Depression, the Dynamic Function of the Autonomic Nervous System and Hypothalamic-Pituitary-Adrenal (HPA) Axis, and Cardiovascular Disease

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Contribution of Authors

For Manuscript One, I took the lead role in choosing the topic and statistical analyses, interpreting the results and writing the manuscript. I also took part in data collection. Co-authors Kim Lavoie, Roxanne Pelletier, Tavis Campbell and André Arsenault provided feedback in the writing of the manuscript though my supervisors Simon Bacon and Blaine Ditto provided the most substantial feedback in both the writing process and in responding to reviewers' comments. Simon Bacon, Blaine Ditto, André Arsenault and Kim Lavoie also designed the MOSMI study. This manuscript is currently published in *Psychophysiology*.

For Manuscript Two, I chose the topic, conducted the analyses and wrote the manuscript. Co-authors Bianca D'Antono and Blaine Ditto provided substantial input in choosing the appropriate statistical analyses, writing and responding to journal reviewers. Furthermore, Bianca D'Antono designed and conducted the study. This manuscript has been conditionally accepted with major revisions at *Psychophysiology* and is currently under revision.

For Manuscript Three, I designed and oversaw the implementation of the study, which was a sub-study of a larger study called MOSMI. I also conducted the statistical analyses and wrote the manuscript. My supervisors Blaine Ditto and Simon Bacon provided substantial input regarding the statistics and writing of the manuscript. Co-authors Kim Lavoie and André Arsenault provided feedback in the writing while Junichiro Hayano provided his expertise in calculating and interpreting the HRV data. This manuscript is currently in preparation for submission to *Psychosomatic Medicine.*

Table of Contents

Abstract

Depression is associated with an increased risk of cardiovascular disease (CVD). One possible mechanism of this effect is dysregulation of the biological stress systems, the autonomic nervous system (ANS) and hypothalamic-pituitary-adrenal (HPA) axis. The current thesis aimed to better understand the relationship between depression and these two systems. In the first study, the effect of major depression on heart rate recovery following exercise, a marker of ANS tone, was examined in cardiac patients. Depression was associated with poor early heart rate recovery, suggesting reduced post-exercise parasympathetic activation. The second study, which included healthy participants, examined the effect of cognitive and somatic depressive symptoms in relation to recovery of heart rate and heart rate variability, two markers of ANS tone, in response to interpersonal laboratory stressors. Both types of symptoms were found to predict post-stress recovery. The third study aimed to examine the relationship between major depression both ANS and HPA axis activity in response to a stressful diagnostic test. Furthermore, it aimed to determine whether antidepressant medication is effective in restoring a normal stress response in depressed individuals. Depressed cardiac patients exhibited elevated cortisol levels in response to the test but this effect was not seen among depressed individuals taking antidepressant medication. However, neither depression nor antidepressant use was associated with heart rate variability. As a whole, these studies suggest a modest and inconsistent relationship between depression and prolonged post-stress ANS activation. On the other hand, the relationship between depression and exaggerated HPA axis activity appears to be relatively strong. Finally,

antidepressant medication may be effective in reversing the excessive HPA axis activation observed in depressed individuals.

Résumé

La dépression est associée à un risque élevé de maladie cardiaque. Un mécanisme qui pourrait expliquer cette association est la dysfonction du système nerveux autonome (SNA) et l'axe hypothalamo-hypophyso-surrénalien (HHS), qui sont les deux systèmes impliqués dans la réaction physiologique au stress. Cette thèse avait comme but de mieux comprendre la relation entre la dépression et ces deux systèmes. Dans la première étude, l'effet de la dépression majeure sur le rétablissement de la fréquence cardiaque après l'exercice, un marqueur de la balance autonome, a été examiné chez des patients cardiaques. La dépression était associée à un pauvre rétablissement cardiaque immédiatement après l'exercice, ce qui suggère un délai dans l'activation du système parasympathique. Dans la deuxième étude, qui incluait des participants en santé, on examinait l'effet des symptômes dépressifs cognitifs et somatiques en relation avec le rétablissement de la fréquence cardiaque et la variabilité de la fréquence cardiaque, deux marqueurs de l'activation du SNA, en réaction à des stress interpersonnels de laboratoire. Les deux types de symptômes étaient associés avec un moins bon rétablissement cardiaque après les stress. Finalement, la troisième étude examinait la relation entre la dépression majeure et l'activité du SNA et de l'axe HHS en réaction à un test diagnostique stressant. De plus, l'étude a eu comme but de déterminer si les antidépresseurs sont efficaces dans le rétablissement d'une réponse normale au stress chez les dépressifs. Les patients cardiaques dépressifs avaient un niveau de cortisol plus élevé tout au long du test, ce qui indique une activation plus forte de l'axe HHS. Cet effet n'a pas été observé chez les dépressifs qui prenaient des antidépresseurs; par contre, ni la dépression ni l'utilisation des

antidépresseurs étaient associées à la variabilité de la fréquence cardiaque. Ces études suggèrent une relation modeste et inconsistante entre la dépression et une activation altérée du SNA. Par contre, la relation entre la dépression et la suractivation de l'axe HHS apparait relativement forte. Finalement, les antidépresseurs semblent être efficaces en annulant la suractivation de l'axe HHS chez les dépressifs.

General Introduction

Cardiovascular Disease (CVD)

CVD accounts for 30% of global deaths, making it the leading cause of mortality worldwide (World Health Organization, 2007). In Canada, CVD accounts for 28% of deaths in men and 30% of deaths in women, accounting for approximately 70 000 people each year (Statistics Canada, 2011). CVD also places an important burden on the Canadian health care system, costing nearly $20.8 billion in 1998 alone, accounting for almost 12% of the total cost of all illnesses (Conference Board of Canada, 2010).

CVD also has important costs to patients' quality of life and emotional well-being. For example, fatigue, shortness of breath, sleep problems and pain are common symptoms reported by patients in the months following coronary bypass surgery (Zimmerman, Barnason, Brey, Caitlin, & Nieveen, 2002). These symptoms are, in turn, associated with a decrease in physical and psychosocial functioning (Barnason et al., 2008). In addition, cardiac patients tend to be heavily medicated with blood pressure, cholesterol and diabetes medications, all of which have potentially very uncomfortable side effects such as dizziness, fatigue, gastrointestinal symptoms and erectile dysfunction (Bardage & Isacson, 2000; Hayes, Bowman, Monahan, Marrero, & McHorney, 2006).

The most important mechanism contributing to the development and progression of CVD is atherosclerosis, the process by which fatty plaques accumulate on the inner walls of arteries, leading to narrowing and loss of elasticity. This process is thought to begin with damage to the vascular endothelium, a layer of cells lining the vascular wall. The endothelium plays a

critical role in many important functions, such as the dilation and constriction of blood vessels and arteries and thrombus (blood clot) formation (Quyyumi, 2003). Endothelial damage also triggers an inflammatory response that is designed to promote self-repair. As part of this inflammatory response, macrophages, which are part of the body's immune system and whose function is to ingest and decompose pathogens found in the body, engulf LDL (low density lipoprotein or "bad" cholesterol) particles that have infiltrated the damaged endothelial layer. This creates what are called "foam cells". An accumulation of foam cells eventually creates a "fatty streak" or yellowish slightly raised area, the precursor to atherosclerotic plaques. Though fatty streaks are believed to be reversible (Libby, 2000), continual endothelial damage will trigger an escalation of the inflammatory response and a fibrous cap eventually covers the lesion and forms a hard plaque. The arterial wall calcifies and hardens. The formation of the plaque and the hardening of the artery cause obstruction of blood flow, also known as myocardial ischemia. If a plaque cap is unstable and becomes damaged, a thrombus (blood clot) can form, increasing the risk of a myocardial infarction (heart attack) or stroke (Stanner, 2005). Given that endothelial damage and inflammation are so critical to the atherosclerotic process, factors that damage the endothelium or promote the inflammatory response indirectly contribute to atherosclerosis and therefore CVD.

Traditional CVD Risk Factors

Two well-known studies, INTERHEART (Yusuf et al., 2004) and INTERSTROKE (O'Donnell et al., 2010), provide the clearest evidence to date regarding the relative importance of CVD risk factors. INTERHEART, a case-

control study of acute myocardial infarction (MI), involved nearly 30 000 participants across 52 countries. Several risk factors for MI were identified, accounting for 90% of the population attributable risk (PAR) among men and 95% of the PAR among women. The risk factor accounting for the greatest proportion of myocardial infarction cases (PAR = 49%) was dyslipidemia, characterized by elevated triglycerides and LDL cholesterol as well as low high density lipoprotein (HDL), commonly known as "good" cholesterol. Any current or past smoking was also an important predictor (PAR = 36%), as was abdominal obesity (PAR = 20%), which is defined as a body mass index (BMI) of 30 kg/m^2 or larger (Soodini & Hamdy, 2004) or a waist circumference greater or equal to 88 cm for women and 102 cm for men (Grundy, 2006).

Hypertension (PAR = 18%), irregular fruit and vegetable consumption (PAR = 14%), physical inactivity (PAR = 12%) and diabetes (PAR = 10%) were also found to be significant risk factors. Regular alcohol consumption (PAR = 7%), when compared to abstinence, was actually found to reduce the risk of MI.

INTERSTROKE, which examined the incidence of stroke among 3000 participants from 22 countries, was able to account for 90% of the PAR for all stroke. Hypertension (PAR = 35%), dyslipidemia (PAR = 25%), current smoking (PAR = 19%), obesity (PAR = 27%), physical inactivity (PAR = 29%) and diabetes (PAR = 5%) were all found to be significant predictors. A J-shaped relationship between alcohol consumption and stroke risk was also found such that 1-30 drinks per month was protective compared to abstinence while consuming >30 drinks or being a binge drinker was associated with an increased risk of stroke (PAR = 4%).

Though the mechanisms through which each of these risk factors impact CV health differ somewhat, they all, in one way or another, contribute to atherosclerosis by promoting vascular inflammation (Bermudez et al., 2002; Reusch & Draznon, 2007) and/or damaging the endothelium, be it by reducing the production or nitric oxide (NO), a compound that is critical for many of the endothelium's functions (Laine et al., 1998; Panza, Casino, Kilcoyne, & Quyyumi, 1993; Petrie, Ueda, Webb, Elliott, & Connell, 1996) or by directly damaging the integrity of endothelial cells (Beltowski et al., 2004; Hoshino et al., 2005).

In addition to the above traditional risk factors, psychosocial variables were also found to predict outcomes in both INTERHEART and INTERSTROKE. In INTERHEART, a model-dependent index, labelled "psychosocial factors" combining exposure to depression, perceived general stress, low locus of control and major life events, was found to account for 33% of the PAR of MI. However, the effects of psychological factors were less impressive for stroke: depression accounted for 5% of the PAR as did "psychosocial stress," a measure combining perceived stress at home and at work. Numerous other studies have examined the contribution of psychosocial factors to CVD using more sophisticated measures and have confirmed that several factors, such as depression, anxiety, hostility, lack of social support, and chronic life stress (Rozanski, Blumenthal, & Kaplan, 1999), play an role in contributing to CVD.

Psychological Factors and CVD

One of the first, and perhaps most well-known, psychological variables to be associated with an increased risk of CVD is the Type A personality. Type A

personality was first described in the late 1950's by Friedman and Rosenman: hostile, impatient, short-fused, competitive and ambitious. In 1959, Friedman & Rosenman reported the results of a cross-sectional study of 212 men finding that the rate of self-reported CVD was seven times higher among the men endorsing a Type A personality compared to men exhibiting the opposite behaviour pattern. Research examining the relationship between Type A behaviour and CVD soared in the following two decades but eventually dwindled as multiple studies failed to find a relationship between the Type A personality and CVD (Case, Heller, Case & Moss, 1985; Ragland & Brand, 1988; Shekelle, Gale & Norusis, 1985).

While research on Type A has become less prominent, several other psychological variables have been identified as being significantly related to an increased risk of CVD, including anxiety, anger/ hostility and depression. In summarising the state of the literature on each of these variables, a review by Suls & Bunde (2005) identified 12 prospective studies examining anxiety and CVD in healthy participants. Of the 12, five studies reported significant findings, with relative risks ranging between 2.40 and 7.80, while two obtained mixed results and two more found no association between anxiety and CVD. Of the 14 studies assessing the association between anxiety and cardiac death in CVD patients, only four studies found a significant association. It was therefore concluded that the relationship between anxiety and CVD is inconsistent and is particularly unimpressive among individuals already diagnosed with CVD.

Similarly inconsistent findings were reported for hostility. Among healthy participants, 11 prospective studies examining hostility and CVD were identified – of these, five found hostility to predict subsequent CVD and two found

marginally significant associations. The four remaining studies found no significant association. Relative risks for the positive studies ranged from 1.40 to 9.60. Of the six studies including participants already diagnosed with CVD, only one found hostility to be a significant predictor of outcomes. Anxiety and hostility have therefore been inconsistent predictors of CVD development and, even more so, progression.

The relationship between depression and CVD was found to be reliable. Of the 19 studies examining depression and risk of MI or cardiac death in healthy populations, only two obtained null findings. Among the studies 44 studies of cardiac patients, 29 obtained significant findings. However, as the authors point out, many of the negative reports may have been due to small sample sizes or too-short follow-up intervals.

Depression and CVD

Major depression is diagnosed according to a set of criteria outlined in the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV). It is characterised by either depressed mood and/or decreased interest or pleasure in activities, as well as five or more of the following for ≥ 2 weeks: significant change (increase or decrease) in appetite or weight, insomnia or hypersomnia, psychomotor agitation or retardation, fatigue or loss of energy, feelings of worthlessness or guilt, diminished ability to concentrate, diminished libido, and suicidal ideation (American Psychiatric Association, 1994). In addition, these symptoms must cause clinically significant distress or impairment in important areas of functioning and cannot be accounted for by the physiological effects of a substance, a medical condition, or bereavement.

Major depression can only be diagnosed properly using a clinical interview. Depressive symptoms, usually measured with multiple-choice questionnaires such as the Beck Depression Inventory (BDI), only capture symptoms at one particular time point and do not rule out the possibility that the symptoms are due to the effects of a substance, a medical condition, or bereavement. This is particularly problematic when studying diseased populations, such as cardiac patients, whose medical conditions and even the side effects of the medications they take, can mimic depressive symptoms. Though depressive symptoms, such as crying or having decreased libido, often accompany major depression and may be related to depression severity, their presence is not sufficient for the diagnosis of major depression. It is therefore important to recognize that although participants reporting a high number of depressive symptoms are often classified as "depressed", this is not technically correct, as clinical diagnoses of depression may only be obtained using structured psychiatric interview measures (e.g., Structured Clinical Interview for DSM, SCID).

Depressed individuals have been found to exhibit many of the risk factors that contribute to atherosclerosis, including hypertension (Davidson, Jonas, Dixon, & Markovitz, 2000; Jonas, Franks, & Ingram, 1997; Rabkin, Charles, & Kass, 1983) and insulin resistance, the precursor to diabetes (Everson-Rose et al., 2004; Timonen et al., 2005). Unsurprising then, both depressive symptoms (Sherwood, Hinderliter, Watkins, Waugh, & Blumenthal, 2005) and diagnosed major depression (Rajagopalan et al., 2001) have been associated with endothelial dysfunction, vascular inflammation (Joynt, Whellan, & O'Connor, 2003), and CVD. One meta-analysis of prospective studies examining the development of

CVD in initially healthy individuals found that major depression was associated with a 2.5-fold increased risk of developing CVD compared to non-depressed individuals (Van der Kooy et al., 2007). Another meta-analysis found that clinical depression in CVD patients was also associated with a 2- to 2.5-fold increased risk of all-cause mortality compared to those without depression (van Melle et al., 2004). Thus, unlike hostility and anxiety, depression appears to be an equally strong risk factor for CVD development among healthy individuals and for disease progression among cardiac patients.

It is unknown why depression is more clearly associated with CVD as compared to other psychological variables. In fact, the same mechanisms, including dysregulation of the biological stress systems, are thought to play a role in linking all psychological phenomena with CVD (Suls & Bunde, 2005). One possibility may be related to the particularly chronic nature of depression, which may result in more constant physiological effects. After all, individuals high in hostility are rarely angry all of the time, only when they encounter triggers that displease them. Anxiety is similar – though some individuals with severe generalized anxiety disorder would report feeling anxious nearly every waking hour, this is likely not the case with most anxious individuals. In the case of depression, depressed mood or anhedonia, as part of the DSM-IV criteria, must be present "on most days for most of the day", a specification that is not made for generalized anxiety disorder. Thus, perhaps depression has the potential to impact one's physiology in a more constant way than other psychological factors. The relatively consistent relationship between CVD risk and measures of chronic life stress, including job strain and stress related to being the caregiver to a sick

individual (Dimsdale, 2008), lend further evidence that this is a plausible explanation. However, little research has been devoted to comparing the physiological effects of different psychological ailments. Research is therefore needed to identify the unique elements of depression that are particularly toxic.

