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Effects of a cognitive stress challenge on myocardial perfusion and plasma cortisol in coronary heart disease patients with depression

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Summary

Although it is well established that coronary heart disease (CHD) patients with depression exhibit increased mortality compared with equally ill cardiac patients without depression, the mechanisms mediating this effect remain obscure. Depression is characterized by vulnerability to stress and heightened stress responsiveness, and stress can theoretically act through several biological pathways to contribute to excess mortality from CHD. Mechanisms connecting stress, depression and cardiovascular mortality have not been previously explored in detail. The purpose of this study was to assess the effects of stress and depression on myocardial perfusion and plasma cortisol concentrations in CHD patients. Patients with CHD with and without depression (n = 28) underwent single photon emission computed tomography imaging of myocardial perfusion at rest and during a stressful cognitive challenge. Severity of ischaemia was measured by summing perfusion defect scores across myocardial segments and subtracting out rest from stress scores. Plasma cortisol concentrations were measured at baseline and in response to the stressful challenge. There were no differences in stress-induced myocardial ischaemia or plasma cortisol response to stress between CHD patients with and without depression. Depressed CHD patients with a history of psychological trauma (n = 5) had an increase in stress-induced ischaemia scores [7; standard deviation (SD) = 5] compared with CHD patients with depression without a history of psychological trauma (2 SD = 2) and CHD patients without depression or psychological trauma (1; SD = 2) (F = 8.51; degree of freedom = 2,23; p = 0.007). Eighty per cent of CHD/depression

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trauma-exposed subjects had stress-induced ischaemia as opposed to 38 per cent of CHD/depression subjects without trauma exposure and 23 per cent of subjects with CHD without depression or trauma. Self-reported nervousness during the cognitive stressor was correlated with stress-induced ischaemia. These preliminary findings suggest that depression with a history of prior exposure to traumatic stress is associated with increased risk for stress-induced cardiovascular ischaemia. Copyright © 2009 John Wiley & Sons, Ltd.

Key Words

stress; depression; cardiovascular disease; cortisol; single photon emission computed tomography

Introduction

Coronary heart disease (CHD) is the leading cause of death in the United States in men by 45 years of age and in women by 65 years of age (CHD) (Hennekens, 1998). The risk factors for CHD which were initially identified, including hypertension, hypercholesterolaemia, cigarette smoking and diabetes, did not account for all of the risk for CHD (Wilson et al., 1998). More recently, other risk factors, such as intra-abdominal fat, have been found to account for additional risk for CHD (Yusuf et al., 2005). Psychosocial factors have also been found to play a role in risk for CHD (Hennekens, 1998). Behavioural risk factors such as depression (Musselman, Evans, & Nemeroff, 1998; Rozanski, Blumenthal, & Kaplan, 1999) are associated with an increased risk for cardiovascular events (Barefoot, Helms, & Mark, 1996; Carney, Rich, & Freedland, 1988; Frasure-Smith, Lesperance, Juneau, Talajic, & Bourassa, 1999; Frasure-Smith, Lesperance, & Talajic, 1993) and cardiovascular death. The mechanisms through which depression increases CHD risk, however, remain unclear.

Studies have shown that stress, which is linked to depression, is associated with an increase in myocardial ischaemia in heart disease patients (Berkman, Vaccarino, & Seeman, 1993; Joynt, Whellan, & O'Connor, 2003). The fact that most episodes of myocardial ischaemia are painless and not associated with an increase in cardiac workload (Deanfield et al., 1983) prompted a search for factors other than increased cardiac workload that contribute to myocardial ischaemia in daily life. In 1984 a laboratory paradigm of mental stress was used to induce myocardial ischaemia in heart disease patients (Deanfield et al., 1984); since then, multiple studies have shown that some individuals are vulnerable to stress-induced myocardial ischaemia (Arrighi et al., 2000; Arrighi, Burg, Cohen, & Soufer, 2003; Burg, Jain, Soufer, Kerns, & Zaret, 1993; Soufer et al., 1998). Painless stress-induced ischaemia can occur in undiseased coronary arteries (Lacy et al., 1995) and is seen at lower heart rates than at exercise stress-induced ischaemia (Deanfield et al., 1984; Rozanski et al., 1988; Schang & Pepine, 1977; Schiffer, Hartley, Schulman, & Abelmann, 1980), and can be seen in patients without exercise or pharmacological stress-induced ischaemia (Ramachandruni et al., 2006). Studies have also shown impaired left ventricular function with mental stress in Coronary artery disease patients (Becker et al., 1996; Jain et al., 1998; Krantz et al., 1991; LaVeau et al., 1989) and a correlation between stress-induced (but not exercise-induced) myocardial ischaemia in the laboratory and ischaemia measured in daily life ambulatory monitoring (Blumenthal et al., 1995; Stone et al., 1999). In summary, these studies showed that stress can induce painless myocardial ischaemia that occurs with emotional activities and is not necessarily associated with increased heart rate and blood pressure.

