Stress-Induced Blood Pressure Reactivity and Silent Cerebrovascular Disease

Shari R. Waldstein, PhD; Eliot L. Siegel, MD; David Lefkowitz, MD; Karl J. Maier, PhD; Jessica R. Pelletier Brown, BA; Abraham M. Obuchowski, MD; Leslie I. Katzel, MD, PhD

Background and Purpose—Exaggerated blood pressure (BP) responses to mental stress, an index of autonomic dysregulation, have been related to enhanced risk for stroke. This study examined cross-sectional relations of stress-induced BP reactivity to silent cerebrovascular disease assessed by magnetic resonance imaging (MRI) in healthy older adults.

Methods—Sixty-seven nondemented, community-dwelling older adults (ages 55 to 81; 75% male) free of major medical, neurological, or psychiatric disease, engaged in: (1) clinical assessment of resting systolic and diastolic BP; (2) assessment of systolic and diastolic BP responses to 3 laboratory-based mental stressors; and (3) MRI. MRIs were rated for small silent infarcts (≥3 mm), infarct-like lesions (<3 mm), and periventricular and deep white matter hyperintensities (WMH).

Results—After adjustment for age, gender, resting clinic BP, and fasting glucose levels, higher systolic BP reactivity was associated with an increased number of small silent infarcts (r²=0.14; P=0.004) and greater severity ratings of periventricular (r²=0.08; P<0.04) and deep WMH (r²=0.06; P<0.05). Higher diastolic BP reactivity was similarly associated with an increased number of small silent infarcts (r²=0.08; P<0.04), and greater severity ratings of periventricular (r²=0.08; P<0.04) and deep WMH (r²=0.11; P=0.009).

Conclusions—These results indicate that greater stress-induced BP reactivity is associated with enhanced silent cerebrovascular disease on MRI in healthy asymptomatic older adults independent of resting BP levels. Exaggerated stress-induced BP reactivity warrants further examination as a potential biobehavioral risk factor for cerebrovascular disease. (Stroke. 2004;35:1294-1298.)

Key Words: blood pressure ■ cerebrovascular disorders ■ magnetic resonance imaging ■ stress

Silent cerebrovascular disease detected on magnetic resonance imaging (MRI) is prevalent among community-dwelling older adults. Silent brain infarction (lesion size >3 mm) was noted in 28% of stroke-free participants in the Cardiovascular Health Study (CHS; n=3647) and 20% of participants in the Rotterdam Scan Study (n=1077). In addition, evidence of white matter disease was found in 83% of stroke-free CHS participants older than 64 years. Silent cerebrovascular disease is a clinically significant public health problem with demonstrated prognostic significance for future cognitive decline, progression to dementia, and stroke.4–7

Higher levels of resting blood pressure (BP) and hypertension have been associated with a greater prevalence of silent brain infarction and white matter disease.2,3,8,9 In addition, various BP indices that reflect autonomic dysregulation have been related to silent cerebrovascular disease in normotensive and hypertensive older adults. In this regard, individuals with abnormal diurnal BP variation on ambulatory monitoring have enhanced silent cerebrovascular damage. Specifically, among a group of elderly hypertensives, those who displayed a marked decrease in nocturnal BP, labeled extreme dippers, and nondippers displayed altered heart rate variability and had significantly greater prevalence of silent brain infarction than did dippers.10,11 Mean ambulatory BP has also shown a superior relation to silent brain infarction and periventricular white matter hyperintensities (WMH) than resting clinic pressures among older normotensives and hypertensives.12 In addition, older adults (90% normotensive) with the highest severity ratings of WMH had higher ambulatory BP and greater BP variability than those with lesser severity ratings.13 Finally, exaggerated BP responses to orthostatic manipulation have been associated with a greater prevalence of silent brain infarction in elderly hypertensives.14