Although it is clear that depression is associated with many CVD risk factors and that it predicts the development of CVD, the mechanisms behind this association are unclear. Two main pathways have been proposed (Joynt et al., 2003): the first suggests that depressed patients' tendency to engage in poor health behaviours, such as smoking and over-eating, is responsible for their unhealthy CV profiles. The second assumes that depression is linked to CVD and its risk factors through an imbalance or dysregulation in the physiological systems involved in the stress response: the autonomic nervous system (ANS) and the hypothalamic-pituitary-adrenal (HPA) axis (Gordon, Lavoie, Arsenault, Ditto, & Bacon, 2011). This thesis will focus on this second potential pathway.

The HPA Axis

The HPA axis also plays a pivotal role in the body's stress response, though its effects are more delayed and longer-lasting than the ANS'. It consists of the paraventricular nucleus in the hypothalamus of the brain, which releases a hormone called corticotropin releasing factor (CRF), which in turn stimulates the release of adrenocorticotropin hormone (ACTH) by the pituitary gland. ACTH activates the adrenal cortex, the outer layer of the adrenal gland, to release glucocorticoids, including cortisol in humans, into the blood stream. Finally, glucocorticoid levels in the body provide negative feedback to the hypothalamus to control CRF release. When glucocorticoid levels are high, the hypothalamus is

inhibited from releasing more CRF, which, down the line, inhibits the release of more glucocorticoids. The sympathoadrenal (SA) system's release of plasma catecholamine levels, discussed in greater detail below, also help activate the HPA axis by stimulating the release of ACTH by the pituitary gland.

Measurement of the HPA axis. Although plasma ACTH and CRF can be measured as markers of HPA axis activation, these are rarely used in current stress research. Both degrade quite quickly and therefore must be processed soon after blood collection (Golden, Wand, Malhotra, Kamel, & Horton, 2011). They are also released in a pulsatile manner – the reliability of a single measurement is therefore relatively low. A final limitation of CRF measurement is that it is produced in several other areas of the body. Thus, plasma levels of CRF do not necessarily reflect HPA axis activation. For these reasons, the HPA axis is most commonly assessed using measures of cortisol at rest and in response to various challenge tests.

Cortisol. Cortisol can be measured in urine, serum or saliva. Since urine does not allow for the measurement of rapid changes in cortisol levels, both serum and salivary cortisol levels are more commonly used in laboratory settings. However, salivary cortisol measurement has several advantages over serum measures. First, the procedure for collecting salivary cortisol is minimally invasive whereas the stress of venepuncture can, itself, activate the HPA axis (Meeran, Hattersley, Mould, & Bloom, 1993). Second, while serum cortisol represents the total amount of cortisol in the body, salivary cortisol represents only the fraction of cortisol that is unbound to proteins such as cortisol binding globulin and is therefore available to exert physiological effects throughout the

body. Furthermore, salivary cortisol levels are not influenced by within-subject changes or between-subject differences in cortisol binding globulin (Gozansky, Lynn, Laudenslager, & Kohrt, 2005).

While resting cortisol measured at a particular time of day or cortisol measured regularly over the course of 24 hours provides information on baseline HPA axis activation, cortisol can also be measured in response to laboratory stressors to evaluate HPA axis reactivity. For example, the Trier Social Stress Task (TSST), a controlled laboratory protocol inducing moderate psychological stress through the use of public speaking and mental arithmetic, has been shown to induce reliable increases in cortisol (Kirshbaum, Pirke, & Hellhammer, 1993) that can be compared between subjects. However, regardless of whether cortisol is measured in urine, plasma or saliva, it is important to consider the time of day at which it is measured since both baseline and stress-related activation of the HPA axis fluctuates in predictable ways throughout the day and night (Burke, Davis, Otte, & Mohr, 2005)

Challenge tests: The dexamethasone and DEX-CRH test. The Dexamethasone Suppression Test was first developed to diagnose Cushing's Disease (Nugent, Nichols, & Tyler, 1965), a disorder characterized by a malfunctioning negative feedback loop and very high cortisol levels. Though challenge tests can provide important information, they require significantly more resources and man-power than simple cortisol measurements. Dexamethasone is a glucocorticoid similar to cortisol that acts on the same receptors but is much more potent. The test involves a patient being injected with a dose of dexamethasone and later having their plasma cortisol measured. The timing of cortisol

measurement is precise. If the patient's negative feedback loop is functioning properly, the administration of dexamethasone should disrupt further production of cortisol, thus resulting in relatively low cortisol levels. The combined Dexamethasone/CRH Test is similar but also requires the administration of CRH following dexamethasone-induced HPA axis suppression. Results from both tests are highly correlated (Watson, Gallagher, Smith, Ferrier, & Young, 2006).

The HPA axis and CVD. As with adrenaline, increased cortisol release is helpful during stress but is thought to contribute to the development of CVD when chronically activated (Miller, Cohen, & Ritchey, 2002). This is most apparent in patients with Cushing's Syndrome, a disorder characterized by the hypersecretion of cortisol, who are at four times the risk of developing CVD compared to the general population (Arnaldi, Mancini, Polenta, & Boscaro, 2004; Mancini, Kola, Mantero, Boscaro, & Arnaldi, 2004; Whitworth, Mangos, & Kelly, 2000). Even individuals with sub-clinical Cushing's Syndrome (Tauchmanova et al., 2002) and people who have been cured from this disorder for five years (Colao et al., 1999) are at an increased risk of developing CVD. Total cortisol exposure while awake (Dekker et al., 2008) and decline in cortisol levels throughout the day (Matthews, Schwartz, Cohen, & Seeman, 2006) are also independently associated with atherosclerosis. A recent study has also shown that urinary cortisol levels predict cardiac mortality – in fact those in the highest tertile of urinary cortisol exhibit a 5-fold increased risk in CV death (Vogelzangs et al., 2010).

Elevated cortisol levels are thought to increase one's risk of developing CVD through several mechanisms. For example, chronically elevated levels of cortisol can lead to the development of hypertension, which has long been known

to be a consequence of Cushing's Syndrome (Whitworth et al., 2000). Many placebo-controlled studies have confirmed that a dose-response relationship exists between cortisol and blood pressure in healthy individuals as well (Whitworth, Gordon, McLachlan-Troup, Scoggins, & Moulds, 1989; Whitworth, Saines, & Scoggins, 1984; Williamson, Kelly, & Whitworth, 1996). Cortisol's hypertension-inducing effect can be partially explained by its tendency to increase both salt and water retention (Panarelli et al., 1998) and to constrict the blood vessels by inhibiting its production of NO, which is a vasodilator (Kelly, Mangos, Williamson, & Whitworth, 1998). High cortisol levels can also contribute to insulin resistance by impairing insulin-dependent glucose uptake and enhancing glucose production in the pancreas (Andrews & Walker, 1999; Reynolds & Walker, 2003).

Cortisol levels are associated with the development of endothelial dysfunction in both clinical and sub-clinical cases of Cushing's Syndrome (Baykan et al., 2007; Colao et al., 1999). Studies blocking the production of cortisol have discovered that it is also responsible for the endothelial dysfunction observed in healthy participants in response to acute stress, for example, a public speaking task (Broadley et al., 2005). Though this effect may be partially due to cortisol's effect on blood pressure and insulin resistance, it is also thought to induce endothelial dysfunction by inducing cell apoptosis, a series of biochemical events that cause endothelium cell death (Vogt & Schmid-Schonbein, 2001) and decreasing the endothelium's production of NO (Johns, Dorrance, Tramontini, & Webb, 2001).

Elevated cortisol levels also contribute to the accumulation of abdominal obesity. The effect of cortisol on fat deposition is not only clear in Cushing's Syndrome patients, studies also show cortisol levels to be associated with abdominal obesity in healthy people (Fraser et al., 1999). Research suggests this may help explain the association between excess cortisol and high cholesterol and triglyceride levels (Walker, Soderberg, Lindahl, & Olsson, 2000).

The HPA axis and depression. Numerous studies have found that depressed patients exhibit abnormally high cortisol and CRF levels (Plotsky, Owens, & Nemeroff, 1998). Depressed coronary artery disease patients have also been found to exhibit lower cortisol levels in the morning and higher levels in the evening (i.e. "flatter" cortisol rhythms) compared to both non-depressed coronary artery disease patients and depressed patients without coronary artery disease (Bhattacharyya, Molloy, & Steptoe, 2008).

The reason behind depressed individuals' elevated cortisol levels is believed to be dysfunctional feedback inhibition (Pariante, 2006). In theory, newly depressed individuals first exhibit elevated cortisol levels due to elevations in subjective stress. These elevated cortisol levels bind to receptors in the hypothalamus and pituitary and, at first, successfully inhibit further cortisol production. However, with time, chronically elevated cortisol levels result in receptors that are desensitized, resulting in failed feedback inhibition. As described by Pariante (2006), this theory is supported by research showing that depressed individuals fail to show glucocorticoid suppression in response to the dexamethasone suppression test (Carroll, Martin, & Davies, 1968; Schatzberg, Rothschild, Bond, & Cole, 1984). In fact, the dexamethasone suppression test was

once thought to be an effective tool for diagnosing major depression, though it has since been abandoned for this use due to its lack of sensitivity and specificity (Arana, Baldessarini, & Ornsteen, 1985). Further evidence of impaired feedback inhibition in depression is provided by some studies finding that depressed individuals exhibit enlarged pituitary and adrenal glands, which suggests that the number of glucocorticoid receptors has increased to compensate for their decreased sensitivity (Kessing, Willer & Knorr, 2011).

Depressed people have also been found to exhibit abnormal cortisol responses to psychological stressors, generally consisting of a blunted stress-induced increase and elevated levels pre and post-stress. A meta-analysis of seven laboratory studies (Burke et al., 2005) found that depressed people exhibit much higher post-stress recovery cortisol levels compared to non-depressed controls. Another study examining cortisol responses to daily stressors (Peeters, Nicholson, & Berkhof, 2003) found that depressed individuals exhibited no change in cortisol levels in response to the stressors. Similarly, a study examining cortisol responses to orthopedic surgery found that while chronically depressed patients had significantly higher cortisol levels than non-depressed controls before the surgery, their cortisol levels failed to increase in response to the stress as did the non-depressed patients' (Kudoh, Ishihara, & Matsuki, 2000).

Abnormalities in the HPA axis are also believed to be involved in the vascular inflammation observed in depressed patients. Although depressed patients are believed to have abnormally high levels of circulating glucocorticoids, which have anti-inflammatory properties, their glucocorticoid immune receptors are thought to be desensitized, perhaps because of their chronic

over-exposure to cortisol, and therefore less responsive to the anti-inflammatory actions of circulating glucocorticoids (Cooney & Dinan, 1996).

The ANS

Along with the HPA axis, the other important physiological system involved in the stress response is the ANS. There are two branches that work together to form the ANS: the parasympathetic nervous system (PNS) and the sympathetic nervous system (SNS) (Goldstein, 2006). The SNS branch consists of cell bodies in the spinal cord projecting to autonomic ganglia, which are clusters of nerve cell bodies located in or around the organs they innervate. The neurons projecting from the central nervous system to the ganglion are called “pre-ganglionic” while neurons projecting from ganglions to target organs are “post-ganglionic”. Acetylcholine is the neurotransmitter released at the pre-ganglionic neuron while adrenaline and noradrenaline are neurotransmitters released at most post-ganglionic sympathetic terminals. By acting on the adrenal medulla, the middle region of the adrenal gland, the SNS also promotes the release of adrenaline and noradrenaline in the form of hormones. This connection is called the sympathoadrenal (SA) system. Though both the neurotransmitter and hormonal forms of adrenaline have similar functions, the hormonal form has a more systemic effect on the body. The role of the SNS and SA system is to prepare the body for "fight or flight" when faced with danger or stress by increasing heart rate, blood pressure and breathing rate.

The PNS consists of cell bodies in the brain stem and spinal cord, projecting to PNS ganglia throughout the body. Acetylcholine is the neurotransmitter that is released at both the pre and post-ganglionic synapses of

the PNS. However, the vagus nerve, which is most relevant to CV research since it controls the functioning of the heart, does not project to a ganglion. Instead, it emerges from the medulla, the lower half of the brain stem, and projects directly to its target organs. Because of the importance of the vagus nerve in controlling the heart, PNS output is often referred to as "vagal tone" in CV research. The role of the PNS is to conserve and restore energy by decreasing heart rate, blood pressure and breathing rate and by facilitating digestion.

Measurement of the ANS. Together, the SNS and PNS contribute to overall autonomic tone. The relative contributions of the SNS and PNS to CV activity are constantly shifting and can be approximated using several non-invasive measures. The most commonly used measures will be described: heart rate, heart rate variability and heart rate recovery. For a more detailed introduction to these measures, see Lahiri, Kannankeril, & Goldberger (2008).

Heart rate (HR). The heartbeat originates from the sino-atrial node of the heart, a grouping of cells that repetitively send electrical impulses creating heart muscle contractions. Unencumbered, the sino-atrial node sends impulses approximately 100 times per minute, though this rate can be influenced by many factors, including age, body weight, exercise, temperature and hypoxia (i.e., lack of oxygen) (Jose & Collison, 1970; Jose & Stitt, 1969; Jose, Stitt, & Collison, 1970). Beyond these factors, however, the SNS and PNS exert important influences on the heart to determine HR at a given time. The PNS and SNS have opposing effects, the PNS lowering HR and the SNS increasing it. HR is therefore the net result of the contributions of the PNS and SNS. An elevated HR therefore usually indicates dominance of the SNS over the PNS' control of the heart at a

particular time point whereas a low HR indicates a relatively greater contribution of the PNS.

An advantage of HR as a measure of autonomic tone is that it is very easy to measure, being minimally invasive and requiring no statistical software. Compared to more complex markers of autonomic tone, HR is reliable in that it responds to stimuli as expected (Goldberger, 1999). However, while HR has the advantages of simplicity and reliability, its main limitation is that it provides no information about the relative contributions of the sympathetic and parasympathetic branches unless the experimenter administers an agent that blocks parasympathetic (e.g., atropine) or sympathetic (e.g., beta-blocker) activity.

Heart rate variability (HRV). HRV is the amount of variation in the interval of time observed between heart beats (Lahiri, et al., 2008). Similar to HR, HRV is a function of both sympathetic and parasympathetic influences on the sino-atrial node. In healthy individuals, sympathetic and parasympathetic inputs are constantly in flux, responding to the individual's environment. The interval of time between heart beats is therefore constantly changing, creating elevated HRV. However, an imbalance in sympathetic and parasympathetic influences, generally resulting from sympathetic dominance, will result in low HRV.

HRV can be calculated using time or frequency domain analysis. Using time domain analysis, the standard deviation of the N-N interval (SDNN), also known as the standard deviation of the R-R interval (SDRR), can be calculated. SDNN is the simplest measure of HRV and results from a simple calculation of the standard deviation of the intervals between successive normal heart beats.

Frequency domain analysis, on the other hand, decomposes oscillations of the HR signal at different frequencies and amplitudes. One advantage of frequency domain analysis is that its parameters are differentially influenced by the SNS and PNS and therefore provides information not obtained with time domain analysis. Ultra low frequency (ULF), very low frequency (VLF) and low frequency (LF) power are influenced by both branches of the ANS. However, high frequency (HF) power is mainly influenced by parasympathetic activity (Akselrod et al., 1981). Finally, the ratio of LF to HF power is generally considered a proxy marker of the balance of sympathetic relative to parasympathetic tone. One reason for which the SNS and PNS are associated with different frequency ranges is that the timing of the HR response is different for either branch. While sudden PNS activation exerts it maximum effect on HR at 0.6 seconds and returns to baseline by 1 second, a burst of SNS activity will take 1 second to exert its effects on HR, the maximal effect occurring at 4 seconds and then the effect returning to baseline by 20 seconds (Spear, Kronhaus, Moore & Kline, 1979). Thanks to this differential timing, the PNS modulates HR at frequencies between 0 and 0.5 Hz while the SNS does so at frequencies below 0.15 Hz.

As Lahiri et al. (2008) argue, although each HRV indice is differentially influenced by the SNS and PNS branches, it is important to recognize that there are individual differences in this relationship, in part due to genetic differences (Kupper et al, 2004). It is therefore incorrect to strictly associate one HRV indice to either ANS branch. However, while HRV should not be treated as a marker of absolute SNS or PNS activation, it is useful as an indicator of relative changes in their activation.