Major depression plagues about 17 per cent of the population at some time in their lives. An important risk factor for the onset of depressive episodes is a recent stressful life event (Kendler, Thornton, & Gardner, 2000) or a history of exposure to a traumatic stressor (Kessler, Sonnega, Bromet, Hughes, & Nelson, 1995). Exposure to traumatic stressors has also been associated with an increased risk of heart disease (Boscarino, 1997). The concentration of stress hormones, including cortisol and noradrenaline, has been reported to be increased in patients with depression (Carroll, 1982; Nemeroff et al., 1984; Traskman et al., 1980; Young, Haskett, & Grunhaus, 1994). In CHD patients, depression is associated with elevated urinary cortisol concentrations (Otte et al., 2004). Patients with depression and a history of early life trauma exhibit increased cortisol responsiveness

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and reduction in volume of the stress-sensitive hippocampus compared with non-traumatized patients with depression and normal individuals (Heim et al., 2000; Vythilingam et al., 2002). Increased neurohormonal activation in patients with stress and depression may represent a mechanism of increased morbidity and mortality in patients with CHD and depression.

Single photon emission computed tomography (SPECT) permits the non-invasive detection of myocardial ischaemia, even in patients without symptoms of CHD. The presence of myocardial ischaemia is detected with 90 per cent sensitivity and 80 per cent specificity (Zaret & Beller, 1999). Some individuals, e.g. those with high hostility, are at increased risk for stress-induced myocardial ischaemia, which can be measured with SPECT, and which often occurs even in the absence of symptoms (Arrighi et al., 2000; Arrighi et al., 2003). Patients with stress-induced myocardial ischaemia as measured with SPECT have a 2–3 per cent increased risk of cardiac events and/or mortality over 2 years (Hachamovitch et al., 1998; Thomas et al., 2004).

The purpose of this current study was to measure myocardial perfusion with SPECT and plasma concentrations of cortisol following exposure to a stressful cognitive challenge in patients with CHD with and without depression. We hypothesized that patients with CHD and depression would exhibit an increase in cognitive stress-induced myocardial ischaemia and plasma cortisol relative to patients with CHD without depression. A secondary hypothesis was that a history of previous traumatic stress exposure would confer increased risk for stress-induced myocardial ischaemia in patients with CHD and depression.

Methods

Subjects

Subjects were recruited through a newspaper advertisement; 37 subjects were initially screened for the study. Subjects with a history of CHD were included. Subjects were determined to have a history of CHD based on past history of myocardial infarction (MI) (n = 13), cardiac catheterization-based documentation of CAD (n = 18), positive nuclear stress test (n = 3) and/or coronary artery bypass graft surgery. All subjects provided written informed consent for participation. Eight subjects declined participation or did not follow-up, and one was excluded based on exclusion criteria (treatment with steroids). There were three patients with depression and six without depression who were excluded or dropped out of the study. In the final sample, there were two women with CHD and depression, and two women with CHD without depression; all were post-menopausal. Patients with depression did not have a history of schizophrenia or bipolar disorder. The project was approved by the Emory University Investigational Review Board.

Twenty-eight men and women participated in the study, including subjects with CHD with depression (n = 13) and CHD patients without depression (N = 15). CHD was defined as a history of documented MI or positive rest/stress myocardial perfusion scan for myocardial ischaemia. The categorical diagnosis of major depression and history of trauma exposure was established with the Structured Clinical Interview for *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition* (SCID) (First, Spitzer, Williams, & Gibbon, 1995); dimensional severity of depressive symptoms was measured with the Hamilton Depression Scale (Ham-D) (Hamilton, 1960). Psychological trauma was defined according to the American Psychiatric Association criteria as a threat to life or integrity of self or other with associated fear, horror or helplessness (APA, 2000). Patients had a range of traumas including childhood abuse and combat exposure.