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From the Department of Psychology (S.R.W., K.J.M., J.R.P.B.), University of Maryland, Baltimore County; Division of Gerontology, Department of Medicine (S.R.W., L.I.K.), and Department of Diagnostic Radiology (E.L.S., D.L., A.M.O.), University of Maryland, School of Medicine; and Geriatric Research Education and Clinical Center (S.R.W., L.I.K.), and Department of Diagnostic Radiology (E.L.S.), Baltimore Veterans Affairs Medical Center, Baltimore, MD.
Correspondence to Dr Shari R. Waldstein, Department of Psychology, University of Maryland, Baltimore County, 1000 Hilltop Circle, Baltimore, MD 21250. E-mail waldstei@umbc.edu
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Exaggerated BP responses to mental stress provide another index of autonomic dysregulation, reflecting activation of the sympathetic nervous system, vagal withdrawal, or both. Greater BP responses to mental stress have been related prospectively to increased risk for hypertension, coronary heart disease, and stroke. Prospective and cross-sectional associations between exaggerated BP reactivity and greater extent of carotid atherosclerosis (measured by Duplex ultrasound) have also been noted. However, to our knowledge, the relation of stress-induced BP reactivity to silent cerebrovascular disease remains unevaluated. Accordingly, the present study examined the cross-sectional relation of stress-induced BP reactivity with indices of silent cerebrovascular disease—silent brain infarction and white matter disease—assessed by MRI in healthy older adults.

Materials and Methods

Subjects

Subjects were 67 consecutive, healthy, community-dwelling older adults (ages 55 to 81; 75% male) who had participated (at the time of data analysis) in an ongoing investigation of cardiovascular risk factors, neuroimaging, and cognitive function. These stroke-free volunteers were recruited from the Baltimore Veterans Affairs Medical Center (B-VAMC), the Geriatric Research Education and Clinical Center at the B-VAMC, and by advertisement in the local community. Exclusionary criteria were history or clinical evidence of cardiovascular disease (except mild-to-moderate hypertension), diabetes mellitus, other major medical disease (eg, renal, hepatic, pulmonary), neurological disease, stroke, dementia (Mini-Mental Status Examination score < 24), psychiatric disorder, heavy alcohol use (> 14 drinks per week), or medications affecting central nervous system function. Thirty-eight percent of participants had a history of physician-diagnosed hypertension. Participants taking antihypertensive medications were weaned for at least 2 weeks before BP reactivity testing. Sample characteristics are depicted in Table 1. All participants provided informed consent according to the guidelines of the Institutional Review Boards of University of Maryland, Baltimore and University of Maryland, Baltimore County.

Method

Participants received a comprehensive medical evaluation including history, physical examination, blood chemistries, graded exercise treadmill test with measurement of maximal aerobic capacity (VO2 max), and an oral glucose tolerance test. Resting BP and fasting lipids and glucose were assessed while participants were taking their routine medications. Clinical assessment of BP was performed on 2 to 3 occasions with patients in a seated position using an automated vital signs monitor (Dinamap Model 1846SX; Critikon) and appropriate sized occluding cuff. Readings were averaged to yield an estimate of participants’ resting clinic systolic and diastolic BPs. Total plasma cholesterol and glucose levels were determined enzymatically.

On a separate day, participants completed a psychophysiological assessment. Persons taking antihypertensive medications had them withdrawn under medical supervision for 2 weeks (> 5 half-lives) before this visit. During the session, BP was monitored while subjects engaged in three 3-minute experimental tasks in fixed order. Each task was preceded by a 10-minute rest period, the last 4.5 minutes of which served as a baseline period for data collection. The tasks (anger recall, speech/role play, and mental arithmetic) were chosen to evoke negative emotions. Anger recall involved detailed description of a personally relevant anger-provoking incident that was identified by the participant. During speech/role play, subjects were presented with a hypothetical interpersonal scenario involving the mistreatment of a close relative by the night staff of his or her nursing home, and then delivered a speech to a confederate responsible nursing home administrator. Speech delivery was interrupted frequently with challenging statements, resulting in a provoking role-played interchange. For mental arithmetic, participants engaged in serial subtraction by 7 (or 3, depending on performance) from 3-digit numbers. Participants responded aloud while being prompted to work faster, make fewer mistakes, and try harder.

Systolic and diastolic BP were measured oscillometrically at 90-second intervals during baseline (rest) periods and at 60-second intervals during task periods with an automated vital signs monitor (Dinamap Model 1846SX). Mean systolic and diastolic BP values were computed from the 3 readings obtained during each respective baseline and task period. The 3 baseline means were averaged to yield an overall index of resting systolic and diastolic BPs. Baseline-adjusted (residualized) change scores were computed for systolic and diastolic BP responses to each laboratory task using the immediately preceding baseline (rest) period. Residualized change scores provide a means of quantifying cardiovascular responses to mental stress after statistically removing the influence of the respective resting baseline measures. These baseline-corrected change scores were then collapsed across the 3 tasks to yield single indexes of systolic and diastolic BP reactivity. Collapsing cardiovascular reactivity scores across tasks has been recommended to improve measurement reliability.