Heart rate recovery. HR increases during exercise due to an increase in SNS activation and a decrease in PNS tone. Once exercise has stopped, HR gradually returns to baseline through further changes in SNS and PNS tone. Studies have attempted to determine the relative contribution of SNS withdrawal and PNS activation in HR recovery by selectively blocking the PNS using atropine and blocking the SNS with propanolol. For example, one study had participants exercise following administration of propanolol and found that HR recovery 30 seconds post-exercise was unaffected but was significantly impaired 2 minutes following exercise (Imai et al., 1994). This suggests that at least for the first minute following exercise cessation, PNS activation is at play while SNS de-activation plays a minimal role until later in the recovery period. A second study confirms that the SNS plays little role in early recovery, finding that healthy participants' HR recovery in the first minute of recovery did not differ whether they had received propanolol (SNS blocker) alone or propanolol and atropine (PNS blocker) together (Sundaram, Shoushtari, Carnethon, Kadish, & Goldberger, 2004).

Research examining the prognostic capabilities of post-exercise HR recovery has found that a drop of less than 12 beats per minute (bpm) from the end of exercise to 1 minute post-exercise or a drop of less than 22 bpm by 2 minutes post-exercise have been identified as prognostic cut-points (Shetler et al., 2001). However, cut-points for later recovery have not been well established.

In addition to exercise, HR recovery following psychological stressors can also be examined. Particularly popular laboratory stressors include public speaking and mental arithmetic tasks. However, although the ANS contributes to

HR recovery from these tasks, psychological processes also play a role. Post-event rumination, for example, has been associated with prolonged physiological activation following emotionally-laden tasks (Glynn, Christenfield & Gerin, 2002). While this does not diminish the potential importance of the information obtained, it is important to note that recovery following psychological stressors are not markers of ANS function, per say, because one's response is mediated by mental processes as well.

Other measures. Several other measures of ANS activation also exist. However, they will only be briefly mentioned here since they are less important in the context of the current thesis. For example, baroreflex sensitivity is a measure of how quickly HR changes in response to changes in blood pressure, whether spontaneous or induced by laboratory manipulations (La Rovere, Pinna, & Raczak, 2008). Lower baroreflex sensitivity indicates sympathetic dominance. Catecholamines adrenaline and noradrenaline have also long been measured in the plasma and urine as a measure of SA system activation (Goldstein, McCarty, Polinsky, & Kopin, 1983; Mason, 1968).

The ANS and CVD. While the SNS plays an important role in preparing the body to react to danger, chronic activation of the SNS can have negative consequences for the CV system. Many indicators of SNS dominance over the PNS have been shown to predict future cardiac mortality. For example, elevated resting HR has been shown to predict CV outcomes (Cooney et al., 2010; Fox et al., 2007). Reduced HRV also predicts MI and cardiac mortality (M. T. La Rovere, Bigger, Marcus, Mortara, & Schwartz, 1998; Nolan et al., 1998; Tsuji et al., 1994). Impaired HR recovery after exercise (Cole, Foody, Blackstone, &

Lauer, 2000; Farrell et al., 1992; Mora et al., 2003; Morshedi-Meibodi, Larson, Levy, O'Donnell, & Vasan, 2002; Nishime, Cole, Blackstone, Pashkow, & Lauer, 2000), as well as reduced baroreflex sensitivity, have similarly been found to predict cardiac outcomes (Farrell et al., 1992; La Rovere et al., 1998). SNS hyperactivity is likely related to cardiac mortality by causing instability in the heart's electrical system, causing the heart to beat abnormally (arrhythmias), which can cause sudden cardiac death (Coker, Koziell, Oliver, & Smith, 1984). In addition, sympathetic dominance likely increases one's risk of CVD through disruption of the SA system.

As is the case with the neurotransmitter form of adrenaline, chronically high levels of plasma adrenaline and noradrenaline can contribute to the development of many CVD risk factors observed in depressed patients. For example, chronically high levels of adrenaline and noradrenaline can induce hypertension by increasing blood flow (Esler, 2000). In healthy individuals, increased blood flow causes the endothelium to release NO, leading the blood vessels to relax and dilate. However, with chronically increased blood flow, the endothelium becomes desensitized to pressure exerted by blood on the inner vessel walls. The endothelium therefore releases less NO and the blood vessels become stiffer and more constricted. With this decrease in functioning, the endothelium becomes impaired in performing its antithrombotic functions as well, resulting in an increased risk of thrombus (blood clot) formation (Anfossi & Trovati, 1996). Hypertension also promotes the development of insulin resistance (the precursor to diabetes) by preventing muscle cells from absorbing the insulin that is in the blood stream, (Lembo et al., 1993; Mancia et al., 2007). Finally,

adrenaline and noradrenaline also impact the CV system by stimulating the HPA axis.

The ANS and depression. Much research supports the hypothesis that an imbalance in the ANS, and subsequently the SA system, is a mechanism linking depression to CVD. For example, numerous studies have found both clinical depression (Carney et al., 2001; 2007; Kemp et al., 2010) and self-reported depressive symptoms (Guinjoan et al., 2007; Stein et al., 2000) to be associated with lower HRV. Depressed mood has also been associated with elevated resting HR (Dawson, Schell, & Catania, 1977; Lahmeyer & Bellur, 1987), reduced baroreflex cardiac control (Watkins & Grossman, 1999) and increased systolic blood pressure during exercise (Pelletier et al., 2009), all indicating sympathetic dominance. Finally, depression is associated with electrical instability of the heart (Nahshoni et al., 2000; Yeragani et al., 2000), likely a consequence of ANS dysfunction, increasing the risk of arrhythmias (Carney, Freedland, Rich, Smith, & Jaffe, 1993). A few studies also suggest that depressive symptoms are associated with delayed HR recovery following exercise (Hughes et al., 2006; Hughes et al., 2008).

Depressed individuals have also been found to exhibit signs of a hyperactive SA system. For example, it has been known for many years that depressed patients exhibit higher plasma noradrenaline levels compared to non-depressed controls (Esler et al., 1982; Lake et al., 1982; Roy, Pickar, De Jong, Karoum, & Linnoila, 1988; Veith, Best, & Halter, 1984; Wyatt, Portnoy, Kupfer, Snyder, & Engelman, 1971). One study had 60 healthy women complete the Beck Depression Inventory (BDI) and compared the catecholamine levels of the 15

women with highest scores to the 15 with the lowest scores in response to a public speaking task. The "depressed" women were found to have higher plasma noradrenaline levels (in addition to greater blood pressure and several other measures of sympathetic activation) during the task compared to the "non-depressed" group (Light, Kothandapani, & Allen, 1998). Another study examined BDI scores and physiological recovery to a stress-inducing public speaking task in non-depressed women. It found that although all participants exhibited high plasma adrenaline levels immediately after the stressor, only the women with scores in the high-normal range had high adrenaline levels 45 minutes post-stressor (Gold, Zakowski, Valdimarsdottir, & Bovbjerg, 2004). In contrast, participants with low BDI scores had similar adrenaline levels to non-stressed controls within 30 minutes of the stressor. These analyses adjusted for perceived stress during the task, reducing the possibility that the more "depressed" participants simply found the task more psychologically stressful. Collectively, these studies suggest that depressive symptoms, even in the sub-clinical range, are associated with enhanced SA system activation, both in general and in response to stressful tasks. Furthermore, the latter study suggests that this physiological response does not result solely from depressed people feeling more psychologically distressed in response to stressful tasks than non-depressed people.

Although there are many studies suggesting that depression is associated with an imbalance in ANS cardiac control, there are others that have failed to find an effect. For example, one study of 873 coronary heart disease outpatients found that 24-hour HRV was not related to depression (Gehi, Mangano, Pipkin,

Browner, & Whooley, 2008). Depression was also not associated with 24-hour HRV in 83 post-MI patients after adjustment for basic covariates (Martens, Nylicek, Szabo, & Kupper, 2008). Thus, although the bulk of the literature supports the existence of ANS imbalance among depressed individuals, this relationship may not be as strong or consistent as the relationship between depression and HPA axis imbalance.

Though the mechanism through which depressed individuals come to develop ANS dysregulation is not well understood, one hypothesis relates to β-adrenergic receptors, which bind catecholamines such as adrenaline (York et al., 2007). It is thought that, through excessive stimulation, the receptors become desensitized and also decrease in density to compensate for the excessive adrenaline levels. In fact, depressed individuals have been shown to exhibit decreased adrenergic receptor sensitivity (Charney, Heninger, Sternber, Hafstad, Giddings, & Landis, 1982) and density (Mills et al., 2003).

The Treatment of Depression and HPA Axis Activation

Considering the relationship between depression and dysregulation of the ANS and HPA axis is fairly well-established and given that ANS and HPA axis dysregulation have, in turn, been shown to have negative consequences on CV health, the next logical step in research is to assess whether treating depression leads to improvements in physiological regulation.

Psychotherapy. The only study to have examined the effect of psychotherapy on HPA axis activation is the study described in the previous section, by Taylor et al. (2009). Despite impressive declines in depressive symptoms following the 16 sessions of cognitive behavioural therapy (CBT), the

48 participants at high risk for CVD exhibited no significant changes in cortisol levels following the intervention.

Antidepressant medication. The dampening effect of antidepressants on baseline HPA axis activity is relatively well-established. A recent meta-analysis included 34 studies examining the effect of antidepressant medication on cortisol levels found that antidepressants had a large overall cortisol-lowering effect (McKay & Zakzanis, 2010). Of the antidepressant classes, selective serotonin reuptake inhibitors (SSRIs) were found to have the greatest impact on cortisol (Cohen's d = 0.87), followed by tricyclic antidepressants (TCAs) (d = 0.65) and serotonin norepinephrine reuptake inhibitors (SNRIs) (d = 0.56). This translated to roughly 44% of antidepressant users exhibiting a decrease in cortisol levels from pre to post-treatment while 56% showed little change. While the effect of antidepressants on cortisol levels tended to be stronger among participants who exhibited the greatest decrease in depressive symptoms, the difference was not found to be statistically significant. It therefore appears that the effect of antidepressants on cortisol was mainly attributable to its physiological rather than its psychological effects. However, this difficulty in attribution is a recurrent issue in antidepressant medication research. No other variables predicting cortisol responses to antidepressant use were identified. However, as the authors acknowledge, the meta-analysis did not consider whether participants exhibited HPA axis abnormalities prior to medication use. This may therefore be an important variable to consider in future studies in helping identify those participants that would most likely exhibit a decrease in cortisol levels following antidepressant use. Antidepressants are believed to lower cortisol levels by

improving negative feedback within the HPA axis through an increase in the expression and function of glucocorticoid receptors in the paraventricular nucleus of the hypothalamus (Pariante, 2006). Thus, it would make sense that those individuals exhibiting the greatest dysfunctional negative feedback loop would stand to benefit the most from the regulating effects of antidepressants. However, further research is needed to confirm whether this is truly the case.

The Treatment of Depression and ANS Balance

Psychotherapy. Few studies to date have examined the effect of psychotherapy on autonomic tone. In one study including 30 depressed participants with stable coronary heart disease, HRV was examined before and after 16 sessions of cognitive-behavioural therapy for depression (Carney et al., 2000). The intervention proved effective, with 84% of mildly depressed participants and 92% of severely depressed participants experiencing partial or complete remission. However, in terms of physiological outcomes, the results were relatively modest. Although average HR decreased and the root mean squared difference of successive N-N intervals (rmSSD) (a marker of parasympathetic tone) increased among severely depressed participants, only rmSSD levels became comparable to a group of non-depressed controls. However, none of the remaining HRV indices changed. Also, no changes were observed among mildly depressed participants, despite their improvements in depressive symptoms.

In a second study, 48 depressed participants at high risk for CVD were randomised to either 16 sessions of individual CBT or to a wait-list control group (Taylor et al., 2009). Several markers of autonomic tone were measured before

and after treatment, including resting HR, respiratory sinus arrhythmia (a measure of parasympathetic activity) as well as HRV in response to a psychological stressor. However, despite the efficacy of CBT in improving depressive symptoms (mean BDI-II scores dropped from 25 to 10), no changes were seen in any markers of ANS tone.

This study, along with the study by Carney et al., seems to suggest that even when psychotherapy is successful in treating depression, autonomic dysfunction remains apparent.

Antidepressant medication. There is considerably more research examining the effect of pharmacological interventions for depression and the ANS. However, inconsistencies in the literature still exist. A fairly recent meta-analysis including intervention studies of the effect of antidepressants on HRV in non-CVD participants found that while tricyclic antidepressants (TCAs) contribute to a decrease in HRV, selective serotonin reuptake inhibitors (SSRIs) and serotonin and noradrenaline reuptake inhibitors (SNRIs) do not exhibit a significant effect (Kemp et al., 2010). However, a few studies not included in this meta-analysis have obtained contradictory findings. For example, a two-year longitudinal study of 2114 participants found that starting treatment with any antidepressant was associated with a decrease in HRV (Licht, de Geus, van Dyck, & Penninx, 2010). Furthermore, discontinuing an antidepressant resulted in an increase in HRV, suggesting the negative effects of antidepressants are somewhat reversible. A second study measured HRV and baroreflex sensitivity among 75 depressed participants and 75 controls, whom were assigned to receive either an SSRI or SNRI for 7-9 days (Koschke et al., 2009). At baseline, the depressed

participants exhibited decreased HRV and decreased baroreflex sensitivity. SNRI, but not SSRI, use further exaggerated this difference.

In contrast to studies in non-CVD individuals, research examining the effect of antidepressants in CVD patients have suggested that antidepressants are helpful in re-establishing autonomic balance (Jiang & Davidson, 2005). For example, one study included 38 post-myocardial infarction depressed patients who were randomized to receive either Sertraline (an SSRI) or placebo for 6 months (McFarlane et al., 2001). At the end of the intervention period, in addition to experiencing a significant drop in depressive symptoms, participants receiving Sertraline were found to exhibit higher SDNN and LF power as well as lower LF/HF compared to participants receiving placebo. A second study assigned depressed CVD patients to receive Paroxetine (an SSRI) or Nortriptyline (a TCA) for six weeks (Yeragani et al., 2000). Nortriptyline use resulted in a decrease in several HRV indices while paroxetine use resulted in an increase in WC-100, a non-linear measure of HRV. This study thus provides further evidence that while TCAs promote sympathetic dominance and are therefore potentially harmful for CVD patients, SSRIs are potentially cardioprotective.

Thus, while the negative effects of TCAs on ANS tone are well-established, there appears to be some contradiction in the literature regarding the effects of SSRIs and SNRIs, with some studies finding that they exhibit no significant effect on the ANS, others finding them to dampen sympathetic output.

The Current Thesis

Though there have been many studies linking depression to dysregulation of the ANS and HPA axis, researchers have, in many instances, been unsuccessful

in reversing this dysregulation through successful treatment of depressive symptoms. Clearly, we do not fully comprehend this complex relationship. The current thesis therefore aimed to help fine-tune our understanding of this relationship since, as has been suggested by others, this may allow us to design more effective intervention studies (Joynt & O'Connor, 2005).

Manuscript One presents a study examining the relationship between major depression and post-exercise HR recovery among cardiac outpatients. This study aimed to improve upon several limitations of previous research. First, by measuring both early and late recovery following exercise, this study helps clarify which branch of the ANS is most important in explaining the reduced HR recovery seen in depressed individuals. Second, this study assessed not only continuous depressive symptoms using a questionnaire but also clinical depression using a diagnostic psychiatric interview. This is particularly important in a sample of cardiac patients in whom the symptoms of CVD might be mistaken for depression without careful questioning.

Manuscript Two describes a study aimed at clarifying whether cognitive (e.g. hopelessness, worthlessness) and somatic (e.g. agitation, fatigue) depressive symptoms are differentially associated with ANS dysfunction in response to psychological stress. Healthy adults underwent a series of interpersonal laboratory stressors while their HR and HRV were measured. They also completed a questionnaire assessing both cognitive and somatic depressive symptoms.

Manuscript Three describes a study of cardiac outpatients undergoing a stressful diagnostic procedure. Three groups of participants were compared: non-depressed controls, depressed participants taking antidepressants and unmedicated

depressed participants. All three groups were compared in terms of their HR, HRV and cortisol levels throughout the test. In doing so, this study aimed to determine whether antidepressants are effective not only in lowering baseline sympathetic and HPA axis activation, as other studies have explored, but also in dampening the prolonged stress-induced physiological activation observed in depressed individuals.

References

Akselrod, S., Gordon, D., Ubel, F. A., Shannon, D. C., Berger, A. C., & Cohen, R. J. (1981). Power spectrum analysis of heart rate fluctuation: a quantitative probe of beat-to-beat cardiovascular control. *Science, 213*(4504), 220-222. doi: 10.1126/science.6166045

American Psychiatric Association. (1994). Diagnostic and statistical manual of mental disorders (DSM-IV). 4th ed.