Subjects were free of major medical illness other than CHD on the basis of history and physical examination and laboratory testing, and were not actively abusing illicit substances or alcohol in the past 6 months. Subjects also included those who were currently receiving antidepressant treatment if they remained symptomatic as confirmed by a current diagnosis of major depression based on the SCID and a Ham-D score of greater than 9. Subjects were excluded if they had unstable angina or a recent MI, a serious medical or neurological illness, organic mental disorders or co-morbid psychotic disorders or current history of alcohol or substance abuse or dependence based on the SCID, a history of head trauma, loss of consciousness for more than 1 min, or cerebral infectious disease.

Cognitive stress challenge

Subjects underwent a baseline SPECT scan of the heart at rest following intravenous injection of 8 mCi (Tc-99m) sestamibi. Subjects then

underwent two periods of counting out loud for 3 min each, followed by two periods of performing a stressful cognitive challenge for 3 min each (Figure 1). The stressful cognitive challenge involved serial subtraction, addition, multiplication and division, performed under time pressure with negative feedback. Difficulty was titrated to individual ability to perform the task. The same individual performed the challenge in all subjects, a physician wearing a white coat who was trained by the first author. Induction of stress response was confirmed by analogue ratings of nervousness and subjective distress. We have previously shown that using these methods, we can induce a stress response as measured with both cortisol and subjective stress response (Bremner et al., 2003; Soufer et al., 1998). Blood samples were obtained from an intravenous catheter at 1 min into each condition and 10 min after the end of the last condition for the measurement of cortisol. Two minutes into the second stressful cognitive challenge, subjects were injected with 20 mCi (Tc-99m) sestamibi, following which, the stressful challenge continued for another minute. This was followed by SPECT imaging of the myocardium. Analogue ratings of nervousness and fearfulness (scale of 0–4, 4 being 'most severe') were collected by self-report during rest and after stress. At the beginning of the study, subjects were shown the analogue scale which consists of a line marked at five points from 0–4, with adjectives of 0 (not at all), 1 (slightly), 2 (moderately), 3 (considerably), 4 (extremely). Subjects are then asked to rate separately their current feelings of fear and nervousness using the analogue scale during rest and during stress.

Image analysis

Cardiac data were scored by a single investigator blinded to subject diagnosis using a 20-segment 'bull's eye diagram' of the heart (Hachamovitch et al., 1998) (Figure 2). This diagram was used to rate blood flow at rest and stress on a scale of 0 (normal) to 4 (absent blood flow) for each of the 20 segments of the heart. Scores in each segment were summed to yield a global perfusion defect score for the rest and cognitive stress conditions. The rest perfusion defect score was subtracted from the stress perfusion defect score to obtain a stress-induced myocardial perfusion defect score, hereafter referred to as a *stress perfusion score*.