MRI was performed using a Picker Edge 1.5 Tesla scanner. The imaging protocol consisted of sagittal T1 (repetition time, echo time, thickness, matrix, field of view, and averages were 465, 14, 6 mm, 192x256, 24, 1, respectively) axial T1 (600, 14, 5 mm, 192x256, 23, and 2), and dual-contrast proton density/T2 (3500, 150 and 96, 5 mm, 192x256, 23 and 2). Images were rated blindly for silent brain infarction by 2 board-certified neuroradiologists (D.L., A.M.O.) using modified CHS criteria. Infarcts displayed abnormal signal in a vascular distribution, but no mass effect. Infarcts of the deep white matter, cortical gray matter, deep nuclear regions, and capsule were bright on proton-density–weighted and T2-weighted images compared with normal gray matter and were isointense or hypointense on T1-weighted images. The CHS requirement for T1 hypointensity for deep white matter infarcts was not used, because this would have resulted in sole coding of cystic lacunes, which were a small minority of the infarcts scored. As per CHS criteria, infarcts were defined as ≥ 3 mm in size and infarct-like lesions as < 3 mm in size.1 Periventricular and deep WMH were rated using the published, and extensively used, method of Fazekas25–30 as follows: periventricular hypertensities: 0 = absent, 1 = cap, 2 = band, and 3 = irregular hypertensity extending into the deep white matter; deep

### Table 1. Sample Characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Mean (SD) or %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (y)</td>
<td>67.7 (63)</td>
</tr>
<tr>
<td>Education (y)</td>
<td>16.2 (3.1)</td>
</tr>
<tr>
<td>Gender (% male)</td>
<td>75</td>
</tr>
<tr>
<td>Race (% white)</td>
<td>88</td>
</tr>
<tr>
<td>Body mass index (kg/m²)</td>
<td>28.1 (3.5)</td>
</tr>
<tr>
<td>VO₂max (L/min)</td>
<td>2.1 (0.6)</td>
</tr>
<tr>
<td>Resting clinic SBP (mm Hg)*</td>
<td>137.5 (19.0)</td>
</tr>
<tr>
<td>Resting clinic DBP (mm Hg)*</td>
<td>76.1 (8.9)</td>
</tr>
<tr>
<td>Total cholesterol (mmol/L)</td>
<td>4.9 (0.8)</td>
</tr>
<tr>
<td>LDL cholesterol (mmol/L)</td>
<td>3.1 (0.7)</td>
</tr>
<tr>
<td>HDL cholesterol (mmol/L)</td>
<td>1.3 (0.4)</td>
</tr>
<tr>
<td>Triglycerides (mmol/L)</td>
<td>1.2 (0.5)</td>
</tr>
<tr>
<td>Fasting glucose (mmol/L)</td>
<td>5.6 (1.2)</td>
</tr>
<tr>
<td>2-Hour glucose (mmol/L)</td>
<td>8.4 (3.4)</td>
</tr>
</tbody>
</table>

*Clinic BP includes medicated values for the 18 participants using antihypertensive medication.

Systolic BP indicates systolic blood pressure; DBP, diastolic blood pressure; LDL, low-density lipoprotein; HDL, high-density lipoprotein.
TABLE 2. Prevalence (%) of MRI Abnormalities as a Function of Gender and Age

<table>
<thead>
<tr>
<th>MRI Abnormality</th>
<th>Men</th>
<th>Women</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Younger (70 y)</td>
<td>70 y or Older</td>
</tr>
<tr>
<td>Periventricular WMH</td>
<td>76</td>
<td>74</td>
</tr>
<tr>
<td>Deep WMH</td>
<td>79</td>
<td>83</td>
</tr>
<tr>
<td>Infarct</td>
<td>55</td>
<td>54</td>
</tr>
<tr>
<td>Infarct-like lesion</td>
<td>17</td>
<td>26</td>
</tr>
</tbody>
</table>