Andrews, R. C., & Walker, B. R. (1999). Glucocorticoids and insulin resistance: old hormones, new targets. *Clinical Science, 96*(5), 513-523. doi: 10.1042/CS19980388

Anfossi, G., & Trovati, M. (1996). Role of catecholamines in platelet function: pathophysiological and clinical significance. *European Journal of Clinical Investigation, 26*(5), 353-370. doi: 10.1046/j.1365-2362.1996.150293.x

Arana, G. W., Baldessarini, R. J., & Ornsteen, M. (1985). The dexamethasone suppression test for diagnosis and prognosis in psychiatry. *Archives of General Psychiatry, 42*(12), 1193-1204. doi: 10.1001%2Farchpsyc.1985.01790350067012

Arnaldi, G., Mancini, T., Polenta, B., & Boscaro, M. (2004). Cardiovascular risk in Cushing's syndrome. *Pituitary, 7*(4), 253-256. doi: 10.1007/s11102-005-1172-7

Bardage, C., & Isacson, D. G. L. (2000). Self-reported side-effects of antihypertensive drugs: an epidemiological study on prevalence and impact on health-state utility. *Blood pressure, 9*, 328-334. doi: 10.1080/080370500300000905

Barnason, S., Zimmerman, L., Schulz, P., Miller, C., Hertzog, M., & Rasmussen, D. (2008). Relationships between fatigue and early postoperative recovery outcomes over time in elderly patients undergoing coronary artery bypass graft surgery. *Issues in Cardiovascular Nursing, 37*(4), 245-256. doi: 10.1016/j.hrtlng.2007.09.003

Baykan, M., Erem, C., Gedikli, O., Hacihasanoglu, A., Erdogan, T., Kocak, M. (2007). Impairment of flow-mediated vasodilatation of brachial artery in patients with Cushing's Syndrome. *Endocrine, 31*(3), 300-304. doi: 10.1007/s12020-007-0033-8

Beltowski, J., Jochem, J., Wojcicka, G., & Zwirska-Korczala. (2004). Influence of intravenously administered leptin on nitric oxide production, renal hemodynamics and renal function in the rat. *Regulatory Peptides, 120*, 59-67. doi: 10.1016%2Fj.regpep.2004.02.012

Berkman, L. F., Blumenthal, J., Burg, M., Carney, R. M., Catellier, D., Cowan, M. J. (2003). Effects of treating depression and low perceived social support on clinical events after myocardial infarction: the Enhancing Recovery in Coronary Heart Disease Patients (ENRICHD) Randomized Trial. *Journal of the American Medical Association, 289*(23), 3106-3116. doi: 10.1001/jama.289.23.3106

Bermudez, E. A., Rifai, N., Buring, J. E., Manson, J. E., & Ridker, P. M. (2002). Relation between markers of systemic vascular inflammation and smoking in women. *American Journal of Cardiology, 89*(9), 1117-1119. doi: 10.1016/S0002-9149(02)02284-1

Bhattacharyya, M. R., Molloy, G. J., & Steptoe, A. (2008). Depression is associated with flatter cortisol rhythms in patients with coronary artery disease. *Journal of Psychosomatic Research, 65*(2), 107-113. doi: 10.1016/j.jpsychores.2008.03.012

Broadley, A. J., Korszun, A., Abdelaal, E., Moskvina, V., Jones, C. J., Nash, G. B. (2005). Inhibition of cortisol production with metyrapone prevents mental stress-induced endothelial dysfunction and baroreflex impairment. *Journal of the American College of Cardiology, 46*(2), 344-350. doi: 10.1016/j.jacc.2005.03.068

Burke, H. M., Davis, M. C., Otte, C., & Mohr, D. C. (2005). Depression and cortisol responses to psychological stress: a meta-analysis. *Psychoneuroendocrinology, 30*(9), 846-856. doi: 10.1016/j.psyneuen.2005.02.010

Carney, R. M., Blumenthal, J. A., Freedland, K. E., Youngblood, M., Veith, R. C., Burg, M. M. (2004). Depression and late mortality after myocardial infarction in the Enhancing Recovery in Coronary Heart Disease (ENRICHD) study. *Psychosomatic Medicine, 66*(4), 466-474. doi: 10.1097/01.psy.0000133362.75075.a6

Carney, R. M., Blumenthal, J. A., Stein, P. K., Watkins, L., Catellier, D., Berkman, L. F. (2001). Depression, heart rate variability, and acute myocardial infarction. *Circulation, 104*(17), 2024-2028. doi: 10.1161/ hc4201.097834

Carney, R. M., Freedland, K. E., Rich, M. W., Smith, L. J., & Jaffe, A. S. (1993). Ventricular tachycardia and psychiatric depression in patients with

coronary artery disease. *American Journal of Medicine, 95*(1), 23-28. doi: 10.1016/0002-9343(93)90228-H

Carney, R. M., Freedland, K. E., Stein, P. K., Skala, J. A., Hoffman, P., & Jaffe, A. S. (2000). Change in heart rate and heart rate variability during treatment for depression in patients with coronary heart disease. *Psychosomatic Medicine, 62*(5), 639-647.

Carney, R. M., Freedland, K. E., Stein, P. K., Miller, G. E., Steinmeyer, B., Roch, M. W., & Duntley, S. P. (2007). *Journal of Psychosomatic Research, 62*(4), 463-467. doi: 10.1016%2Fj.jpsychores.2006.12.004

Carroll, B. J., Martin, F. I., & Davies, B. (1968). Pituitary-adrenal function in depression. *Lancet, 1*(7556), 1373-1374. doi: 10.1016%2FS0140-6736%2868%2992072-2

Case, R. B., Heller, S. S., Case, N. B., & Moss, A. J. (1985) The Multicenter Post Infarction Research Group: type A behavior and survival after acute myocardial infarction. *New England Journal of Medicine, 312*, 737-741.

Charney, D. S., Heninger, G. R., Sternberg, D. E., Hafstad, K. M., Giddings, S., & Landis, D. H. (1982). Adrenergic-Receptor Sensitivity in Depression - Effects of Clonidine in Depressed-Patients and Healthy-Subjects. *Archives of General Psychiatry, 39*(3), 290-294.

Coker, R., Koziell, A., Oliver, C., & Smith, S. E. (1984). Does the sympathetic nervous system influence sinus arrhythmia in man? Evidence from combined autonomic blockade. *Journal of Physiology, 356*, 459-464.

Colao, A., Pivonello, R., Spiezia, S., Faggiano, A., Ferone, D., Filippella, M. (1999). Persistence of increased cardiovascular risk in patients with

Cushing's disease after five years of successful cure. *Journal of Clinical Endocrinology & Metabolism, 84*(8), 2664-2672. doi: 10.1210/jc.84.8.2664

Cole, C. R., Foody, J. M., Blackstone, E. H., & Lauer, M. S. (2000). Heart rate recovery after submaximal exercise testing as a predictor of mortality in a cardiovascularly healthy cohort. *Annals of Internal Medicine, 132*(7), 552-555.

Conference Board of Canada. (2010). The canadian heart health strategy: risk factors and future cost implications. Retrieved from http://www.conferenceboard.ca/temp/14874e6d-f532-4e78-8518-bf472c3d1582/CDN-Heart--Health-Strategy_WEB.pdf

Cooney, J. M., & Dinan, T. G. (1996). Type II (glucocorticoid) receptors mediate fast-feedback inhibition of the hypothalamic-pituitary-adrenal axis in man. *Life Sciences, 59*(23), 1981-1988. doi: 10.1016/S0024-3205(96)00549-8

Cooney, M. T., Vartiainen, E., Laatikainen, T., Laakitainen, T., Juolevi, A., Dudina, A. (2010). Elevated resting heart rate is an independent risk factor for cardiovascular disease in healthy men and women. *American Heart Journal, 159*(4), 612-619.e613. doi: 10.1016/j.ahj.2009.12.029

Davidson, K., Jonas, B. S., Dixon, K. E., & Markovitz, J. H. (2000). Do depression symptoms predict early hypertension incidence in young adults in the CARDIA study? Coronary Artery Risk Development in Young Adults. *Archives of Internal Medicine, 160*(10), 1495-1500. doi: 10.1001%2Farchinte.160.10.1495

Dawson, M. E., Schell, A. M., & Catania, J. J. (1977). Autonomic correlates of depression and clinical improvement following electroconvulsive shock therapy. *Psychophysiology, 14*(6), 569-578. doi: 10.1111%2Fj.1469-8986.1977.tb01201.x

Dekker, M. J. H. J., Koper, J. W., van Aken, M. O., Pols, H. A. P., Hofman, A., de Jong, F. H. (2008). Salivary cortisol is related to atherosclerosis of carotid arteries. *Journal of Clinical Endocrinology & Metabolism, 93*(10), 3741-3747. doi: 10.1210/jc.2008-0496

Dimsdale, J. (2009). Psychological stress and cardiovascular disease. *Journal of the American College of Cardiology, 51*(13), 1237-1246. doi: 10.1016/j.jacc.2007.12.024

Esler, M. (2000). The sympathetic system and hypertension. *American Journal of Hypertension, 13*(6 Pt 2), 99S-105S. doi: 10.1016/S0895-7061(00)00225-9

Esler, M., Turbott, J., Schwarz, R., Leonard, P., Bobik, A., Skews, H. (1982). The peripheral kinetics of norepinephrine in depressive illness. *Archives of General Psychiatry, 39*(3), 295-300. doi: 10.1001%2Farchpsyc.1982.04290030035006

Everson-Rose, S. A., Meyer, P. M., Powell, L. H., Pandey, D., Torrens, J. I., Kravitz, H. M. (2004). Depressive symptoms, insulin resistance, and risk of diabetes in women at midlife. *Diabetes Care, 27*(12), 2856-2862. doi: 10.2337/diacare.27.12.2856

Farrell, T. G., Odemuyiwa, O., Bashir, Y., Cripps, T. R., Malik, M., Ward, D. E. (1992). Prognostic value of baroreflex sensitivity testing after acute

myocardial infarction. *British Heart Journal, 67*(2), 129-137. doi: 10.1136/hrt.67.2.129

Fox, K., Borer, J. S., Camm, A. J., Danchin, N., Ferrari, R., Lopez Sendon, J. L. (2007). Resting heart rate in cardiovascular disease. *Journal of the American College of Cardiology, 50*(9), 823-830. doi: 10.1016/j.jacc.2007.04.079

Fraser, R., Ingram, M. C., Anderson, N. H., Morrison, C., Davies, E., & Connell, J. M. (1999). Cortisol effects on body mass, blood pressure, and cholesterol in the general population. *Hypertension, 33*(6), 1364-1368. doi: 10.1161/01.HYP.33.6.1364

Friedman, M, & Rosenman, R. H. (1959). Association of specific overt behavior patter with blood and cardiovascular findings. *Journal of the American Medical Association, 169*(12), 1286-1296. doi: 10.1001/jama.1959.03000290012005

Gehi, A., Mangano, D., Pipkin, S., Browner, W. S., & Whooley, M. A. (2005). Depression and heart rate variability in patients with stable coronary heart disease: findings from the Heart and Soul Study. *Archives of General Psychiatry, 62*(6), 661-666. doi: 10.1001%2Farchpsyc.62.6.661

Glynn, L. M., Christenfeld, N., & Gerin, W. (2002). The role of rumination in recovery from reactivity: cardiovascular consequences of emotional states. *Psychosomatic Medicine, 64*(5), 714-726. doi: 10.1097/01.PSY.0000031574.42041.23

Gold, S. M., Zakowski, S. G., Valdimarsdottir, H. B., & Bovbjerg, D. H. (2004). Higher Beck depression scores predict delayed epinephrine recovery after

acute psychological stress independent of baseline levels of stress and mood. *Biological Psychology, 67*(3), 261-273. doi: 10.1016/j.biopsycho.2003.12.001

Goldberger, J. J. (1999). Sympathovagal balance: how should we measure it? *American Journal of Physiology - Heart & Circulatory Physiology, 276*(4), H1273-H1280.

Golden, S. H., Wand, G. S., Malhotra, S., Kamel, I., & Horton, K. (2011). Reliability of hypothalamic-pituitary-adrenal axis assessment methods for use in population-based studies. *European Journal of Epidemiology, 26*(7), 511-525. doi: 10.1007%2Fs10654-011-9585-2

Goldstein, D. S. (2006). *Adrenaline and the inner world*. Baltimore: The John Hopkins University Press.

Goldstein, D. S., McCarty, R., Polinsky, R. J., & Kopin, I. J. (1983). Relationship between plasma norepinephrine and sympathetic neural activity. *Hypertension, 5*(4), 552-559. doi: 10.1161/01.HYP.5.4.552

Gordon, J. L., Lavoie, K. L., Arsenault, A, Ditto, B, & Bacon, S. L. (2008). Health behaviors and endothelial function. *Journal of Behavioral Medicine, 31*(1), 5-21. doi: 10.1007%2Fs10865-007-9129-0

Gordon, J. L., Lavoie, K. L., Arsenault, A, Ditto, B, & Bacon, S. L. (2011). *Mood disorders and cardiovascular disease*. Rijeka, Croatia: Intech.

Gozansky, W. S., Lynn, J. S., Laudenslager, M. L., & Kohrt, W. M. (2005). Salivary cortisol determined by enzyme immunoassay is preferable to serum total cortisol for assessment of dynamic hypothalamic--pituitary--

adrenal axis activity. *Clinical Endocrinology, 63*(3), 336-341. doi: 10.1111/j.1365-2265.2005.02349.x

Grundy, S. M. (2006). Metabolic Syndrome: Connecting and Reconciling Cardiovascular and Diabetes Worlds. *Journal of the American College of Cardiology, 47*(6), 1093-1100. doi: 10.1016/j.jacc.2005.11.046

Guinjoan, S. M., Castro, M. N., Vigo, D. E., Weidema, H., Berbara, C., Fahrer, R. D. (2007). Depressive symptoms are related to decreased low-frequency heart rate variability in older adults with decompensated heart failure. *Neuropsychobiology, 55*(3-4), 219-224. doi: 10.1159/000108381

Hayes, R. P., Bowman, L., Monahan, P. O., Marrero, D. G., & McHorney, C. A. (2006). Diabetes medications from the perspective of patients with type 2 diabtes: prerequisite to medication concordance. *The Diabetes Educator, 32*(3), 404-414. doi: 10.1177/0145721706288182

Hoshino S, Yoshida M, Inoue K, Yano Y, Yanagita M, Mawatari H, … Kawase, I. (2005). Cigarette smoke extract induces endothelial cell injury via JNK pathway. *Biochemical and Biophysical Research Communications, 329*(1)**,** 58-63. doi: 10.1016%2Fj.bbrc.2005.01.095

Hubert, H. B., Feinleib, M., McNamara, P. M., & Castelli, W. P. (1983). Obesity as an independent risk factor for cardiovascular disease: a 26-year follow-up of participants in the Framingham Heart Study. *Circulation, 67*(5), 968-977. doi: 10.1161/01.CIR.67.5.968

Hughes, J. W., Casey, E., Luyster, F., Doe, V. H., Waechter, D., Rosneck, J., & Josephson, R. (2006). Depression symptoms predict heart rate recovery

after treadmill stress testing. *American Heart Journal, 151*(5), 1121e1-e6. doi: 10.1016%2Fj.ahj.2006.02.004

Hughes, J. W., York, K. M., Li, Q., Freedland, K. E., Carney, R. M., & Sheps, D. S. (2008). Depressive symptoms predict heart rate recovery after exercise treadmill testing in patients with coronary artery disease: results from the Psychophysiological Investigation of Myocardial Ischemia study. *Psychosomatic Medicine, 70*(4), 456-460. doi: 10.1016/j.ahj.2006.02.00

Imai, K., Sato, H., Hori, M., Kusuoka, H., Ozaki, H., Yokoyama, H. (1994). Vagally mediated heart rate recovery after exercise is accelerated in athletes but blunted in patients with chronic heart failure. *Journal of the American College of Cardiology, 24*(6), 1529-1535. doi: 10.1016/0735-1097(94)90150-3

Jiang, W., & Davidson, J. R. (2005). Antidepressant therapy in patients with ischemic heart disease. *American Heart Journal, 150*(5), 871-881. doi: 10.1016/j.ahj.2005.01.041

Johns, D. G., Dorrance, A. M., Tramontini, N. L., & Webb, R. C. (2001). Glucocorticoids inhibit tetrahydrobiopterin-dependent endothelial function. *Experimental Biology & Medicine, 226*(1), 27-31.