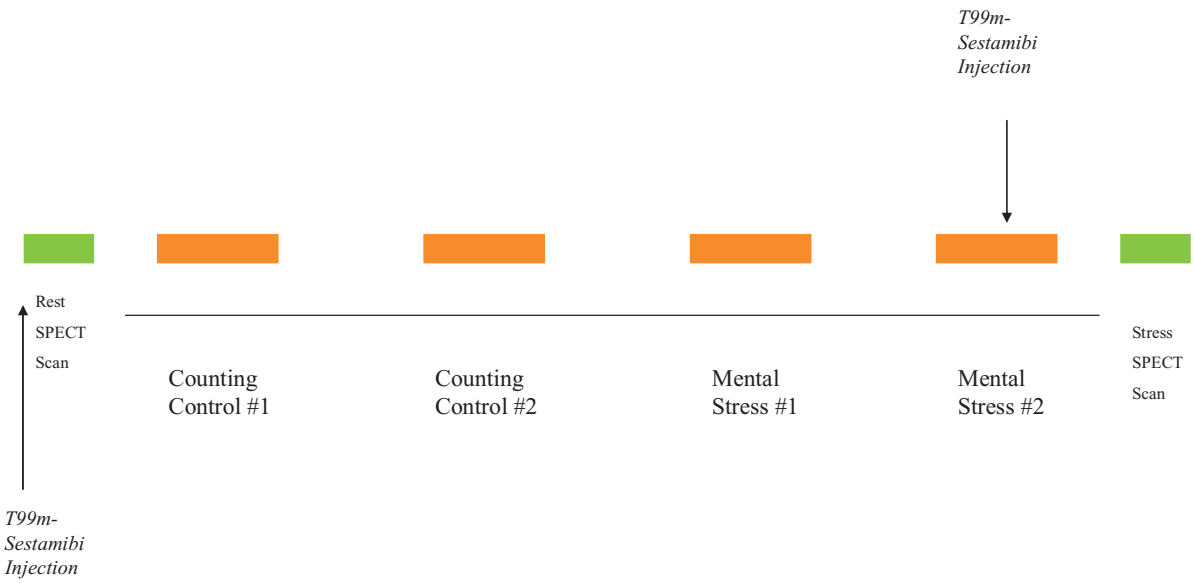

Figure 1. Diagram illustrating the mental stress protocol. Subjects underwent baseline single photon emission computed tomography (SPECT) imaging of the heart after injection of (Tc-99m) sestamibi, then underwent two counting control conditions and two mental stress conditions. Two minutes into the second mental stress condition they were injected with (Tc-99m) sestamibi followed by SPECT imaging of the myocardium with mental stress.

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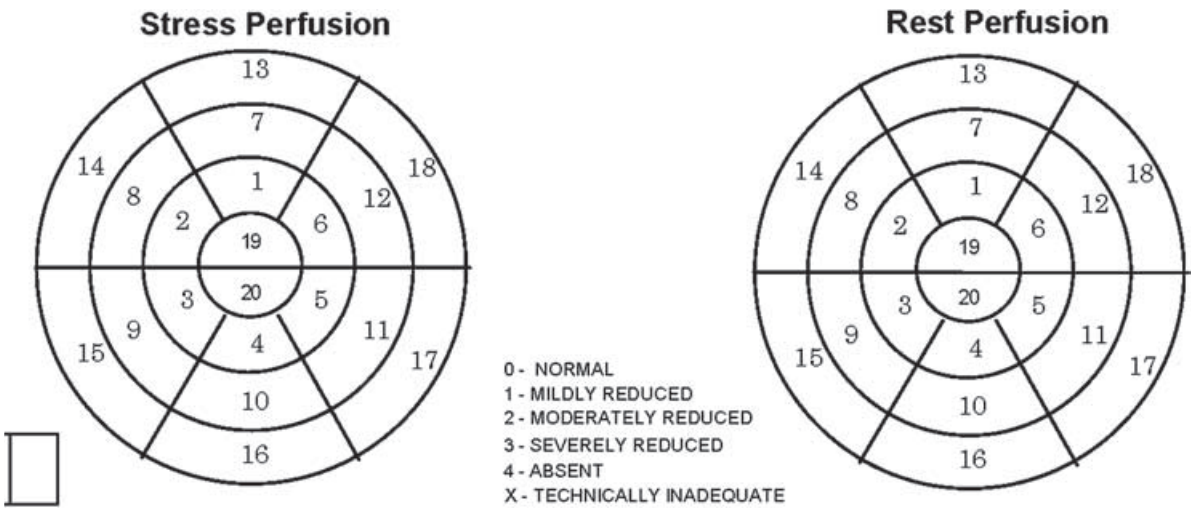

Figure 2. Myocardial segments scored for perfusion defects. Twenty segments corresponding to segments of the heart are scored on a 0–4 scale (0 = no defect, 4 = absent perfusion). Scores for each segment are summed for rest and stress, and the difference between rest and stress is calculated to attain the stress perfusion score.

Plasma cortisol measurement

Samples for measurement of plasma cortisol concentrations were drawn and placed in a chilled tube containing ethylenediaminetetraacetic acid. Samples were placed on ice, separated in a refrigerated centrifuge within 2 h and stored at –80°C for later analysis using methods previously described (Ritchie, Belkin, Krishnan, Nemeroff, & Carroll, 1990). Plasma cortisol was assayed in duplicate 10 µL plasma aliquots by a solid phase radioimmunoassay using materials obtained from Incstar Corporation (Stillwater, MN, USA). The sensitivity of the assay is approximately 0.2 µg/dL (2 ng/mL), and inter- and intra-assay coefficients of variation using an automated sampling method were less than 4 per cent.

