Stress responses and baroreflex function in coronary disease

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Deley G, Lipman RD, Kannam JP, Bartolini C, Taylor JA. Stress responses and baroreflex function in coronary disease. J Appl Physiol 106: 576–581, 2009. First published December 18, 2008; doi:10.1152/japplphysiol.91053.2008—Exaggerated pressor responses to mental stress in patients with coronary artery disease (CAD) are associated with increased risk for subsequent cardiovascular events. The integrated baroreflex gain and its mechanical and neural component were estimated and then related to the blood pressure and heart rate responses to simulated real-life stressors: mental arithmetic and public speaking. Eighteen healthy individuals (aged 61 ± 8 yr) and 29 individuals with documented CAD but no other comorbidities (aged 59 ± 8 yr) were studied. Heart rate and blood pressures were continuously assessed before, during preparation for, and during performance of a math task and a speech task. The assessment of beat-to-beat carotid diameters during baroreflex engagement was used to estimate the integrated baroreflex gain and its mechanical and neural component. The CAD subjects demonstrated significantly greater increases in heart rate and blood pressures for the performance of the speech task. However, there were no group differences in integrated cardiocovelar baroreflex gain or either mechanical or neural baroreflex component. These findings indicate that the augmented pressor responses in CAD do not result from a generalized arterial baroreflex deficit.

GREATER BLOOD PRESSURE RESPONSES to mental stress are associated not only with increased risk for development of hypertension (4, 35), carotid atherosclerosis (1, 21, 37), stroke (9), and coronary heart disease (4) but also with greater rates of adverse cardiac events in coronary artery disease (CAD) patients (34, 43). Research suggests that surges in blood pressure evoked by mental activation can trigger disruption of plaques in vulnerable individuals, leading to sudden death and myocardial infarction (19). As an example, Wilbert-Lampen et al. (54) have recently found a significant increase in the incidence of cardiovascular events in German supporters during the soccer World Cup in Germany in 2006. Furthermore, ischemia occurs at a lower myocardial oxygen demand (heart rate × systolic pressure product) (11) during mental stress than during physical exertion (48) and is associated with higher rates of fatal and nonfatal cardiac events (19). In addition, mental stress is associated with more than half of all silent ischemic episodes, whereas exertion is associated with less than a third (25), even though both are encountered at similar rates in daily life (14). Thus a confluence of evidence indicates that exaggerated pressor responses during mental stress pose a significant risk for cardiac patients.

Blood pressure responses to stress are increased by disruption of the arterial baroreflexes (3, 15), indicating that insufficient baroreflex buffering may augment stress-related pressor responses. Although augmented pressor responses to mental stress may be secondary to low baroreflex sensitivity, they may, in essence, reflect increased vascular stiffness. Inelastic barosensory arteries cannot effectively transduce blood pressure increases, thereby decreasing baroreflex gain (18) and possibly increasing blood pressure responses to stress (31). Baroreflex control of blood pressure represents the only reflex system that can act quickly enough to accommodate the rapid pressor responses to mental stress; therefore, it is important to examine autonomic and mechastructural (i.e., arterial stiffness related) components of the baroreflex in relation to mental stress. This may be of especial importance for CAD patients given the established risk of augmented pressor responses to stress (1, 4, 5, 8, 21, 34, 35, 37) and of reduced cardiovelar baroreflex control (27).

We investigated the relationship of mental stress-induced cardiovascular responses to baroreflex function and carotid stiffness in healthy individuals and CAD patients. All patients were screened for the presence of comorbidities to exclude individuals whose baroreflex function and/or hemodynamic responses to mental stress might be affected by confounders such as hypertension, carotid vascular disease, and/or diabetic neuropathy. We hypothesized that CAD patients would demonstrate depressed baroreflex function compared with healthy age-matched individuals and that those patients with the lowest baroreflex gain and greatest carotid stiffness would demonstrate the largest pressor responses to psychological stress. We employed our technique for baroreflex assessment (17) to estimate mechanical and neural components of arterial baroreflex function and related these parameters to the blood pressure and heart rate responses to simulated real life stressors: mental arithmetic and public speaking.

METHODS

Subjects. Fifty-two male individuals aged 50–75 yr volunteered for this study. Twenty of these were apparently healthy volunteers and were screened and selected according to the following criteria: 1) no recent cardiac medication use and no signs or symptoms of heart disease, hypertension (pressures >150/90 mmHg), diabetes, neurological disease, or cancer; 2) normal resting electrocardiogram (ECG); 3) no recent weight change; 4) no regular tobacco use; 5) negative results for coronary heart disease from a Bruce graded exercise test; and 6) negative results for carotid vascular disease from a full carotid ultrasound examination. Eighteen volunteers met the criteria for the healthy subject group. Thirty-two volunteers had CAD based on...
Fig. 1. Schematic view of the experimental protocol.