Jonas, B. S., Franks, P., & Ingram, D. D. (1997). Are symptoms of anxiety and depression risk factors for hypertension? Longitudinal evidence from the National Health and Nutrition Examination Survey I Epidemiologic Follow-up Study. *Archives of Family Medicine, 6*(1), 43-49. doi: 10.1001%2Farchfami.6.1.43

Jose, A. D., & Collison, D. (1970). The normal range and determinants of the intrinsic heart rate in man. *Cardiovascular Research, 4*(2), 160-167. doi: 10.1093/cvr/4.2.160

Jose, A. D., & Stitt, F. (1969). Effects of hypoxia and metabolic inhibitors on the intrinsic heart rate and myocardial contractility in dogs. *Circulation Research, 25*(1), 53-66. doi: 10.1161/01.RES.25.1.53

Jose, A. D., Stitt, F., & Collison, D. (1970). The effects of exercise and changes in body temperature on the intrinsic heart rate in man. *American Heart Journal, 79*(4), 488-498. doi: 10.1016/0002-8703(70)90254-1

Joynt, K. E., Whellan, D. J., & O'Connor, C. M. (2003). Depression and cardiovascular disease: mechanisms of interaction. *Biological Psychiatry, 54*(3), 248-261. doi: 10.1016/S0006-3223(03)00568-7

Kelly, J. J., Mangos, G., Williamson, P. M., & Whitworth, J. A. (1998). Cortisol and hypertension. *Clinical & Experimental Pharmacology & Physiology - Supplement, 25*, S51-56. doi: 10.1111%2Fj.1440-1681.1998.tb02301.x

Kemp, A. H., Quintana, D. S., Gray, M. A., Felmingham, K. L., Brown, K., & Gatt, J. M. (2010). Impact of depression and antidepressant treatment on heart rate variability: a review and meta-analysis. *Biological Psychiatry, 67*(11), 1067-1074. doi: 10.1016%2Fj.biopsych.2009.12.012

Kessing, L. V., Willer, I. S., & Knorr, U. (2011). Volume of the adrenal and pituitary glands in depression. *Psychoneuroendocrinology, 36*(1), 19-27. doi: 10.1016/j.psyneuen.2010.05.007

Kirschbaum, C., Pirke, K. M., & Hellhammer, D. H. (1993). The 'Trier Social Stress Test' – a tool for investigating psychobiological stress responses in

a laboratory setting, *Neuropsychobiology, 28*(1-2), 76-81. doi: 10.1159%2F000119004

Koschke, M., Boettger, M. K., Schulz, S., Berger, S., Terhaar, J., Voss, A. (2009). Autonomy of autonomic dysfunction in major depression. *Psychosomatic Medicine, 71*(8), 852-860. doi: 10.1097%2FPSY.0b013e3181b8bb7a

Kudoh, A., Ishihara, H., & Matsuki, A. (2000). Inhibition of the cortisol response to surgical stress in chronically depressed patients. *Journal of Clinical Anesthesia, 12*(5), 383-387. doi: 10.1016%2FS0952-8180%2800%2900179-3

Kupper, N., Willemsen, G., Van den Berg, M., de Boer, D., Posthuma, D., Boomsma, D. J., & de Geus, E. J. C. (2004). Heritability of ambulatory heart rate variability. *Circulation, 110,* 2792-2796. doi: 10.1161/01.CIR.0000146334.96820.6E

La Rovere, M. T., Bigger, J. T., Jr., Marcus, F. I., Mortara, A., & Schwartz, P. J. (1998). Baroreflex sensitivity and heart-rate variability in prediction of total cardiac mortality after myocardial infarction. ATRAMI (Autonomic Tone and Reflexes After Myocardial Infarction) Investigators. *Lancet, 351*(9101), 478-484. doi: 10.1016/S0140-6736(97)11144-8

La Rovere, M. T., Pinna, G. D., & Raczak, G. (2008). Baroreflex sensitivity: measurement and clinical implications. *Annals of Noninvasive, 13*(2), 191-207. doi: 10.1111/j.1542-474X.2008.00219.x

Lahiri, M. K., Kannankeril, & Goldberger, J. J. (2008). Assessment of autonomic function in cardiovascular disease, *Journal of the American College of Cardiology, 51*(18), 1725-1733. doi: 10.1016/j.jacc.2008.01.038

Lahmeyer, H. W., & Bellur, S. N. (1987). Cardiac regulation and depression. *Journal of Psychiatric Research, 21*(1), 1-6. doi: 10.1016/0022-3956(87)90004-5

Laine, H., Yki-Jarvinen, H., Kirvela, O., Tolvanen, T., Raitakari, M., Solin, O. (1998). Insulin resistance of glucose uptake in skeletal muscle cannot be ameliorated by enhancing endothelium-dependent blood flow in obesity. *Journal of Clinical Investigation, 101*(5), 1156-1162. doi: 10.1172%2FJCI1065

Lake, C. R., Pickar, D., Ziegler, M. G., Lipper, S., Slater, S., & Murphy, D. L. (1982). High plasma norepinephrine levels in patients with major affective disorder. *American Journal of Psychiatry, 139*(10), 1315-1318. doi: 10.1097%2F00004714-198304000-00028

Lembo, G., Rendina, V., Iaccarino, G., Lamenza, F., Volpe, M., & Trimarco, B. (1993). Insulin reduces reflex forearm sympathetic vasoconstriction in healthy humans. *Hypertension, 21*(6 Pt 2), 1015-1019. doi: 10.1161/01.HYP.21.6.1015

Libby, P. (2000). Changing concepts of atherogenesis. *Journal of Internal Medicine, 247*(3), 349-358. doi: 10.1046/j.1365-2796.2000.00654.x

Licht, C. M. M., de Geus, E. J., van Dyck, R., & Penninx, B. W. (2010). Longitudinal evidence for unfavorable effects of antidepressants on heart rate variability. *Biological Psychiatry, 68*(9), 861-868. doi: 10.1016/j.biopsych.2010.06.032

Light, K. C., Kothandapani, R. V., & Allen, M. T. (1998). Enhanced cardiovascular and catecholamine responses in women with depressive

symptoms. *International Journal of Psychophysiology, 28*(2), 157-166. doi: 10.1016/S0167-8760(97)00093-7

Maggi, E., Chiesa, R., Melissano, G., Castellano, R., Astore, D., Grossi, A. (1994). LDL oxidation in patients with severe carotid atherosclerosis. A study of in vitro and in vivo oxidation markers. *Arteriosclerosis & Thrombosis, 14*(12), 1892-1899. doi: 10.1161%2F01.ATV.14.12.1892

Mancia, G., Bousquet, P., Elghozi, J. L., Esler, M., Grassi, G., Julius, S. (2007). The sympathetic nervous system and the metabolic syndrome. *Journal of Hypertension, 25*(5), 909-920. doi: 10.1097%2FHJH.0b013e328048d004

Mancini, T., Kola, B., Mantero, F., Boscaro, M., & Arnaldi, G. (2004). High cardiovascular risk in patients with Cushing's syndrome according to 1999 WHO/ISH guidelines. *Clinical Endocrinology, 61*(6), 768-777. doi: 10.1111%2Fj.1365-2265.2004.02168.x

Martens, E. J., Nyklicek, I., Szabo, B. M., & Kupper, N. (2008). Depression and anxiety as predictors of heart rate variability after myocardial infarction. *Psychological medicine, 38*(3), 375-383. doi: 10.1017/S0033291707002097

Mason, J. W. (1968). A review of psychoendocrine research on the sympathetic-adrenal medullary system. *Psychosomatic Medicine, 30*(5), Suppl:631-653.

Matthews, K., Schwartz, J., Cohen, S., & Seeman, T. (2006). Diurnal cortisol decline is related to coronary calcification: CARDIA study. *Psychosomatic Medicine, 68*(5), 657-661. doi: 10.1097/01.psy.0000244071.42939.0e

McFarlane, A., Kamath, M. V., Fallen, E. L., Malcolm, V., Cherian, F., & Norman, G. (2001). Effect of sertraline on the recovery rate of cardiac autonomic function in depressed patients after acute myocardial infarction. *American Heart Journal, 142*(4), 617-623. doi: 10.1067/mhj.2001.116766

McKay, M. S., & Zakzanis, K. K. (2010). The impact of treatment on HPA axis activity in unipolar major depression. *Journal of Psychiatric Research, 44*(3), 183-192. doi: 10.1016/j.jpsychires.2009.07.012

Meeran, K., Hattersley, A., Mould, G., & Bloom, S. R. (1993). Venepuncture causes rapid rise in plasma ACTH. *The British Journal of Clinical Practice, 47*(5), 246-247.

Miller, G. E., Cohen, S., & Ritchey, A. K. (2002). Chronic psychological stress and the regulation of pro-inflammatory cytokines: a glucocorticoid-resistance model. *Health Psychology, 21*(6), 531-541.

Mills, P., Adler, K., Dimsdale, J., Perez, C., Ziegler, M., Ancoli-Isreal, S., Patterson, T., & Grant, I. Vulnerable caregivers of Alzheimer disease patients have a deficit in β2-adrenergic receptor sensitivity and density. *American Journal of Geriatric Psychiatry, 12*(3), 281-286. doi: 10.1176%2Fappi.ajgp.12.3.281

Mora, S., Redberg, R. F., Cui, Y., Whiteman, M. K., Flaws, J. A., Sharrett, A. R. (2003). Ability of exercise testing to predict cardiovascular and all-cause death in asymptomatic women: a 20-year follow-up of the lipid research clinics prevalence study. *Journal of the American Medical Association, 290*(12), 1600-1607. doi: 10.1001/jama.290.12.1600

Morshedi-Meibodi, A., Larson, M. G., Levy, D., O'Donnell, C. J., & Vasan, R. S. (2002). Heart rate recovery after treadmill exercise testing and risk of cardiovascular disease events (The Framingham Heart Study). *American Journal of Cardiology, 90*(8), 848-852. doi: 10.1016/S0002-9149(02)02706-6

Nahshoni, E., Aizenberg, D., Strasberg, B., Dorfman, P., Sigler, M., Imbar, S. (2000). QT dispersion in the surface electrocardiogram in elderly patients with major depression. *Journal of Affective Disorders, 60*(3), 197-200. doi: 10.1016/S0165-0327(99)00142-1

Nishime, E. O., Cole, C. R., Blackstone, E. H., Pashkow, F. J., & Lauer, M. S. (2000). Heart rate recovery and treadmill exercise score as predictors of mortality in patients referred for exercise ECG. *Journal of the American Medical Association, 284*(11), 1392-1398. doi: 10.1001/jama.284.11.1392

Nolan, J., Batin, P. D., Andrews, R., Lindsay, S. J., Brooksby, P., Mullen, M. (1998). Prospective study of heart rate variability and mortality in chronic heart failure: results of the United Kingdom heart failure evaluation and assessment of risk trial (UK-heart). *Circulation, 98*(15), 1510-1516. doi: 10.1161/01.CIR.98.15.1510

Nugent, C. A., Nichols, T., & Tyler, F. H. (1965). Diagnosis of cushing's syndrome: single dose dexamethasone suppression test *Archives of Internal Medicine, 116*, 172-176. doi: 10.1001%2Farchinte.1965.03870020012006

O'Donnell, M. J., Xavier, D., Liu, L., Hongye, Z., Chin, S. L. …& Yusuf, S. (2010). Risk factors for ischaemic and intracerebral haemorrhagic stroke

in 22 countries (the INTERSTROKE study): a case-control study. *Lancet*, 376, 112-113. doi: 10.1016/S0140-6736(10)60834-3

Panarelli, M., Holloway, C. D., Fraser, R., Connell, J. M., Ingram, M. C., Anderson, N. H. (1998). Glucocorticoid receptor polymorphism, skin vasoconstriction, and other metabolic intermediate phenotypes in normal human subjects. *Journal of Clinical Endocrinology & Metabolism, 83*(6), 1846-1852. doi: 10.1210/jc.83.6.1846

Panza, J. A., Casino, P. R., Kilcoyne, C. M., & Quyyumi, A. A. (1993). Role of endothelium-derived nitric oxide in the abnormal endothelium-dependent vascular relaxation of patients with essential hypertension. *Circulation, 87*(5), 1468-1474. doi: 10.1161/01.CIR.87.5.1468

Pariante, C. M. (2006). The glucocorticoid receptor: part of the solution or part of the problem? *Journal of Psychopharmacology, 20*(4 Suppl), 79-84. doi: 10.1177/1359786806066063

Peeters, F., Nicholson, N. A., & Berkhof, J. (2003). Cortisol responses to daily events in major depressive disorder. *Psychosomatic Medicine, 65*(5), 836-841. doi: 10.1097/01.PSY.0000088594.17747.2E

Pelletier, R., Lavoie, K. L., Gordon, J., Arsenault, A., Campbell, T. S., & Bacon, S. L. (2009). The role of mood disorders in exercise-induced cardiovascular reactivity. *Psychosomatic Medicine, 71*(3), 301-307. doi: 10.1097/PSY.0b013e3181988175

Petrie, J. R., Ueda, S., Webb, D. J., Elliott, H. L., & Connell, J. M. (1996). Endothelial nitric oxide production and insulin sensitivity. A physiological

link with implications for pathogenesis of cardiovascular disease. *Circulation, 93*(7), 1331-1333. doi: 10.1161/01.CIR.93.7.1331

Plotsky, P. M., Owens, M. J., & Nemeroff, C. B. (1998). Psychoneuroendocrinology of depression. Hypothalamic-pituitary-adrenal axis. *Psychiatric Clinics of North America, 21*(2), 293-307. doi: 10.1016/S0193-953X(05)70006-X

Quyyumi, A. A. (2003). Prognostic significance of endothelial function. *American Journal of Cardiology, 91*(suppl), 19H-24H. 10.1016%2FS0002-9149%2803%2900430-2

Rabkin, J. G., Charles, E., & Kass, F. (1983). Hypertension and DSM-III depression in psychiatric outpatients. *American Journal of Psychiatry, 140*(8), 1072-1074.

Ragland, D. R., & Brand, R. J. (1988). Type A behavior and mortality from heart disease. *New England Journal of Medicine, 318*(4), 65-69. doi: 10.1097%2F00008483-198804000-00016

Rajagopalan, S., Brook, R., Rubenfire, M., Pitt, E., Young, E., & Pitt, B. (2001). Abnormal brachial artery flow-mediated vasodilation in young adults with major depression. *American Journal of Cardiology, 88*(2), 196-198. doi: 10.1016/S0002-9149(01)01623-X

Reusch, J. E., & Draznin, B. B. (2007). Atherosclerosis in diabetes and insulin resistance. *Diabetes, Obesity & Metabolism, 9*(4), 455-463. doi: 10.1111/j.1463-1326.2006.00620.x

Reynolds, R. M., & Walker, B. R. (2003). Human insulin resistance: the role of glucocorticoids. *Diabetes, Obesity & Metabolism, 5*(1), 5-12. doi: 10.1046/j.1463-1326.2003.00221.x

Roy, A., Pickar, D., De Jong, J., Karoum, F., & Linnoila, M. (1988). Norepinephrine and its metabolites in cerebrospinal fluid, plasma, and urine. Relationship to hypothalamic-pituitary-adrenal axis function in depression. *Archives of General Psychiatry, 45*(9), 849-857. doi: 10.1001%2Farchpsyc.1988.01800330081010

Rozanski, A., Blumenthal, J. A., & Kaplan, J. (1999). Impact of psychological factors on the pathogenesis of cardiovascular disease and implications for therapy. *Circulation, 99*(16), 2192-2217. doi: 10.1161/01.CIR.99.16.2192

Rugulies, R. (2002). Depression as a predictor for coronary heart disease. a review and meta-analysis. *American Journal of Preventive Medicine, 23*(1), 51-61.

Schatzberg, A. F., Rothschild, A. J., Bond, T. C., & Cole, J. O. (1984). The DST in psychotic depression: diagnostic and pathophysiologic implications. *Psychopharmacology Bulletin, 20*(3), 362-364.

Shekelle, R. B., Gale, M., & Norusis. (1985). Type A score (Jenkins Activity Survey), and risk of recurrent coronary heart disease in the aspirin myocardial infarction study. *American Journal of Cardiology, 56*(4), 222-225. doi: 10.1016/0002-9149(85)90838-0

Shetler, K., Marcus, R., Froelicher, V. F., Vora, S., Kalisetti, D., Prakash, M., … Myers, J. (2001). Heart rate recovery: validation and methodologic issues.