Data analysis

Categorical data was analysed using χ^2, and continuous data was analysed using analysis of variance and Duncan's multiple range test to compare differences between groups. Analogue ratings of nervousness were compared between the second control task and the first cognitive stress task. Pearson correlations were performed to assess the relationship between nervousness at the time of the cognitive challenge and stress-induced myocardial ischaemia. Significance was defined as $p < 0.05$.

Results

There were no differences in demographic factors or risk factors for heart disease, including age, sex and race, hypercholesterolaemia, diabetes, or smoking, between subjects with and without depression (Table I). Subjects with a diagnosis of major depression had significantly greater scores on the Ham-D than subjects without current major depression. Of the CHD subjects with current depression, one had a history of past alcohol dependence, three had past alcohol abuse, one had a history of past marijuana abuse, two had current PTSD, one had panic disorder without agoraphobia, one had panic disorder with agoraphobia, one had current obsessive–compulsive disorder, one had current social phobia and one had generalized anxiety disorder. Five reported a history of exposure to a traumatic event. Of the 15 CHD subjects without current depression, one had a history of past alcohol abuse and one had a history of past marijuana abuse. Two

Table I. Demographic factors in coronary heart disease patients with and without depression and trauma exposure.

Variables	Depression (n = 13) (%)	Non-depression (n = 15) (%)
Hypercholesterolaemia	69	87
Hypertension	69	67
Diabetes	27	33
Smoking	20	27
Statins	62	80
Beta blockers	69	53
ACE inhibitors	77	60
Calcium channel blockers	23	13
Diuretics	23	13
Antidepressants	77	7
Benzodiazepines	15	0

ACE: angiotensin-converting enzyme.

reported a history of exposure to a psychological trauma.

The depressed CHD patients reported greater nervousness at all time points relative to the non-depressed CHD subjects (Figure 3). Depressed patients did not show a statistically significant increase in nervousness with stress relative to non-depressed patients (no significant interaction between diagnosis and time).

There was no significant difference between CHD patients with depression [4.0; standard deviation (SD) = 4.5] and CHD patients without depression (2.1; SD = 2.8) in stress-induced ischaemia as measured by the stress perfusion score (representing a combination of severity and number of ischaemic myocardial segments). Patients with CHD and depression and a history of psychological trauma (7.4; SD = 5.3) had more ischaemia than CHD patients with depression without trauma (1.2; SD = 1.8) and CHD patients without depression or trauma (1.9; SD = 2.4), but not CHD patients without depression with trauma (7.5; SD = 2.1) [main effect for trauma $F = 19.48$, degree of freedom (df) = 1,24, $p = 0.0002$; main effect for diagnosis $F = 3.14$; df = 1,24, $p = 0.09$]. Four out of five (80 per cent) CHD patients with depression and trauma exposure had stress-induced ischaemia (at least one ischaemic segment with a moderate perfusion defect) as opposed to three out of eight (38 per cent) CHD patients with depression without trauma (Figure 4). Myocardial perfusion with cognitive stress in a patient with depression and a history of trauma exposure is illustrated in Figure 5.

The cognitive stress challenge resulted in an increase in cortisol in all subjects with no difference between CHD patients with and without depression (Figure 6). There were no differences between patients with and without a history of trauma exposure in cortisol response to stress. There was also no correlation between myocardial perfusion and cortisol response to cognitive challenge.

