movement artifacts and noise. Pediatric, adult, and obese cuffs were used according to the arm size of the participant. The device is connected with a Baumanometer mercury column to permit simultaneous BP readings. High correlations (0.99 and 0.93 for SBPs and DBPs, respectively; P<0.001) were obtained between BP measured manually and by the automated BP monitor for a single reading before the rest period at the beginning of the mental stress protocol.

Subjects rested quietly for the first 10 minutes of the testing. During this time the BP was measured three times—at 5, 7, and 9 minutes—to establish an average of resting baseline BP. Maximal inflation for the automatic BP cuff was then adjusted to a predetermined value, which was ≥50 mm Hg above the baseline SBP. The mirror image tracing task was then administered. During this task, subjects traced the outline of a star via a mirror image (direct vision of the star was blocked by a screen) as many times as possible in 3 minutes, and BP was measured at 30 and 120 seconds. The mirror image tracing task was chosen because it tends to elicit an increase in peripheral resistance and was used successfully in our previous studies of middle-aged women.

After a second rest period of 10 minutes with BP recorded at 6 and 8 minutes, participants were given instructions to prepare a speech on an assigned topic covering specific points. Participants were instructed to pretend that they had been shopping and were examining a wallet, when a plainclothes detective approached them and accused them of shoplifting. Their task was to prepare a speech defending themselves before a magistrate and include what they thought should happen to the plainclothes detective. Participants had 2 minutes to mentally prepare their speech, after which they delivered their speech for 3 minutes. The speech was recorded, and BP was measured at 30 and 120 seconds. The content of the speech was chosen because it worked successfully in other studies conducted in our laboratory with middle-aged women. The speech task elicits a strong β-adrenergic response and typically elicits the largest cardiovascular response in our battery of mental stress tasks.

Carotid Ultrasound Protocol

A Toshiba SSA-270A scanner equipped with a 5-MHz linear array imaging probe was used. Sonographers, who were blind to the mental stress testing, scanned the right and left common carotid artery, carotid bulb, and the first 1.5 cm of the internal and external carotid arteries. For each location, the sonographer imaged the vessel in multiple planes and then focused on the interfaces required to measure IMT and also on any areas of focal plaque. The best images were taped and later digitized for scoring. Trained readers measured the mean IMT across 1-cm segments of the near and far walls of the distal common carotid artery and the far wall of the carotid bulb and the internal carotid artery on both right and left sides. Measures from each location were then averaged to produce an overall mean value for the entire IMT; three women could not be scored for mean IMT because of missing data from at least one site. A computerized reading program developed for the Cardiovascular Health Study and modified in Pittsburgh was used. Readers also scored the ultrasound images for plaque in the proximal common artery, distal common artery, carotid bulb, internal carotid artery, and external carotid artery; one woman lacked a plaque score. Plaque was defined as a distinct area of hypercholesterogeneity and/or a focal protrusion into the lumen of the vessel. For each segment, the degree...
of plaque was graded as follows: 0 = no plaque; 1 = one small plaque <30% of vessel diameter; 2 = one medium plaque between 30% and 50% of the vessel diameter or multiple small plaques; 3 = one large plaque >50% of the vessel diameter or multiple plaques with at least one medium plaque. The grades were summed across right and left carotid arteries to create an overall measure of extent of focal plaque.

Reproducibility of IMT and the plaque index was assessed in five women who underwent two ultrasound examinations within 1 week. Each time the women were scanned by two separate sonographers, and each scan was scored by two readers. When we accounted for both sonographer and reader variation, the intraclass correlation was 0.86 for IMT and 0.96 for the plaque index.

Data Analysis

The last two measures of SBP, DBP, HR, and pulse pressure during the initial testing period, the two measures during the mirror image tracing task, and the two measures during the public speaking task were averaged within period or task. Baseline values were subtracted from task levels to yield individual task scores for illustrative purposes. To have a baseline-free measure of stress responses, baseline values were regressed onto each task level and standardized. Because mental stress measures are more reproducible when responses to individual tasks are summed, these standardized individual task residualized scores were summed.

Because the distribution of IMT was skewed, the IMT data were first transformed to yield a normal distribution. Then Pearson correlations between IMT and the summed standardized residual stress scores were calculated to evaluate the association of overall task reactivity and carotid disease. IMT scores for individual sites were not analyzed separately because of lower reproducibility of individual sites than for mean values across sites. Because mental stressors elicit different patterns of hemodynamic responses, the overall stress analysis was followed by correlational analyses for each stressor separately with the use of residualized scores.