Results

Fifty-five percent of participants displayed silent brain infarction, and 19% had infarct-like lesions (Table 2 shows prevalence by gender and age). Participants had an average of 3.9 (SD=7.4) infarcts (range=0 to 31) and 0.7 (SD=1.4) infarct-like lesions (range=0 to 7). Evidence of periventricular and deep WMH was apparent in 73% and 75% of the sample, respectively. Interrater reliability for MRI coding was indexed as r=0.90 for infarcts and r=0.72 for infarct-like lesions. WMH were coded as present if hyperintense on T2-weighted and proton-density-weighted images. Punctate lesions seen only on T2 but not proton-density were generally considered to be perivascular spaces and were not counted.

TABLE 3. Blood Pressure Reactivity: Arithmetic Change from Baseline to Task Level

<table>
<thead>
<tr>
<th></th>
<th>Anger Recall Mean (SD)</th>
<th>Speech/Role Play Mean (SD)</th>
<th>Mental Arithmetic Mean (SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>SBP (mm Hg)</td>
<td>24.4 (13.6)</td>
<td>28.8 (16.3)</td>
<td>11.8 (1.4)</td>
</tr>
<tr>
<td>DBP (mm Hg)</td>
<td>13.0 (7.7)</td>
<td>15.5 (9.1)</td>
<td>7.9 (7.9)</td>
</tr>
</tbody>
</table>

Individual differences in stress-induced BP reactivity, assessed in laboratory settings, have been shown to be stable over time and to be generalizable to everyday situations. One may therefore presume that such pronounced stress-
induced BP responses occur repeatedly in daily life. Given the known relation of higher resting BP to silent cerebrovascular disease, it is reasonable to theorize that repeated episodes of intermittent hypertension caused by mental stress, particularly in older persons (some hypertensive) with potentially poor autoregulatory function, may enhance cerebrovascular damage. For instance, the largest systolic and diastolic BP changes noted in the present study were changes of 80 and 47 mm Hg, respectively with peak systolic and diastolic BPs (task averages) of 231 and 119 mm Hg, respectively. Indeed, the magnitude of BP responses noted in this investigation placed 65% to 75% of individuals within the range of systolic hypertension across the 3 tasks, and 13% to 21% of individuals within the range of diastolic hypertension during the tasks. It is possible that the hemodynamic mechanisms associated with such pronounced BP changes are involved in inducing periods of cerebral hyperperfusion. Hemodynamic contributions to silent cerebrovascular disease have previously been suggested, and recent findings indicate a strong relation between impaired vasomotor reactivity, assessed by CO2-enhanced transcranial Doppler, and greater presence and extent of periventricular and deep WMH. It is also conceivable that pronounced stress-induced BP responses may be associated with vasospasm induced by impaired autoregulation, which may further exacerbate cerebrovascular damage.

Limitations of the present investigation include the cross-sectional design. In this regard, it is feasible to posit that individuals with greater cerebrovascular damage have exaggerated BP reactivity via disturbance of sympathetic outflow. Future longitudinal designs must address whether enhanced BP reactivity precedes silent cerebrovascular disease, because it has been shown to precede stroke and other vascular diseases. Another possibility is that higher BP reactivity and greater cerebrovascular damage may be attributable to an unassessed third variable. Other study limitations include the small, relatively homogeneous, and nonrepresentative sample that was largely male and white, thus limiting the generalizability of these findings. In addition, because of the limited sample size, we were unable to explore potential interactions among predictor variables. Finally, it is notable that a greater prevalence of silent infarction was detected in our investigation as compared with the CHS and Rotterdam studies. This discrepancy was likely explained predominantly by our use of modified CHS coding criteria, which resulted in superior detection of deep white matter infarction. In addition, both CHS and Rotterdam were population-based investigations, whereas we specifically recruited participants, many of whom were overweight or obese, for a study of cardiovascular risk factors. Our sample may therefore have included individuals with relatively greater cardiovascular risk as compared with the general population.

To conclude, results of the present study demonstrate for the first time to our knowledge an association between enhanced stress-induced BP reactivity and greater silent cerebrovascular disease assessed by MRI, including silent brain infarction and periventricular and deep white matter disease. Stress-induced BP reactivity warrants further examination as a potential biobehavioral risk factor for cerebrovascular disease.

**Acknowledgments**

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