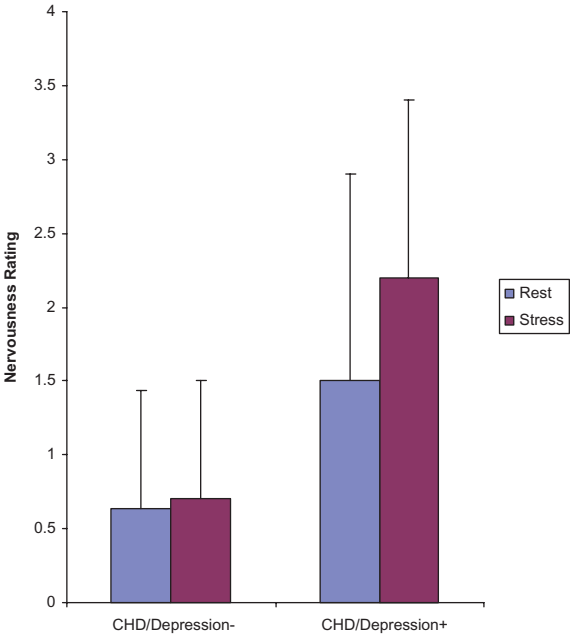

Figure 3. Behavioural response to a cognitive stress challenge. Coronary heart disease (CHD) patients with depression had higher self-rated nervousness with both rest and stress than CHD patients without depression (main effect for time; 16.45; degree of freedom 1,50; $p = 0.0002$). CHD patients with depression did not have a greater increase in self-rated nervousness with stress than CHD patients without depression (i.e. there was no significant time by diagnosis interaction).

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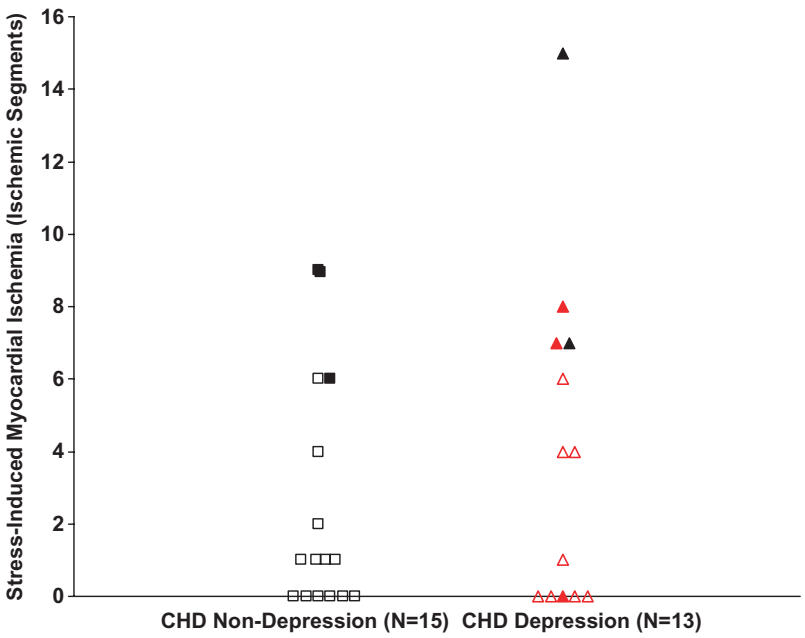

Figure 4. Myocardial ischaemia induced by the stressful cognitive challenge in subjects with coronary heart disease (CHD) with (n = 13) and without (n = 15) depression. There were no differences in stress-induced myocardial ischaemia scores between CHD patients with (triangles) and without (squares) depression. A comparison of CHD patients with depression and a history of psychological trauma (filled triangles) showed a significant increase in ischaemia as measured by the number of cognitive stress-induced myocardial perfusion defects when compared to CHD patients with depression without trauma (open triangles) and CHD patients without depression or trauma (open squares) but not to CHD patients without depression with trauma (filled squares) (main effect for trauma, p = 0.0002). Subjects with CHD and depression and co-morbid PTSD are shown as filled black triangles.

Subjective nervousness (r = 0.51; df = 24, p = 0.005) after stressful challenge was significantly correlated with stress-induced perfusion defects in all subjects.

Discussion

A cognitive stress challenge did not result in a difference in stress-induced myocardial ischaemia or cortisol response between CHD patients with and without depression. These results do not support the original primary hypothesis of this study that patients with CHD and depression have an increase in stress-induced myocardial ischaemia. However, a secondary analysis suggested that CHD patients with depression and trauma had significantly greater increases in myocardial ischaemia after the stressful cognitive challenge compared with CHD patients with depression without trauma, and normal CHD patients. In fact a history of trauma was the strongest predictor of stress-induced ischaemia regardless of diagnosis, although with a small number of subjects the results are preliminary. There was a positive correlation between self-reported nervousness during the stressful challenge and stress-induced myocardial ischaemia in all subjects.