Because the venous catheter placement (for drug infusion) can be a stressful procedure, baroreflex testing commenced at least 1 h after the last stress task. After an adequate image of the common carotid artery was obtained, data acquisition began, and 30 s later nitroprusside was injected, followed 1 min later by injection of phenylephrine (17). The acquisition was stopped when the systolic pressure increase had resolved and plateaued, i.e., approximately 1–2 min after the phenylephrine injection. This allows estimation of mechanical transmission of pressure into barosensory vessel stretch (diameter/pressure), neural transmission of stretch into vagal outflow (R-R interval/diameter), and conventional integrated cardiovascular baroreflex gain (R-R interval/pressure). Three trials of this infusion sequence were performed in each subject; each trial was separated by at least 15 min of recovery.

Analysis. Commercially available software (Windaq, Dataq Instruments, Cambridge, MA; Matlab, Mathworks, Natick, MA) was used for artifact detection, signal conditioning, and data analysis. All signals were digitized at 500 Hz. R-R intervals and arterial pressures were derived from their respective waveforms. Heart rate, arterial pressures (diastolic, systolic), and rate pressure product (heart rate × systolic pressure) were used to assess the pressor response to mental stress. Responses to the stress tasks were calculated as the differences in global averages from average baseline values. The accuracy of the beat-by-beat values of blood pressure was checked throughout the study using values from an oscillometric arm cuff. Beat-by-beat values of blood pressure were then used in the data analysis to have multiple values during the 4-min periods.

Vessel diameters were calculated by using a previously validated algorithm (47) in commercially available software (CVI acquisition, Information Integrity, Maynard, MA). Common carotid internal diameters were determined from digitized images by custom software. Pulsatile stiffness of the carotid artery was calculated from vessel diameters and the simultaneously acquired beat-by-beat photoplethysmographic measures of blood pressure from 30 s of data before nitroprusside injections for baroreflex assessment from the formula: \( \frac{[\log (SBP/DBP)/systolic carotid diameter - diastolic carotid diameter]/carotid diameter during diastole]}{P} \) (28). An average value for carotid stiffness was calculated for each subject from beat-by-beat values.

Cardiovascular baroreflex gain, as well as neural and mechanical components, were derived from the associations between R-R interval, systolic pressure, and systolic carotid diameter during the drug-induced rise in arterial pressure. Beat-by-beat values for each parameter were averaged across 3 mmHg pressure increments to account for respiration-related variations and to increase confidence in the relations among variables. Three linear relations were extracted from the sigmoid relations to estimate the linear gain of the integrated (pressure/R-R interval), mechanical (pressure/diameter), and neural (R-R interval/diameter) baroreflex responses.

Image consistency throughout pharmacological interventions requires three baroreflex trials to obtain duplicate trials with adequate images for analysis on all subjects. Values were averaged across two trials or across the two best trials, i.e., highest \( r \) values in subjects with three adequate trials (\( r \) values indicate the strength of the linear relation within each individual). A minimum value of \( r = 0.65 \) identified adequate trials. High reproducibility of these measures has been shown previously (32), and it was comparable in these subjects.

Statistics. Subjects’ characteristics were compared using an unpaired Student’s \( t \)-test. A three-way analysis of variance (task \( \times \) group \( \times \) time) with repeated measures was performed to examine the stress responses to preparation for and performance of the math and speech tasks in the two groups. The analysis was performed on the changes in each variable from baseline to task preparation and from baseline to task performance. Differences were considered significant at \( P < 0.05 \). Data are presented as means ± SD.
RESULTS

Table 1 shows the characteristics of all subjects. The CAD patients had greater body mass index, and despite being screened for high blood pressure, they had slightly higher resting systolic pressure after medication withdrawal ($P < 0.05$). CAD patients tended to report higher state anxiety ($P = 0.097$) and hostility ($P = 0.115$) and significantly greater self-reported depression scores ($P < 0.05$) than healthy individuals. However, there were no differences in trait anxiety ($P = 0.413$) or social desirability ($P = 0.174$) between CAD and healthy subjects. The perception of task difficulty was assessed in response to both stressors. There were no differences between the CAD patients and the control subjects ($P = 0.11$). Moreover, the results show that both groups perceived the math task as more stressful ($P < 0.05$).