Then the associations were evaluated by multiple regression by adjustment for age at the time of the ultrasound scan, use of HRT and baseline BP or HR at stress testing, ever-smoking status, and triglyceride levels at the time of the scan. Ever-smoking status, triglycerides, and BP were included because a separate report showed that these variables were the strongest independent predictors of IMT and plaque in 200 of the women included in the present analysis as well as in 292 of the 294 women who were candidates for the present analysis21; other risk factors, eg, total cholesterol or HDL cholesterol, were nonsignificant when the above variables were included.12 To illustrate the significant associations, women were categorized into four nearly equal groups according to the distribution of IMT scores, and the unadjusted task minus baseline mean values are presented.

Women were categorized into three groups: no plaque, plaque score of 1, and plaque score of ≥2. Then association of the plaque index and the residualized stress scores was evaluated by one-way ANOVA with tests for linear trend. With the use of logistic regression analyses, we then examined those variables that were significant in the ANOVA analyses independent of age, use of HRT, baseline BP or HR at stress testing, ever-smoking status, and triglyceride levels.

Results

Characteristics of Sample

The women in the analysis were almost all white, and a majority were currently married (Table 1). The women were relatively well educated, with approximately three fourths having at least some college. At the time of the mental stress testing, the mean age of the women was 55.7 years, with a range of 50 to 60 years; at the time of the ultrasound scan, the mean age of the women was 57.6 years, with a range of 52 to 62 years. A mean of 2.3 years separated the mental stress and ultrasound assessments, (median, 2.9 years; range, 0 to 5.3 years). Approximately 40% of the women were on HRT at the time of the mental stress protocol.

Because of eligibility criteria to enter the study in 1983, the women were relatively healthy in the present sample. In addition, the sample for analysis excluded 40 women who were on medication at the time of the mental stress testing because those medications would affect the magnitude of the stress-induced BP or HR response. In consequence, the remaining women described in this report can be considered healthy, without known clinical disease. The mean IMT of the sample was 0.77, with a range of 0.60 to 1.37. Approximately half the women had at least one plaque, with 25% having a plaque index of 1 and 27% having a plaque index of ≥2. The Spearman correlation between mean IMT and the plaque index was r = 0.49, P < 0.001.

The mean baseline BP and HR of the sample were in the normal range (Table 2). The magnitude of the changes in BP and HR is comparable to that obtained in our laboratory among middle-aged women, although the increase in SBP during mirror image tracing is somewhat greater than previously observed. As in other studies, the increase in SBP and

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<tr>
<th>TABLE 1. Sample Characteristics (n=254)</th>
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<tbody>
<tr>
<td>Characteristic</td>
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<tr>
<td>White, n</td>
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<tr>
<td>Married, n</td>
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<tr>
<td>Education, n</td>
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<tr>
<td>High school or less</td>
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<td>Some college</td>
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<td>Advanced</td>
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<tr>
<td>Hormone users at time of mental stress testing, n</td>
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<td>Plaque index, n</td>
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<tr>
<td>0</td>
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<tr>
<td>1</td>
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<td>≥2</td>
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<td>Age at time of mental stress testing, y*</td>
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<td>Age at time of ultrasound scan, y*</td>
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<td>IMT, mm*</td>
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*Values are expressed as mean ± SD.

<table>
<thead>
<tr>
<th>TABLE 2. BP and HR During Mental Stress Testing</th>
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<tr>
<td>Measure</td>
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<tr>
<td>-----------------------------------------------</td>
</tr>
<tr>
<td>Baseline</td>
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<tr>
<td>Increase during mirror tracing</td>
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<td>Increase during speech</td>
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Values are mean ± SD.
HR was greater during the public speaking task than during the mirror image tracing task. This pattern is thought to reflect a greater myocardial response during public speaking and a greater resistance response during mirror image tracing. The Pearson correlations between the two task levels, adjusted for the common baseline level, were 0.55, 0.24, 0.39, and 0.38 ($P<0.01$) for SBP, DBP, pulse pressure, and HR, respectively.

### Associations Between Stress-Induced Cardiovascular Responses and Early Carotid Disease

Greater IMT was associated with higher resting SBP and pulse pressure and lower resting HR (Table 3). The magnitude of the increase in pulse pressure during both tasks combined (and adjusted for baseline pulse pressure) was positively related to IMT (Figures 1 and 2) both because of a nonsignificant positive association of stress-induced SBP as well as nonsignificant negative association of stress-induced DBP. An examination of the associations separately by task showed that pulse pressure residualized change was positively associated with IMT and DBP change was negatively associated with IMT during the mirror image tracing task.

Multiple regression analysis adjusted for potential confounders showed that IMT was correlated with the pulse pressure during the combined tasks ($b=0.18, P<0.006$) and during the mirror image tracing task ($b=0.22, P<0.0006$). In addition, IMT was correlated with DBP during mirror image tracing ($b=-0.14, P=0.03$).