Although prior studies have demonstrated that depression is associated with increased rates of myocardial ischaemia in CHD patients, few prior studies have examined the role of prior exposure to trauma in potentially underlying the susceptibility to myocardial ischaemia in these patients. This link between trauma exposure and mental stress-induced ischaemia suggests that this may be as relevant as the diagnosis of depression per se. Because trauma exposure increases the risk for depression, it may be that trauma exposure, rather than depression, is the aetiological factor

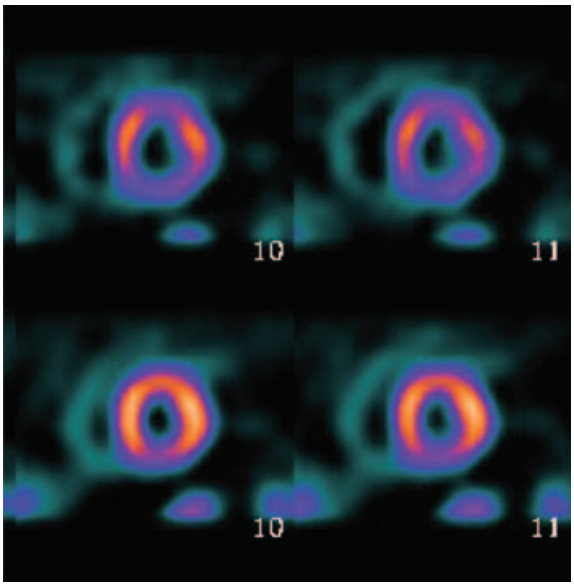

Figure 5. Myocardial perfusion in a representative patient with coronary heart disease depression and a history of psychological trauma. There is a visible decrease in perfusion in the anterior (top of the doughnut) and inferior (bottom of the doughnut) walls of the myocardium with mental stress (top images) compared to control (bottom images).

behind the increased risk for mortality in CHD patients with depression. Functional changes in brain areas that modulate peripheral sympathoadrenal function (e.g. limbic and frontal cortical areas) via efferent outputs to the heart through the hypothalamus may increase the vulnerability of susceptible individuals to stress-induced myocardial dysfunction susceptible individuals (Soufer et al., 1998).

Prior studies showed that women with depression and early life trauma had increased cortisol responsivity to stress (Heim et al., 2000) and smaller volume of a brain structure sensitive to stress (hippocampus) (Bremner et al., 2004) compared with depressed women without early life stress and healthy women. These findings not only show that trauma exposure is an important factor but also that depressed subjects with and without trauma may represent different subtypes of depression. The current study is consistent with that idea, extending findings into cardiovascular functioning. Other studies have also shown that trauma influences physical health. For instance, subjects with early life trauma have increased obesity, which is a risk factor for cardiovascular disease (Williamson, Thompson, Anda, Dietz, & Felitti, 2002), while some epidemiological studies showed a link between child-

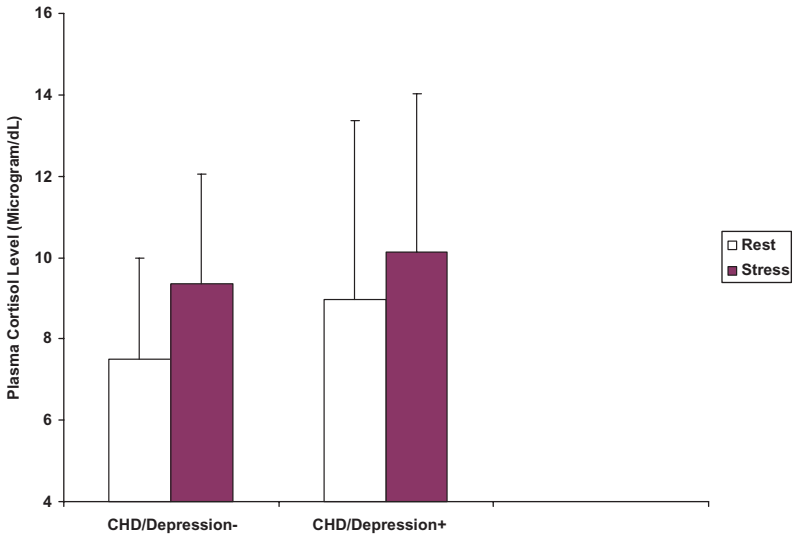

Figure 6. Plasma cortisol levels at rest and after cognitive stress in patients with coronary heart disease (CHD) with and without depression. Stress resulted in an increase in cortisol (main effect for time, $F = 6.23$; degree of freedom = 1,23; $p = 0.02$) with no differences between groups.