At baseline, values of heart rate, blood pressures, and rate-pressure product were similar in both group and for both tasks. Figure 2 shows the mean blood pressure and heart rate responses to each stress task. The two groups demonstrated increases in heart rate from baseline during each phase of both task ($P < 0.05$). These increases were significantly greater in the CAD group ($P < 0.05$) and for the speech task ($P < 0.05$). Mean arterial pressure, as well as systolic and diastolic blood pressures, increased similarly from baseline to preparation in both groups and for both tasks. For these three parameters, the further increase from baseline to the task performance was greater in the CAD group ($P < 0.05$). Although the math task was perceived as more stressful, the speech task induced greater increases ($P < 0.05$). Moreover, although CAD patients had higher resting systolic pressure than healthy subjects, the analysis of covariance showed that this did not explain higher pressor responses in CAD. In addition, although CAD patients tended to be more depressed and anxious than healthy subjects, the analysis of covariance showed that these psychometric variables did not explain higher pressor responses in CAD.

We found no difference in common carotid stiffness (16.7 ± 6.0 vs. 15.4 ± 5.8, $P = 0.39$) between the two groups. Accordingly, there was no difference between the healthy and CAD groups in integrated arterial baroreflex gain or in either the mechanical or neural components (Fig. 3).

Table 1. Subjects characteristics

<table>
<thead>
<tr>
<th></th>
<th>Healthy Control Subjects (n = 18)</th>
<th>CAD Patients (n = 29)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex (M/F)</td>
<td>18/0</td>
<td>29/0</td>
<td></td>
</tr>
<tr>
<td>Age, yr</td>
<td>61 (7.7)</td>
<td>59.1 (7.9)</td>
<td>0.42</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>24.4 (2.5)</td>
<td>28.3 (2.7)*</td>
<td>0.0003</td>
</tr>
<tr>
<td>HR, beats/min</td>
<td>60 (11)</td>
<td>63 (10)</td>
<td>0.26</td>
</tr>
<tr>
<td>SBP, mmHg</td>
<td>117.1 (14.1)</td>
<td>125.2 (13.2)*</td>
<td>0.05</td>
</tr>
<tr>
<td>DBP, mmHg</td>
<td>73.3 (7.5)</td>
<td>76.8 (7.4)</td>
<td>0.12</td>
</tr>
<tr>
<td>1 Artery revascularized, n</td>
<td>17</td>
<td>6</td>
<td></td>
</tr>
<tr>
<td>2 Arteries revascularized, n</td>
<td>6</td>
<td>6</td>
<td></td>
</tr>
<tr>
<td>3 Arteries revascularized, n</td>
<td>6</td>
<td>2.6</td>
<td></td>
</tr>
<tr>
<td>Time since MI, yr</td>
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<td></td>
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</tbody>
</table>

Values are means ± SD; n, no. of subjects. CAD, coronary artery disease; M, male; F, female; MI, myocardial infarction; BMI, body mass index; HR, heart rate; SBP, systolic blood pressure; DBP, diastolic blood pressure. $P$ value: difference between healthy control subjects and CAD patients (Student’s $t$-test, $P < 0.05$). *$P < 0.05$.

DISCUSSION

These data provide insight to the mechanisms that may distinguish blood pressure responses to acute stress in CAD patients. We found that individuals with CAD but without other comorbidities manifest an augmented pressor response to mental stress. However, our data suggest that these exaggerated responses are not associated with depressed cardiovagal baroreflex function or increased arterial stiffness. Thus the risk associated with greater blood pressure responses to mental stress in CAD patients appears to be independent of the established risk of either reduced cardiovagal baroreflex control or increased arterial stiffness. One possibility is that the risk of augmented pressor responses to stress in CAD patients relates to heightened sympathetic activation rather than depressed vagal function.

Cardiovascular comorbidities such as heart failure, hypertension, diabetes, neurological disease, cancer, tobacco use, and carotid disease can alter baroreflex gains and hemodynamic responses to mental stress. For example, congestive heart failure due to ischemic heart disease or idiopathic dilated cardiomyopathy is characterized by enhanced sympathetic activation and baroreflex impairment (12, 39). Similarly, baroreflex sensitivity is reduced in Type 2 diabetes (41, 44) and these patients demonstrate augmented systolic blood pressure reactions to mental stress (49). Therefore, we thoroughly screened our coronary artery disease patients for comorbidities to isolate the effect of coronary disease per se on baroreflex function, arterial stiffness, and hemodynamic reactivity to mental stress.