Journal of the American College of Cardiology, 38(7), 1980-1987. doi: 10.1016%2FS0735-1097%2801%2901652-7

Sherwood, A., Hinderliter, A. L., Watkins, L. L., Waugh, R. A., & Blumenthal, J. A. (2005). Impaired endothelial function in coronary heart disease patients with depressive symptomatology. *Journal of the American College of Cardiology, 46*(4), 656-659. doi: 10.1016%2Fj.accreview.2005.11.015

Soodini, G. R., & Hamdy, O. (2004). Obesity and endothelial function. *Current Opinion in Endocrinology & Diabetes, 11*(4), 186-191. doi: 10.1097%2F01.med.0000140930.71370.36

Spear, J., Kronhais, K., Moore, E., & Kline, R. (1979). The effect of brief vagal stimulation on the isolated rabbit sinus node. *Circulation Research, 44*, 75-88. doi: 10.1161/ 01.RES.44.1.75

Stanner, S. (Ed.). (2005). *Cardiovascular disease: diet, nutrition and emerging risk factors*. Oxford: Blackwell Publishing.

Statistics Canada. (2008). Mortality, summary lost of causes. Retrieved from http://www.statcan.gc.ca/pub/84f0209x/84f0209x2008000-eng.pdf

Stein, P. K., Carney, R. M., Freedland, K. E., Skala, J. A., Jaffe, A. S., Kleiger, R. E., & Rottman, J.N. (2000). Severe depression is associated with markedly reduced heart rate variability in patients with stable coronary heart disease. *Journal of Psychosomatic Research, 48*(4-5), 493-500. doi: 10.1016%2FS0022-3999%2899%2900085-9

Suls, J., & Bunde, J. (2005). Anger, anxiety, and depression as risk factors for cardiovascular disease: the problems and implications of overlapping

affective dispositions. *Psychological Bulletin, 131*(2), 260-300. doi: 10.1037/0033-2909.131.2.260

Sundaram, S., Shoushtari, C., Carnethon, M., Kadish, A., & Goldberger, J. J. (2004). Autonomic and nonautonomic determinants of heart rate recovery. *Heart Rhythm, 1*, S100-101.

Tauchmanova, L., Rossi, R., Biondi, B., Pulcrano, M., Nuzzo, V., Palmieri, E. A. (2002). Patients with subclinical Cushing's syndrome due to adrenal adenoma have increased cardiovascular risk. *Journal of Clinical Endocrinology & Metabolism, 87*(11), 4872-4878. doi: 10.1210/jc.2001-011766

Taylor, C. B., Conrad, A., Wilhelm, F. H., Strachowski, D., Khaylis, A., Neri, E. (2009). Does improving mood in depressed patients alter factors that may affect cardiovascular disease risk? *Journal of Psychiatric Research, 43*(16), 1246-1252. doi: 10.1016%2Fj.jpsychires.2009.05.006

Timonen, M., Laakso, M., Jokelainen, J., Rajala, U., Meyer-Rochow, V. B., & Keinanen-Kiukaanniemi, S. (2005). Insulin resistance and depression: cross sectional study. *British Medical Journal, 330*(7481), 17-18. doi: 10.1136%2Fbmj.38313.513310.F71

Tsuji, H., Venditti, F. J., Jr., Manders, E. S., Evans, J. C., Larson, M. G., Feldman, C. L. (1994). Reduced heart rate variability and mortality risk in an elderly cohort. The Framingham Heart Study. *Circulation, 90*(2), 878-883. doi: 10.1161/01.CIR.90.2.878

Van der Kooy, K., van Hout, H., Marwijk, H., Marten, H., Stehouwer, C., & Beekman, A. (2007). Depression and the risk for cardiovascular diseases:

systematic review and meta analysis. *International Journal of Geriatric Psychiatry, 22*(7), 613-626. doi: 10.1002%2Fgps.1723

van Melle, J. P., de Jonge, P., Spijkerman, T. A., Tijssen, J. G., Ormel, J., van Veldhuisen, D. J. (2004). Prognostic association of depression following myocardial infarction with mortality and cardiovascular events: a meta-analysis. *Psychosomatic Medicine, 66*(6), 814-822. doi: 10.1097%2F01.psy.0000146294.82810.9c

Veith, R. C., Best, J. D., & Halter, J. B. (1984). Dose-dependent suppression of norepinephrine appearance rate in plasma by clonidine in man. *Journal of Clinical Endocrinology & Metabolism, 59*(1), 151-155. doi: 10.1210/jcem-59-1-151

Vogelzangs, N., Beekman, A. T. F., Milaneschi, Y., Bandinelli, S., Ferrucci, L., & Penninx, B. W. J. H. (2010). Urinary cortisol and six-year risk of all-cause and cardiovascular mortality. *The Journal of Clinical Endocrinology and Metabolism, 95*(11), 4959-4964. doi: 10.1210/jc.2010-0192

Vogt, C. J., & Schmid-Schonbein, G. W. (2001). Microvascular endothelial cell death and rarefaction in the glucocorticoid-induced hypertensive rat. *Microcirculation, 8*(2), 129-139. doi: 10.1111/j.1549-8719.2001.tb00163.x

Walker, B. R., Soderberg, S., Lindahl, B., & Olsson, T. (2000). Independent effects of obesity and cortisol in predicting cardiovascular risk factors in men and women. *Journal of Internal Medicine, 247*(2), 198-204. doi: 10.1046/j.1365-2796.2000.00609.x

Watkins, L. L., & Grossman, P. (1999). Association of depressive symptoms with reduced baroreflex cardiac control in coronary artery disease. *American Heart Journal, 137*(3), 453-457. doi: 10.1016/S0002-8703(99)70491-6

Watson, S., Gallagher, P., Smith, M. S., Ferrier, I. N., & Young, A. H. (2006). The dex/CRH test - is it better than the DST? *Psychoneuroendocrinology, 31*, 889-894. doi: 10.1016/j.psyneuen.2006.03.001

Whitworth, J. A., Gordon, D., McLachlan-Troup, N., Scoggins, B. A., & Moulds, R. W. (1989). Dexamethasone suppression in essential hypertension: effects on cortisol and blood pressure. *Clinical & Experimental Hypertension, 11*(2), 323-335. doi: 10.3109%2F10641968909035345

Whitworth, J. A., Mangos, G. J., & Kelly, J. J. (2000). Cushing, cortisol, and cardiovascular disease. *Hypertension, 36*(5), 912-916. doi: 10.1161/01.HYP.36.5.912

Whitworth, J. A., Saines, D., & Scoggins, B. A. (1984). Blood pressure and metabolic effects of cortisol and deoxycorticosterone in man. *Clinical & Experimental Hypertension, 6*(4), 795-809. doi: 10.3109%2F10641968409044039

Williamson, P. M., Kelly, J. J., & Whitworth, J. A. (1996). Dose-response relationships and mineralocorticoid activity in cortisol-induced hypertension in humans. *Journal of Hypertension, 14*(5), S37-41.

World Health Organization. (2007). Cardiovascular diseases fact sheet. Retrieved February 18, 2008

Wyatt, R. J., Portnoy, B., Kupfer, D. J., Snyder, F., & Engelman, K. (1971). Resting plasma catecholamine concentrations in patients with depression

and anxiety. *Archives of General Psychiatry, 24*(1), 65-70. doi: 10.1001%2Farchpsyc.1971.01750070067009

Yeragani, V. K., Pohl, R., Jampala, V. C., Balon, R., Ramesh, C., & Srinivasan, K. (2000). Increased QT variability in patients with panic disorder and depression. *Psychiatry Research, 93*(3), 225-235. doi: 10.1016/S0165-1781(00)00119-0

Yusuf, S., Hawken, S., Ounpuu, S., Dans, T., Avezum, A., Lanas, F. (2004). Effect of potentially modifiable risk factors associated with myocardial infarction in 52 countries (the INTERHEART study): case-control study. *Lancet, 364*(9438), 937-952. doi: 10.1016/S0140-6736(04)17018-9

Zimmerman, L., Barnason, S., Brey, B. A., Caitlin, S. S, & Nieveen, J. (2002). Comparison of recovery patterns for patients undergoing coronary artery bypass grafting and minimally invasive direct coronary artery bypass in the early discharge period. *Progress in Cardiovascular Nursing, 17*, 132-141. doi: 10.1111/j.0889-7204.2002.00764.x

Manuscript One

The Effect of Major Depression on Post-Exercise Cardiovascular Recovery

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Abstract

Major depressive disorder (MDD) is associated with increased cardiovascular (CV) mortality. Dysfunctional autonomic control of the CV system may represent a mechanism explaining this relationship. Poor CV recovery after exercise, indicative of dysfunctional autonomic control of the CV system, predicts CV events and death. This is the first study to examine the association between MDD and post-exercise CV recovery. 886 patients underwent exercise stress tests. Heart rate (HR), systolic blood pressure (SBP) and diastolic blood pressure (DBP) were measured at rest, peak exercise, 1 minute and 5 minutes post-exercise. Patients with MDD had slower HR recovery ($p = .026$) 1 minute post-exercise than non-MDD patients. No other effects of MDD were found. MDD is accompanied by a dysregulation in autonomic control of exercise-related CV recovery, suggesting that depressed individuals have a slow parasympathetic recovery from exercise.

Keywords: Depression, Heart Rate (HR), Blood Pressure (BP), Cardiovascular Recovery, Exercise, Autonomic Nervous System (ANS).

Major depressive disorder (MDD) is associated with both the development of cardiovascular disease (CVD) and poorer outcomes in patients with established CVD (Barth, Schumacher, & Herrmann-Lingen, 2004; Carney et al., 2008; Lavoie & Fleet, 2000; Lesperance, Frasure-Smith, Talajic, & Bourassa, 2002; Rozanski, Blumenthal, & Kaplan, 1999; Rutledge et al., 2006). For example, depressed individuals in a community sample were found to be twice as likely to have a myocardial infarction (MI) over a 17-year follow-up compared to non-depressed individuals (Barefoot & Schroll, 1996). In patients with established CVD, the impact of depression appears even more striking: in one study, patients who were depressed following an MI were over four times more likely to die in the following five years compared to non-depressed post-MI patients (Lesperance et al., 2002). However, the mechanisms underlying this relationship remain unclear.

Dysfunction of the autonomic nervous system (ANS) has been proposed as a potential mechanism linking MDD to CVD (Joynt, Whellan, & O'Connor, 2003). While heart rate (HR) variability has long been used as a measure of autonomic dysfunction, HR recovery from exercise, the decrease in HR after exercise, has recently gained attention as an important complementary indicator of ANS imbalance (Hughes et al., 2006; Lahiri, Kannankeril, & Goldberger, 2008). Mounting evidence suggests that HR recovery is a powerful prognostic tool. For example, several studies have found slow HR recovery to be associated with a 2-fold increased mortality risk after adjusting for important covariates (Cole, Blackstone, Pashkow, Snader, & Lauer, 1999; Jouven et al., 2005; Mora et al., 2003; Nishime, Cole, Blackstone, Pashkow, & Lauer, 2000), which is comparable

to HR variability's prognostic power (Dekker et al., 2000; Kleiger, Miller, Bigger, & Moss, 1987; Nolan, et al., 1998).

To date, three studies (Hughes et al., 2006; Hughes et al., 2008; von Kanel et al., 2009) have examined relations between depression and HR recovery following exercise with mixed results. In the first study of 260 cardiac rehabilitation patients undergoing a treadmill exercise test, Hughes et al. (2006) found that Beck Depression Inventory-II (BDI-II) scores were significantly negatively correlated with HR recovery two minutes after exercise. However, the results were somewhat difficult to interpret given the high rate of beta-blocker use (83%) and the fact that inclusion of exercise capacity eliminated the relationship between depression and HR recovery. This may indicate that poor HR recovery in depressed individuals is due partly to poorer physical fitness (Lavoie et al., 2004). However, these results were extended in another study of 188 patients with coronary artery disease (CAD) but not taking beta-blockers. Once again, BDI-II scores were predictive of poor HR recovery one minute after an exercise stress test (Hughes et al., 2008). The relationship between depression and HR recovery remained even after adjustment for resting HR, peak HR, and total test time. On the other hand, a more recent study from another group found that depressive symptoms as measured using the Hospital Anxiety and Depression Scale (HADS) did not predict one minute post-exercise HR recovery in patients (Von Kanel et al., 2009).

These results are encouraging but raise a number of questions. For example, can the association between depression and HR recovery be replicated by another group? Are stronger results associated with higher levels of

depression? Are results clearer using a structured clinical interview to diagnose depression as opposed to self-report questionnaires? Is the association between depression and HR recovery due solely to lower fitness as opposed to more general autonomic recovery following exercise? And finally, what are the effects, if any, of depression on the timing of HR recovery? The studies discussed above examined only immediate HR recovery (maximum two minutes post-exercise). While this is understandable given the focus on parasympathetic activity in the development and progression of CVD, combined with research indicating that short-term HR recovery from exercise is mediated almost exclusively by parasympathetic reactivation, this ignores potential differences associated with depression later in the recovery period. Pharmacologic blockade studies using agents such as atropine and propranolol confirm that HR decrease during the first 30 seconds is produced almost exclusively by an increase in parasympathetic activity but afterwards the decrease in sympathetic activity becomes increasingly important (Imai et al., 1994). Mathematical models aimed at quantifying sympathetic and parasympathetic contributions to HR during the recovery period support this conclusion (Pierpont & Voth, 2004). As a result, it would be very informative to examine the relationship between depression and both early and a later-stage HR recovery from exercise.

Thus, the objectives of the current study were to 1) extend the current knowledgebase by measuring depression with a structured diagnostic interview as well as a self-report questionnaire, 2) look at the association between clinical levels of depression as well as continuous variation in BDI-II scores and CV recovery, 3) control for the effects of a number of potential confounds, and 4)

examine the relationship between depression on CV recovery to exercise at two time points to provide further information about the details of autonomic dysregulation. It was possible to accomplish these objectives in part due to the use of a significantly larger sample of patients than previous research.

Method

Participants

This research was a secondary analysis of the Mechanisms and Outcomes of Silent Myocardial Ischemia (MOSMI) study, a longitudinal study aimed at examining the risk factors for silent (painless) ischemia and the impact of silent ischemia on cardiovascular outcomes. Patients were eligible for this study if they had been referred for an exercise stress test using single photon emission computed tomography (SPECT) imaging in the Department of Nuclear Medicine of the Montreal Heart Institute. Patients are most often referred for an exercise stress test either as a screening procedure because their doctor judges them to be at high risk for a cardiac event (e.g. family history, dyslipidimia or atypical chest pain) or because the patient complains of symptoms of ischemia (e.g. chest pain, fatigue or increased breathlessness during exercise). A total of 905 patients were recruited. While there were no age, sex, or race restrictions for inclusion, patients were excluded if they were unable to understand French or English fluently enough to reliably answer questions during the medical and psychiatric interviews. The study also required that participants be excluded if they were pregnant or nursing, suffering from a serious non-CV co-morbid condition (e.g., chronic obstructive pulmonary disease, cancer), a pain disorder other than angina, used a non-steroidal anti-inflammatory agent (NSAID) in the last week, or used

an analgesic on the day of the exercise test. Written consent was obtained from all participants. The MOSMI study was approved by the Human Ethics Committee of the Montreal Heart Institute. Of this sample, 886 individuals, the focus of these analyses, had interview, questionnaire, and exercise data.

Procedure

Overview. Participants underwent a two-day protocol SPECT rest-stress test during which HR and BP were measured at rest, at peak exercise, 1 minute and 5 minutes post-exercise. After completing the stress test, they were administered a structured, psychiatric diagnostic interview, the Primary Care Evaluation of Mental Disorders (PRIME-MD) (Spitzer et al., 1994). The PRIME-MD contains modules for the assessment of mood and anxiety disorders. Finally, participants completed a sociodemographic and medical history questionnaire including details regarding medication usage and depressive symptoms.

Depressive symptoms. The Beck Depression Inventory-II (BDI-II) (Beck, Steer, & Brown, 1996) was used to measure depressive symptoms. This widely-used questionnaire consists of 21 items scored from 0 to 3, with higher numbers indicating greater symptom severity. According to a meta-analysis of 165 studies, the BDI-II has an internal consistency of .837 (.007) and a test-retest reliability of .690 (.009) (Yin & Fan, 2000). The BDI-II has been shown to have good sensitivity (.82-.90) and specificity (.84-.89) in diabetic patients, a population similar to that used in this study (Lustman et al., 1997).

Assessment of major depression. The PRIME-MD (Spitzer et al., 1994) is a structured psychiatric diagnostic interview designed to detect some of the most common disorders listed in the Diagnostic and Statistical Manual of Mental

Disorders, Fourth Edition (DSM-IV) (American Psychiatric Association, 1994). For the present study, a trained research assistant administered the mood and anxiety disorders modules of the electronic version of the PRIME-MD, which assess major and minor depressive disorder, dysthymia and bipolar disorder, as well as panic disorder, generalized anxiety disorder, and other anxiety disorder. Though the PRIME-MD takes between 10 and 20 minutes to administer, it has been shown to be of comparable reliability, sensitivity, and specificity as longer structured interviews such as the Structured Clinical Interview for DSM (SCID) (Spitzer et al., 1994). It has been used successfully in previous studies (Douglas, Taylor, & O'Malley, 2004; Miller, Stetler, Carney, Freedland, & Banks, 2002) assessing the prevalence of psychiatric disorders in CVD patients.