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hood trauma and risk for cardiovascular disease (Dong et al., 2004).

We did not find a relationship between cortisol and stress-induced ischaemia. It is possible that other mechanisms, such as catecholamine activation, or greater coronary artery vascular reactivity, account for the increase in stress-induced ischaemia seen in patients with trauma and depression in the current study. In addition, there were no differences in cortisol response to stress between the groups. Prior studies have shown greater stress-induced cortisol increases in patients with trauma and depression (Heim et al., 2000), as well as trauma and PTSD (Bremner et al., 2003; Elzinga, Schmahl, Vermetten, van Dyck, & Bremner, 2003). Differences between the current study and prior studies may be related to the fact that the current sample was primarily composed of men (unlike the other studies which were primarily or exclusively women), or the fact that the type of mental arithmetic task that can be performed in the scanner is less stressful than the complicated task solving (Bremner et al., 2003) or public speaking (Heim et al., 2000), both with negative feedback, that was performed out of the scanner in prior studies.

Anger and other strong emotions have been associated with increased cardiac risk (Gabbay et al., 1996). In a study of 1623 post-MI patients, it was found that the risk of MI in the 2 h after an episode of anger was increased by 2.3-fold (Mittleman et al., 1995). In one study 12 patients with myocardial ischaemia were asked to recall a personal incident involving anger during cardiac catheterization. Reported levels of anger were significantly correlated with reductions in coronary artery diameter in stenotic coronary arteries (Boltwood, Taylor, Boutte Burke, Grogin, & Giacomini, 1993). Patients with mental stress-induced silent myocardial ischaemia showed higher patterns of trait anger (Burg et al., 1993). Anger was associated with a two-fold increase in risk of acute coronary syndrome compared with a 3.5-fold increased risk with physical exertion (Strike, Perkins-Porras, Whitehead, McEwan, & Steptoe, 2006).

The mechanisms involved in mental stress-induced myocardial ischaemia continue to be a subject of investigation. One proposed mechanism is increased endothelial reactivity, or the capacity of strong emotions to cause constriction of the coronary arteries. Mental stress-induced vasoconstriction has been shown to correlate with response to acetylcholine infusion, suggesting that mental stress-induced ischaemia is related to a failure of endothelium-related coronary artery dilation (Yeung et al., 1991). Mental stress has been shown to result in a blunting of blood flow response (Schoder et al., 2000) and a paradoxical constriction of diseased coronary arteries and constriction of coronary arteries without evidence of atherosclerosis (Kop et al., 2001). Other studies show a decrease in coronary vascular resistance with mental stress. Administration of phentolamine (an alpha-1 and alpha-2 antagonist) resulted in a 25 per cent decline in coronary vascular resistance, suggesting that the effects are mediated by alpha-adrenergic activation (Dakak, Quyyumi, Eisenhofer, Goldstein, & Cannon, 1995). Patients with acute stressors were found to have a reversible left ventricular dysfunction with myocardial inflammation on biopsy; markedly elevated levels of plasma adrenaline and noradrenaline showed that the patients were under severe stress (Wittstein et al., 2005). Mental stress was also associated with a decrease in heart rate variability (Lampert, Ickovics, Viscoli, Horwitz, & Lee, 1998) which increases the risk of sudden death from dysrhythmia.

There are several limitations to the current study. There were differences in medication used between CHD patients with and without depression which could have affected study results, most notably the fact that CHD patients with depression were more likely to be treated with an antidepressant. In addition, non-depressed patients more frequently took statins, and less frequently took beta blockers and calcium channel blockers. The sample size in general was also small, and the results need to be replicated in a larger trial. Future studies should look prospectively at CHD patients with and without trauma exposure for quality of life and survival, and at the correlation between subjective nervousness and myocardial ischaemia.

In conclusion, patients with depression and a history of psychological trauma had an increase in stress-induced myocardial ischaemia compared with patients with depression without trauma, and non-depressed non-traumatized subjects. These differences were not related to differences in stress-induced cortisol release. The increase in stress-induced ischaemia was clinically significant, with 2–3 per cent per year increased risk of cardiac events or mortality (Hachamovitch et al., 1998; Thomas et al., 2004). The results suggest

that a history of prior traumatic stress in patients with depression increases the risk of stress-induced ischaemia and represents one possible mechanism by which depression increases morbidity and mortality related to CHD.

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