Nonetheless, we were surprised to find that our CAD population did not demonstrate reduced baroreflex sensitivity or...
increased arterial stiffness compared with healthy, age-matched individuals. Stiffness of the vascular tree increases with age (53) and cardiovascular disease (10), and prior studies have shown that age-related declines in mechanical transduction of arterial pressure into carotid stretch significantly reduce baroreflex sensitivity (19, 24, 31). Thus it is reasonable to hypothesize that CAD increases arterial stiffness, thereby reducing baroreflex function. Other studies have shown that baroreflex sensitivity is reduced in patients with CAD and that the decrease is correlated with the extent and severity of the disease (23).

However, fewer than half of our patients had more than one-vessel disease. Moreover, not only were our CAD subjects free of comorbidities, they were not taking cardiovascular medications when they were studied and all had been revascularized. β-Blockers, ACE inhibitors, and calcium channel blockers have variable effects on baroreflex function (16, 29, 42, 52), and data suggest that revascularization improves baroreflex sensitivity (51). Thus it may not be surprising that this CAD population had normal baroreflex function. However, in the CAD group, there was greater heterogeneity in the two components that determine overall gain compared with the control group. This may suggest that there was a greater variability in the contribution of either vagal neural and/or vascular mechanical effectors to baroreflex control. A range of relative contributions of these two components has been shown previously by Hunt et al. (17). Also, our laboratory previously reported that a correlation between the mental stress blood pressure response and both carotid stiffness and baroreflex sensitivity in healthy older individuals (31), but these correlations were not observed in the present study. This may be explained by the narrower age range in the present study: subjects studied by Lipman et al. (31) were aged 51 to 86 yr, whereas in the present study the oldest subject was 72 yr. Given the progressive effects of aging on arterial stiffness and cardiovagal baroreflex function (7, 50), the inclusion of older subjects in the prior work may have allowed the observation of a correlation between the stress response and baroreflex physiology.

Depression symptoms are usually associated with larger blood pressure (30) and vascular resistance (38) responses to stress and greater likelihood of ischemia during mental stress (20), but the greater responses in our CAD patients could not be explained by higher depression scores. In addition, other psychological traits, such as emotional defensiveness and hostility, which promote heightened hemodynamic reactivity to stress (8, 13), did not explain the greater pressor responses. This may suggest that differences in hemodynamic stress response are not a manifestation of perceptual differences and may be due to a difference in central control of nervous outflow. For example, hyperactive cerebral cortical responses have been observed during mental stress in CAD patients, particularly in those who exhibit silent myocardial ischemia (45). Thus, despite the fact that the perceived level of stress may be similar, the response to a given level of stress can be augmented.

Limitations. We did not measure cardiovagal baroreflex gain during mental stress, and stress may reset gain. Nonetheless, direct engagement of baroreceptors through rapid, bolus injections of nitroprusside and phenylephrine should be sufficiently robust to accurately reflect gain of the system, and gain during mental stress should closely correspond to its values during rest (22). Although spontaneous indexes of baroreflex gain could have been employed, we have found that these estimates do not relate to directly measured baroreflex gain (32). Also, we did not assess sympathetic outflow during mental stress or baroreflex control of sympathetic outflow. The fact that pressor responses to mental stress differ between CAD patients and healthy controls, but that cardiovagal baroreflex control does not, suggests that it may have been helpful to examine the vascular sympathetic limb of the autonomic nervous system. However, although direct measures of sympathetic activity
during the stress tasks may have provided information on the role of sympathetic activation in the greater blood pressure during stress in CAD patients, the difficulty of obtaining these measures via microneurography may be considered a mental stressor in of itself (e.g., Ref. 33). Also, despite screening for hypertension, our CAD subjects had slightly higher resting blood pressure. However, resting blood pressure did not correlate to blood pressure responses to mental stress, suggesting that heightened reactivity was not due to unrecognized hypertension in CAD. Lastly, the body mass index was greater in CAD than in control subjects. Although previous results have shown that blood pressure and sympathetic nerve activity levels during mental stress are augmented in obese women (26), this may not fully explain augmented pressor responses in our male CAD patients, who had body mass indexes below the cutoff for obesity.

Conclusions. Our findings suggest that coronary disease, per se, independent of comorbidities, is associated with augmented pressor responses to mental stress. Moreover, these responses are not secondary to deficits in cardiovagal baroreflex function or to increases in arterial stiffness. Further studies are needed to elucidate the critical role of vasoconstrictor responses in the augmented blood pressure increases with mental stress in coronary disease.

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GRANTS

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REFERENCES