Exercise stress test. The exercise stress test was conducted using a treadmill and followed the modified Bruce protocol (Okin, Ameisen & Kligfield, 1986). Like the standard Bruce protocol, the speed and incline of the treadmill increases at three-minute intervals. However, the first two stages of the modified protocol begin with a lower workload than the standard test, beginning at a speed of 1.7 mph and 0% grade, then increasing to a 5% grade but remaining at the same speed. The third stage of the modified protocol corresponds to the first stage of the standard protocol. These modifications are meant to adapt the test to elderly and sedentary patients. Participants' heart rate (HR), systolic blood pressure (SBP) and diastolic blood pressure (DBP) were measured before, every 2 minutes during, 1 minute after the exercise and 5 minutes after the exercise. BP was measured by an experienced technician using a manual sphygmomanometer (Welch Allyn Tycos-767 series, Skaneateles Falls, NY, USA). HR was recorded

during the test using a standard 12-lead ECG configuration (Marquette Medical Systems Inc., Milwaukee, WI, USA). The test ended when patients reached self-reported fatigue, when they had reached at least 85% of their maximum HR, or showed signs of malignant arrhythmias, severe hypertension (SBP > 240 mm Hg) or hypotension (20 mm Hg decline in SBP).

Data Analysis

Missing data were handled using missing at random (MAR) assumptions following Rubin's rules (Rubin, 1987). The PROC MI method of multivariate imputation in SAS V 9.2 (SAS Institute, Cary, NC) was used to generate five copies of the dataset. These were analyzed independently, each with missing values imputed. PROC MIANALYZE was used to average estimates of the variables to give a single mean estimate and adjusted standard error according to Harrell's guidelines (Harrell, 2001). As such all analyses included 886 participants.

Cardiovascular recovery was defined as the difference between the SBP, DBP and HR measured at peak exercise and the same variable at 1 and 5 minutes post-exercise. Given the time pressures of a busy hospital unit and demand for the equipment, there were significantly more missing data in the 5-minute post-exercise values than the 1-minute values (21% vs. 0%). As a result, separate analyses were conducted examining the relationship between depression and HR recovery at 1 and 5 minutes. Two sets of General Linear Models (GLMs) were conducted for each CV measure (SBP, DBP and HR): the first examining the effects of MDD on the CV recovery variables measured at 1 minute post-exercise and the second assessing the effects of MDD on the variables 5 minutes post-

exercise. All models included age, sex, CVD history (i.e., having had a previous myocardial infarction, PCI, CABG, or cerebrovascular event), BP medication prescription and on-the-day usage, anxiolytic prescription, and anti-depressant prescription as covariates. CV reactivity (defined as the difference between the baseline and peak level) of the given variable and exercise capacity in METS were also included as covariates to adjust for the likelihood that depressed patients would fatigue more quickly than non-depressed patients and therefore achieve lower maximal HR and BP, as previous research has shown (Lavoie et al., 2004).

Results

Participant Characteristics

Characteristics of the 886 participants are presented in Table 1. The sample included 610 (68.8%) men and had a mean age of 60 (10) years. Fifty-one participants met diagnostic criteria for MDD, making the overall rate 5.8%. Interestingly, similar to Hughes et al. (2006), people with MDD had significantly lower exercise capacity in terms of metabolic equivalents ($F = 6.80$, $p = .009$). Patients with MDD did not differ from non-MDD patients in terms of their reasons for stopping the stress test, with shortness of breath being the most common reason for stopping in both groups (61.1% in MDD patients, 62.0% in non-MDD patients) and fatigue being the second most common reason (36.0% for MDD patients, 33.1% for non-MDD patients).

1-Minute Recovery Analyses

There was a significant effect of MDD on 1-minute HR recovery (β (SEM) = -3.70 (1.67), $p = .026$) such that patients with MDD had slower HR

recovery compared to those without MDD (Figure 1). However, there was no significant effect of MDD on SBP (β (SEM) = -1.31 (2.26), p = .561) or DBP recovery (β (SEM) = -0.31 (1.01), p = .764). When similar analyses tested the effect of BDI-II score on CV recovery, no significant results were found. Covariates significantly predicting 1-minute recovery included reactivity (predicting SBP, DBP and HR recovery), age (SBP, HR), anxiolytic prescription (SBP) and exercise capacity (HR).

5-Minute Recovery Analyses

There was no significant effect of MDD on 5-minute HR recovery (β (SEM) = -0.15 (1.31), p = .910), SBP recovery (β (SEM) = 1.56 (2.86), p = .590) or DBP recovery (β (SEM) = 2.06 (1.48), p = .182). No significant results were found when the main effect of BDI-II score on CV recovery was tested. Covariates significantly predicting 5-minute recovery included reactivity (SBP, DBP, RPP and HR), age (SBP), CVD status (SBP), sex (HR), anxiolytic prescription (HR) and exercise capacity (HR).

Discussion

The primary purpose of this study was to assess the relationship between diagnosed MDD and post-exercise HR and BP recovery one and five minutes post-exercise. We hypothesized that patients with MDD would have slower HR and BP recovery compared to patients without MDD at both time points. This hypothesis was partially supported as MDD was associated with slower HR recovery one minute post-exercise. This suggests that poor autonomic control of the CV system may be a mechanism explaining depressed patients' increased risk of developing CVD. However, our finding that BDI-II scores were not predictive

of recovery suggests that sub-clinical levels of depression are not as reliably associated with ANS dysfunction. This may explain some of the variance in previous studies examining the relation between depression and exercise recovery.

While a full explanation of the finding that MDD was associated with slower HR recovery at one minute but not five minutes post-exercise awaits further research, this may be due to the relative contributions of parasympathetic and sympathetic activity to recovery. For example, Imai et al. (1994) found that whereas atropine but not propranolol influenced the immediate decrease in heart rate upon cessation of exercise, propranolol had a greater impact on the degree of heart rate recovery several minutes later. As a result, the findings suggest that in the present sample MDD was associated more with parasympathetic than sympathetic dysregulation. Previous studies have found depression to be linked to parasympathetic dysregulation, as indicated by high-frequency heart rate variability (Hughes & Stoney, 2000; Stein et al., 2000) as well as sympathetic activity as indicated by elevated plasma and urinary catecholamines (Esler et al., 1982; Lake et al., 1982; Roy, Pickar, De Jong, Karoum, & Linnoila, 1988).

A competing explanation for the delayed HR recovery among patients with MDD may relate to depressed individuals' well-known tendency to ruminate (Nolen-Hoeksema, 2000). Studies have found that increased rumination following an emotionally laden task is associated with reduced cardiovascular recovery (Glynn et al., 2002). Considering a test screening for the presence of CVD would likely be emotionally laden for most patients, depressed patients' reduced early CV recovery could, in fact, be attributed to increased rumination over the stress

test compared to their non-depressed counterparts. Future research examining the relationship between depression and CV recovery should assess post-task rumination to explore this possibility.

The adjusted difference of 3.7 bpm one minute after exercise between depressed and non-depressed participants may have clinical significance. For example, Shetler et al. (2001) followed 2193 men who underwent a similar treadmill test for seven years. They found that individuals who died during the follow-up period had a 2.9 bpm smaller decrease in HR following exercise compared to survivors, independent of a number of characteristics. Regardless of whether or not the samples are entirely comparable, this suggests that the difference in HR change observed in the present study is potentially important.

The study had several strengths including a large sample size and clinical assessment of MDD. Also, while corroborating previous findings indicating poorer fitness in many depressed individuals (Lavoie et al., 2004; Marchionni et al., 2000; Ruo, Rumsfeld, Pipkin & Whooley, 2004), by statistically adjusting for exercise capacity, the results indicate that the association between MDD and HR recovery is unlikely to be solely due to differences in fitness. In this respect, the results are consistent with Hughes et al.'s second study (Hughes et al., 2008).

As far as additional limitations, the study was purely cross-sectional making it impossible to infer causal relationships. As well, although the results are adjusted for recent beta blocker and psychotropic use, statistical adjustments are limited in that they only control for the average effect of these medications whereas the effects of these medications vary widely across individuals. The fact that there are patients with and without MDD taking antidepressants may also

complicate the interpretation of the diagnostic categories. However, when the interaction between MDD status and antidepressant use was tested, it was found to be non-significant, suggesting that current symptoms of depression are associated with poor HR recovery, regardless of antidepressant treatment. Furthermore, the overall percentage of individuals with MDD in the present sample (5.8%) was somewhat lower than might be expected based on rates observed in other samples of CVD patients (Herrmann, Brand-Driehorst, Buss, & Ruger, 2000). While this may limit the study's generalizability to CVD patients with more typical rates of MDD, several points must be considered. First, the sex ratio of MDD in the current study (8.2% in women versus 4.7% in men) was consistent with the typical 2:1 ratio (Kessler, McGonagle, Swartz, Blazer, & Nelson, 1993). Second, clinical interviews tend to produce more stringent diagnoses and can lower rates of observed psychopathology. While self-report instruments such as the BDI are often used with CVD patients, interviews are probably better able to distinguish symptoms such as lack of energy and sleep problems that are due to CVD rather than depression. Finally, there may be local differences in rates of depression.

In conclusion, the present findings suggest that MDD is associated with slower HR recovery from exercise. Post-exercise recovery is an informative, important characteristic reflecting autonomic regulation and risk for cardiovascular disease.

Table 1

Participant characteristics

	Non-Depressed	Depressed	p-value	Missing (%)
Demographics				
N	778	48		
Sex (% women)*	30.4	43.1	.057	0%
Age (yrs)*	60.5 ± 9.8	56.0 ± 9.7	.002	0%
Caucasian (%)	95.9	95.1	.807	16%
High school diploma (%)	53.5	43.1	.149	0%
BDI-II score	8.0 ± 6.4	19.0 ± 9.7	<.001	16%
Exercise capacity (METS)	8.3 ± 1.7	7.6 ± 1.4	.014	1%
% of max HR reached	88.4	83.3	.006	1%
CVD Risk Factors and Events				
Body Mass Index	27.5 ± 4.3	28.9 ± 5.6	.046	14%
Current Smoker (%)	17.2	33.3	.021	15%
CVD (%)	33.4	35.3	.783	0%
Hypertension (%)	61.3	66.0	.524	9%
Hypercholesterolemia (%)	61.8	59.6	.764	10%
Past MI (%)	22.6	20.0	.708	24%
PCI (%)	24.7	33.3	.228	25%
CABG (%)	14.1	10.3	.504	26%
Stroke (%)	2.5	3.2	.801	38%
Medication Usage				
Anxiolytics (%)*	15.1	17.6	.622	0%
Anti-depressants (%)*	5.9	19.6	<.0001	0%
Ace inhibitors (%)	21.7	27.7	.338	10%
Beta-blockers (%)	29.9	29.8	.985	10%
ARBs (%)	15.2	10.6	.399	10%
Antihypertensives (%)*	52.4	48.9	.646	10%
Antihypertensive on-the-day usage (%)*	44.3	41.1	.662	0%
Statins (%)	50.7	46.8	.609	10%

BDI, Beck Depression Inventory *included in multiple imputation analyses

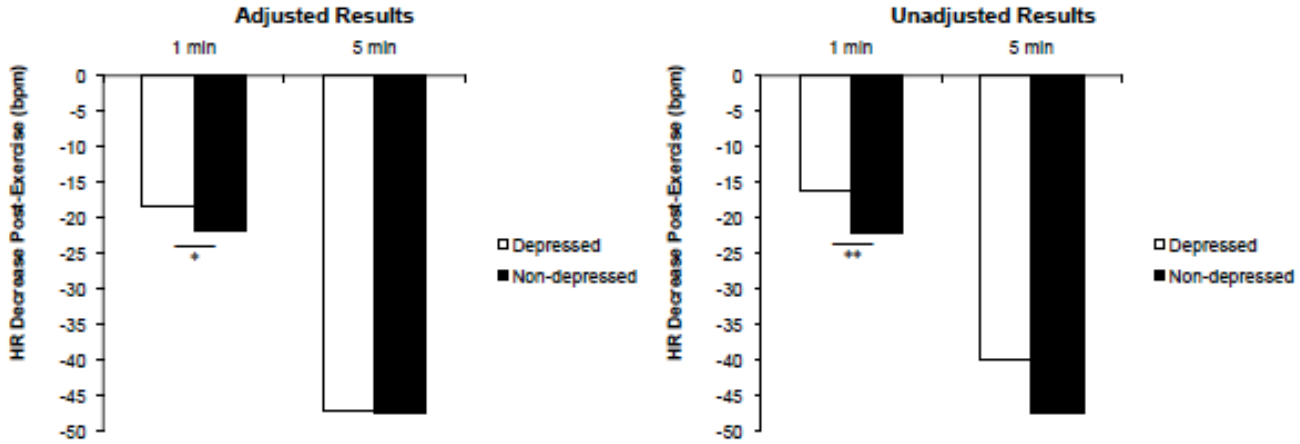
MI, myocardial infarction

PCI, percutaneous coronary intervention

CABG, coronary artery bypass surgery

ARB, angiotensin receptor blockers

Figure 1. Heart rate recovery at 1 and 5 minutes according to depression status, bpm, Beats per minute, N = 886, **p<0.0001, *p = 0.026.



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References

American Psychological Association. (1994). Diagnostic and statistical manual of mental disorders (4th ed.). Washington, DC: American Psychological Association.

Barefoot, J. C., & Schroll, M. (1996). Symptoms of depression, acute myocardial infarction, and total mortality in a community sample. *Circulation, 93*(11), 1976-1980. doi: 10.1161/01.CIR.93.11.1976

Barth, J., Schumacher, M., & Herrmann-Lingen, C. (2004). Depression as a risk factor for mortality in patients with coronary heart disease: a meta-analysis. *Psychosomatic Medicine, 66*(6), 802-813. doi: 10.1097/01.psy.0000146332.53619.b2

Beck, A. T. Steer, R. A & Brown, G. K. (1996). Manual for Beck Depression Inventory-II. San Antonio, TX: Psychological Corporation.

Carney, R. M., Freedland, K. E., Steinmeyer, B., Blumenthal, J. A., Berkman, L. F., Watkins, L. L., … Jaffe, A.S. (2008). Depression and five year survival following acute myocardial infarction: a prospective study. *Journal of Affective Disorders, 109*(1-2), 133-138. doi: 10.1016/j.jad.2007.12.005

Cole, C. R., Blackstone, E. H., Pashkow, F. J., Snader, C. E., & Lauer, M. S. (1999). Heart-rate recovery immediately after exercise as a predictor of mortality. *New England Journal of Medicine, 341*(18), 1351-1357. doi: 10.1056/NEJM199910283411804

Dekker, J. M., Crow, R. S., Folsom, A. R., Hannan, P. J., Liao, D., Swenne, C. A., … Schouten, E.G. (2000). Low heart rate variability in a 2-minute rhythm strip predicts risk of coronary heart disease and mortality from several

causes: the ARIC Study. Atherosclerosis Risk In Communities. *Circulation, 102*(11), 1239-1244. doi: 10.1161/01.CIR.102.11.1239

Douglas, K. M., Taylor, A. J., & O'Malley, P. G. (2004). Relationship between depression and C-reactive protein in a screening population. *Psychosomatic Medicine, 66*(5), 679-683. doi: 10.1097/01.psy.0000138132.66332.85

Esler, M., Turbott, J., Schwarz, R., Leonard, P., Bobik, A., Skews, H., … Jackman, G. (1982). The peripheral kinetics of norepinephrine in depressive illness. *Archives of General Psychiatry, 39*(3), 295-300.

Glynn, L. M., Christenfeld, N., & Gerin, W. (2002). The role of rumination in recovery from reactivity: cardiovascular consequences of emotional states. *Psychosomatic Medicine, 64*(5), 714-726. doi: 10.1097/01.PSY.0000031574.42041.23

Herrmann, C., Brand-Driehorst, S., Buss, U., & Ruger, U. (2000). Effects of anxiety and depression on 5-year mortality in 5,057 patients referred for exercise testing. *Journal of Psychosomatic Research, 48*(4-5), 455-462. doi: 10.1016/S0022-3999(99)00086-0

Hoshino, S., Yoshida, M., Inoue, K., Yano, Y., Yanagita, M., … Kawase, I., (2005) Cigarette smoke extract induces endothelial cell injury via JNK pathway. *Biochemical & Biophysical Research Communications, 329*(1), 58-63. doi: 10.1016/j.bbrc.2005.01.095

Hughes, J. W., Casey, E., Luyster, F., Doe, V. H., Waechter, D., Rosneck, J., & Josephson, R. (2006). Depression symptoms predict heart rate recovery

after treadmill stress testing. *American Heart Journal, 151*(5), 1122.e1121-1126. doi: 10.1016/j.ahj.2006.02.004

Hughes, J. W., & Stoney, C. M. (2000). Depressed mood is related to high-frequency heart rate variability during stressors. *Psychosomatic Medicine, 62*(6), 796-803.