Plaque index was not related to the residual scores summed across tasks but was associated with decreasing DBP residualized scores ($P<0.02$) and increasing pulse pressure residualized scores ($P=0.02$) during mirror image tracing (Figure 3). Logistic regression showed that after adjustment for potential confounders, relative to women with a plaque score of 1 or 0, women with a plaque score of $\geq 2$ were at risk for a lower DBP residual mirror image tracing score ($B=0.32, P<0.04$; odds ratio = 1.37; confidence interval, 1.02 to 1.84) and for a higher pulse pressure residual mirror image tracing score ($B=0.38, P=0.01$; odds ratio = 1.47; confidence interval, 1.09 to 1.97).

### Discussion

This study sought to evaluate the hypothesis that stress-induced changes in cardiovascular responses were related to early carotid atherosclerosis in middle-aged women. The sample entered the study in 1983 to 1984 free of hypertension, insulin-dependent diabetes, and other diseases requiring long-term pharmacological treatment and, at the time of stress testing starting in 1993, were free of medications known to influence the cardiovascular system. The stress testing was administered several years before the ultrasound testing and included measures of BP and HR during the mirror image tracing task and public speaking. Results showed that baseline measures of SBP and pulse pressure were related to IMT, a finding previously reported in the present group. More importantly for our purposes, IMT was related to the magnitude of change in pulse pressure summed across tasks, independent of age, use of HRT, baseline measures of pulse pressure, smoking status, and triglyceride levels. Independent of the same covariates, the plaque index was related to pulse pressure change but only during the mirror image tracing task. Taken together, these findings suggest that a large pulse pressure response to mental stress is an important predictor of subsequent IMT.

### Figure 1

Mean pulse pressure change scores during mirror image tracing task of women partitioned into four nearly equal groups according to the distribution of IMT scores.

### Figure 2

Mean pulse pressure change scores during speech task of women partitioned into four nearly equal groups according to the distribution of IMT scores.
It is thought that stress-induced cardiovascular responses lead to increased atherosclerosis because of changes in shear stress and catecholamine release, which damage the endothelium and allow the infiltration of lipids and macrophages into the intima, leading to intimal thickening and the development of fibrous plaque. However, given that stress-induced SBP and HR change scores were not associated with subsequent IMT or plaque index, it is more likely that other factors played a role in this sample of relatively healthy, middle-aged women.

Pulse pressure, which was associated with subsequent IMT and plaque index during mirror image tracing, is determined approximately by the ratio of stroke volume output to compliance of the arterial tree, which is, in turn, affected by change in mean arterial pressure and pathological changes affecting the distensibility of the arterial wall. As arterial walls age, they lose much of their elasticity and muscular tissue, and sometimes these are replaced by fibrous tissue and plaque that cannot stretch. In consequence, compliance of the arterial system is reduced, which causes the arterial pressure to rise greatly during systole and to fall greatly during diastole as the blood runs off from the arteries to the veins. Furthermore, aging of the arteries, especially in the presence of high BP, leads to abnormal response to endothelium-dependent vasodilator, such as acetylcholine. Individuals who exhibit frequent increases in pulse pressure during stress may accelerate the rate of aging in their arterial tree. On the other hand, it is also possible that prevalence of diffuse disease or focal plaque may lead to an increase in pulse pressure both during rest and during stress, even after statistical adjustment for stress levels. We cannot discount this possibility because carotid ultrasound measures were added to the study protocol after the inclusion of mental stress measures. Future research on progression of carotid disease will allow more definitive conclusions about the direction of effect in healthy postmenopausal women.

Although the findings from this study point to the importance of stress-induced changes in pulse pressure for early carotid atherosclerosis in women, they do not preclude the importance of stress-induced increases in BP, cardiac output, or catecholamine release in the early development of atherosclerosis. The sample is unique, ie, middle-aged women with low levels of risk factors and no frank clinical disease at the time of stress testing. Perhaps in individuals with high levels of risk factors or overt disease, as studied elsewhere, these indicators of sympathetic activation may be more critical. Stress-induced sympathetic responses may be more important in men, who develop atherosclerosis earlier than women. The associations between pulse pressure and carotid disease were stronger for the mirror image tracing task, a task validated to elicit a vasoconstrictive response, than for the speech task, a task validated to elicit a β-adrenergic response. This could be interpreted as suggesting that pulse pressure responses during stimuli that normally elicit a vasoconstrictive response are especially prognostic. Because the tasks were administered in fixed order as a result of being embedded in a long, complex epidemiological protocol, it is also possible that the effects were stronger for the mirror image tracing task because that task was administered first and was more stressful to the participants. Arguing against that explanation is that the magnitude of change was smaller during the mirror image tracing task than during the speech task. Nonetheless, this study demonstrates the importance of stress-induced changes in pulse pressure in predicting the development of early atherosclerosis in the carotid artery. Widening of pulse pressure during stress, as well as at rest, may be a marker of compromised compliance in the vessel wall indicative of heightened risk in women.

Acknowledgments

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