Hughes, J. W., York, K. M., Li, Q., Freedland, K. E., Carney, R. M., & Sheps, D. S. (2008). Depressive symptoms predict heart rate recovery after exercise treadmill testing in patients with coronary artery disease: results from the Psychophysiological Investigation of Myocardial Ischemia study. *Psychosomatic Medicine, 70*(4), 456-460. doi: 10.1097/PSY.0b013e31816fcab3

Imai, K., Sato, H., Hori, M., Kusuoka, H., Ozaki, H., Yokoyama, H., … Kamada, T. (1994). Vagally mediated heart rate recovery after exercise is accelerated in athletes but blunted in patients with chronic heart failure. *Journal of the American College of Cardiology, 24*(6), 1529-1535. doi: 10.1016/0735-1097(94)90150-3

Jouven, X., Empana, J. P., Schwartz, P. J., Desnos, M., Courbon, D., & Ducimetiere, P. (2005). Heart-rate profile during exercise as a predictor of sudden death. *New England Journal of Medicine, 352*(19), 1951-1958. doi: 10.1056/NEJMoa043012

Joynt, K. E., Whellan, D. J., & O'Connor, C. M. (2003). Depression and cardiovascular disease: mechanisms of interaction. *Biological Psychiatry, 54*(3), 248-261. doi: 10.1016/S0006-3223(03)00568-7

Kessler, R. C., McGonagle, K. A., Swartz, M., Blazer, D. G., & Nelson, C. B. (1993). Sex and depression in the National Comorbidity Survey. I: Lifetime prevalence, chronicity and recurrence. *Journal of Affective Disorders, 29*(2-3), 85-96. doi: 10.1016/0165-0327(93)90026-G

Kleiger, R. E., Miller, J. P., Bigger, J. T., Jr., & Moss, A. J. (1987). Decreased heart rate variability and its association with increased mortality after acute myocardial infarction. *American Journal of Cardiology, 59*(4), 256-262. doi: 10.1016/0002-9149(87)90795-8

Lahiri, M. K., Kannankeril, P. J., & Goldberger, J. J. (2008). Assessment of autonomic function in cardiovascular disease: physiological basis and prognostic implications. *Journal of the American College of Cardiology, 51*(18), 1725-1733. doi: 10.1016/j.jacc.2008.01.038

Lake, C. R., Pickar, D., Ziegler, M. G., Lipper, S., Slater, S., & Murphy, D. L. (1982). High plasma norepinephrine levels in patients with major affective disorder. *American Journal of Psychiatry, 139*(10), 1315-1318.

Lavoie, K. L., & Fleet, R. P. (2000). The impact of depression on the course and outcome of coronary artery disease: review for cardiologists. *Canadian Journal of Cardiology, 16*(5), 653-662.

Lavoie, K. L., Fleet, R. P., Lesperance, F., Arsenault, A., Laurin, C., Frasure-Smith, N., & Bacon, S.L. (2004). Are exercise stress tests appropriate for assessing myocardial ischemia in patients with major depressive disorder?. *American Heart Journal, 148*(4), 621-627.

Lesperance, F., Frasure-Smith, N., Talajic, M., & Bourassa, M. G. (2002). Five-year risk of cardiac mortality in relation to initial severity and one-year

changes in depression symptoms after myocardial infarction. *Circulation, 105*(9), 1049-1053. doi: 10.1161/ hc0902.104707

Lustman, P. J., Clouse, R. E., Griffith, L. S., Carney, R. M., & Freedland, K.E. (1997). Screening for depression in diabetes using the Beck Depression Inventory. *Psychosomatic Medicine, 59*(1)*, 24-31*.

Marchionni, N., Fattirolli, F., Fumagalli, S., Oldridge, N. B., Del Lungo, F., Bonechi, F., … Masotti, G. (2000). Determinants of exercise tolerance after acute myocardial infarction in older persons. *Journal of the American Geriatrics Society, 48*(2), 146-153.

Miller, G. E., Stetler, C. A., Carney, R. M., Freedland, K. E., & Banks, W. A. (2002). Clinical depression and inflammatory risk markers for coronary heart disease. *American Journal of Cardiology, 90*(12), 1279-1283. doi: 10.1016/S0002-9149(02)02863-1

Mora, S., Redberg, R. F., Cui, Y., Whiteman, M. K., Flaws, J. A., Sharrett, A. R., & Blumenthal, R.S. (2003). Ability of exercise testing to predict cardiovascular and all-cause death in asymptomatic women: a 20-year follow-up of the lipid research clinics prevalence study. *Journal of the American Medical Association, 290*(12), 1600-1607. doi: 10.1001/jama.290.12.1600

Nishime, E. O., Cole, C. R., Blackstone, E. H., Pashkow, F. J., & Lauer, M. S. (2000). Heart rate recovery and treadmill exercise score as predictors of mortality in patients referred for exercise ECG. *Journal of the American Medical Association, 284*(11), 1392-1398. doi: 10.1001%2Fjama.284.11.1392

Nolan, J., Batin, P. D., Andrews, R., Lindsay, S. J., Brooksby, P., Mullen, M., … Fox, K.A.A. (1998). Prospective study of heart rate variability and mortality in chronic heart failure: results of the United Kingdom heart failure evaluation and assessment of risk trial (UK-heart). *Circulation, 98*(15), 1510-1516.

Nolen-Hoeksema, S. (2000). The role of rumination in depressive disorders and mixed anxiety/depressive symptoms. *Journal of Abnormal Psychology, 109*(3), 504-511. doi: 10.1037%2F0021-843X.109.3.504

Okin, P. M., Ameisen, O., & Kligfield, P. (1986). A modified treadmill exercise protocol for computer-assisted analysis of the ST segment/ heart rate slope: methods and reproducibility. *Electrocardiology, 19*(4), 311-318.

Pierpont, G. L., & Voth, E. J. (2004). Assessing autonomic function by analysis of heart rate recovery from exercise in healthy subjects. *American Journal of Cardiology, 94*(1), 64-68. doi: 10.1016%2Fj.amjcard.2004.03.032

Roy, A., Pickar, D., De Jong, J., Karoum, F., & Linnoila, M. (1988). Norepinephrine and its metabolites in cerebrospinal fluid, plasma, and urine. Relationship to hypothalamic-pituitary-adrenal axis function in depression. *Archives of General Psychiatry, 45*(9), 849-857. doi: 10.1001%2Farchpsyc.1988.01800330081010

Rozanski, A., Blumenthal, J. A., & Kaplan, J. (1999). Impact of psychological factors on the pathogenesis of cardiovascular disease and implications for therapy. *Circulation, 99*(16), 2192-2217.

Ruo, B., Rumsfeld, J. S., Pipkin, S., & Whooley, M. A. (2004). Relation between depressive symptoms and treadmill exercise capacity in the Heart and Soul

Study. *American Journal of Cardiology, 94*(1), 96-99. doi: 10.1016%2Fj.amjcard.2004.03.035

Rutledge, T., Reis, S. E., Olson, M., Owens, J., Kelsey, S. F., Pepine, C. J., … Merz, C.N. (2006). Depression is associated with cardiac symptoms, mortality risk, and hospitalization among women with suspected coronary disease: the NHLBI-sponsored WISE study. *Psychosomatic Medicine, 68*(2), 217-223. doi: 10.1097%2F01.psy.0000195751.94998.e3

Shetler, K., Marcus, R., Froelicher, V. F., Vora, S., Kalisetti, D., Prakash, M., … Myers, J. (2001). Heart rate recovery: validation and methodologic issues. *Journal of the American College of Cardiology, 38*(7), 1980-1987. doi: 10.1016%2FS0735-1097%2801%2901652-7

Spitzer, R. L., Williams, J. B., Kroenke, K., Linzer, M., deGruy, F. V., Hahn, S. R., … Johnson, J.G. (1994). Utility of a new procedure for diagnosing mental disorders in primary care. The PRIME-MD 1000 study. *Journal of the American Medical Association, 272*(22), 1749-1756. doi: 10.1001%2Fjama.1994.03520220043029

Stein, P. K., Carney, R. M., Freedland, K. E., Skala, J. A., Jaffe, A. S., Kleiger, R. E., & Rottman, J.N. (2000). Severe depression is associated with markedly reduced heart rate variability in patients with stable coronary heart disease. *Journal of Psychosomatic Research, 48*(4-5), 493-500. doi: 10.1016%2FS0022-3999%2899%2900085-9

von Kanel, R., Saner, H., Kohls, S., Barth, J., Znoj, H., Saner, G., & Schmid, J. (2009). Relation of heart rate recovery to psychological distress and quality of life in patients with chronic heart failure. *European Journal of*

Cardiovascular Prevention and Rehabilitation, 16(6), 645-650. doi: 10.1097%2FHJR.0b013e3283299542

Yin, P., & Fan, X. (2000). Assessing the reliability of Beck Depression Inventory scores: Reliability generalization across studies. *Educational and Psychological Measurement 60*(2), 201-223. doi: 10.1177%2F00131640021970466

Transition

Manuscript One suggests that major depression is associated with poor post-exercise HR recovery, a marker of ANS imbalance and predictor of poor CV outcome. Manuscript Two aimed to extend our understanding of the relationship between depression and ANS imbalance by testing whether different depressive symptoms are differentially associated with ANS imbalance. Depressive symptoms have traditionally been broadly separated into symptoms related to thoughts and feelings (cognitive-affective) and symptoms related to physical discomfort (somatic). Some have argued that associations between depression and CVD are related primarily to somatic symptoms of depression, perhaps an artifact of physical symptoms of CVD (e.g. weakness, fatigue). Thus, Manuscript Two aimed to compare these two types of symptoms in predicting ANS tone in response to stress. To eliminate the issue of symptoms due to CVD, the study employed only healthy adults. In addition, because previous studies comparing the relative importance of these depressive symptom types had either examined baseline ANS tone or ANS responses to physical stressors such as exercise, the study in Manuscript Two used psychological stressors to assess whether this would influence the outcome.

Manuscript Two

Cognitive Depressive Symptoms Associated with Delayed Heart Rate Recovery Following Interpersonal Stress in Healthy Men and Women

Gordon, J. L., Ditto, B., D'Antono, B. (in press). Cognitive depressive symptoms associated with delayed heart rate recovery following interpersonal stress in healthy men and women. *Psychophysiology*. doi 10.1111/j.1469-8986.2012.01397.x

Abstract

Among cardiac patients, research suggests that somatic depressive symptoms are more strongly associated with altered cardiovascular (CV) responses to stress than cognitive depressive symptoms. This study sought to determine whether this was also the case in healthy individuals. 199 adults from the community completed the Beck Depression Inventory II (BDI-II) and underwent psychological laboratory stressors while their blood pressure, heart rate and heart rate variability were monitored. A cognitive-affective factor and somatic-affective factor were identified within the BDI-II but only the cognitive factor was associated with reduced heart rate recovery following the stressors in multivariate analyses examining both factors simultaneously. This suggests that cognitive depressive symptoms may be more strongly related to altered stress physiology following psychological stressors.

Key Words: Depression, Autonomic nervous system, Heart rate, Blood pressure, Heart rate variability

Depression is associated with an increased risk of developing cardiovascular disease (CVD) in healthy individuals as well as an increased risk of mortality in CVD patients (Barth, Schumacher, & Herrmann-Lingen, 2004; Rugulies, 2002). Sub-clinical depressive symptoms are also linearly associated with the risk of CVD (Van der Kooy et al., 2007). Prolonged activation of the sympathetic nervous system has been proposed as one potential mechanism linking depression to CVD (Brosschot, Gerin, & Thayer, 2006; Joynt, Whellan, & O'Connor, 2003). Supporting this theory, a number of studies have found both clinical depression and depressive symptoms to be associated with indicators of sympathetic dominance, including reduced heart rate (HR) recovery following exercise (Gordon et al., 2011; Hughes et al., 2008) and elevated catecholamine levels (Lake et al., 1982; Light, Kothandapani, & Allen, 1998). These indicators have, in turn, been shown to predict CVD events and CVD-related mortality (Christensen & Schultz-Larsen, 1994; Cole, Blackstone, Pashkow, Snader, & Lauer, 1999).

The Beck Depression Inventory-II (BDI-II) is one of the most widely-used questionnaires assessing depressive symptoms. When it was first released in 1996, the psychometric data in the manual suggested that the BDI-II could be divided into two broad factors, but the factors differed slightly according to the population. In a psychiatric sample, the two factors corresponded to Somatic-Affective and Cognitive symptoms while in a student sample, these factors corresponded to Cognitive-Affective and Somatic dimensions (Beck, Steer, & Brown, 1996). Numerous researchers have since examined the psychometric properties of the BDI-II in various populations and while they have consistently obtained two distinct factors that broadly separate “cognitive” and “somatic”

symptoms, the factor to which "affective" symptoms belong changes depending on the population (Dozois, Dobson, & Ahnberg, 1998; Poole, Bramwell, & Murphy, 2006; Steer, Ball, Ranieri, & Beck, 1999; Vanheule, Desmet, Groenvynck, Rosseel, & Fontaine, 2008; Viljoen, Iverson, Griffiths, & Woodward, 2003; Whisman, Perez, & Ramel, 2000).

Emerging research suggests that the somatic and cognitive factors may be differentially associated with CVD. For example, one study recently found that among 1019 patients with stable coronary heart disease, each somatic depressive symptom on the Patient Health Questionnaire, including fatigue and appetite problems, was associated with 14% greater risk for a CV event or death in the following 6 years (Hoen et al., 2010). On the other hand, cognitive-affective depressive symptoms, including depressed mood and worthlessness, were not significantly associated with increased risk. Similar results have been obtained in studies of post-myocardial infarction (MI) patients (de Jonge et al., 2006; Linke et al., 2009; Martens, Hoen, Mittelhaeuser, de Jonge, & Denollet, 2010; Smolderen et al., 2009). Most recently, in 2442 depressed and/or socially isolated post-MI patients participating in the ENRICHD trial, each standard deviation increase in somatic BDI symptoms one year post-MI was associated with a subsequent 60% increased risk of CV mortality (Bekke-Hansen, Trockel, Burg, & Taylor, 2011).

While the mechanisms through which cognitive and somatic depressive symptoms impact CV health differentially are uncertain, a few studies suggest that dysregulation of the autonomic nervous system may play a role. One study of 863 outpatients with stable coronary heart disease found that somatic, but not cognitive, BDI symptoms were significantly associated with reduced heart rate

variability (HRV). However, this association was explained largely by comorbidities and poor health behaviours (de Jonge, Mangano, & Whooley, 2007). A second study of 2049 preadolescents found that somatic depressive symptoms, measured using the Youth Self-Report, were associated with reduced HRV and baroreflex sensitivity (Bosch et al., 2009) while cognitive-affective symptoms were associated with increased HRV and baroreflex sensitivity.

These studies suggest that somatic depressive symptoms, more than cognitive symptoms, increase the risk of CVD, perhaps through an effect on the autonomic nervous system. Indeed, this has even led some researchers to suggest that the relationship between depressive symptoms and CVD may be due to an overlap in the somatic symptoms of depression and CVD and that depression may not be an independent risk factor for CVD (de Jonge et al., 2006). However, not all findings support this view. One study (Barefoot et al., 2000) examined the relationship between scores on the Zung Self-Rating Depression Scale and cardiac mortality over 19 years among 1250 coronary artery disease patients. Of four scale factors - well-being, negative affect, somatic symptoms and appetite - only negative affect predicted mortality in multivariate analyses. A second study (Barefoot & Schroll, 1996) examined the relationship between depressive symptoms measured by the MMPI in a community sample and cardiac outcomes 17-27 years later. It was found that even when all somatic depressive symptoms were excluded from the analyses, the remaining symptoms continued to predict myocardial infarction and mortality.

These results call into question the idea that somatic depressive symptoms are entirely responsible for the relationship between depression and CVD. Further

research is needed to clarify this issue. Studies examining the relationships between depressive symptoms and cardiac health in initially healthy adults are also needed considering the only such study (Barefoot & Schroll, 1996) obtained findings that contradict those found in cardiac populations. In a previous study of people undergoing exercise stress tests for evaluation of possible CVD (Gordon et al., 2011), we found that depression was associated with delayed HR recovery from exercise, which may have important clinical implications. By definition, CV recovery reflects activity following the cessation of a stressor, which may have a longer time course than the immediate response to the stressor. Several authors (Gerin & Pickering, 1995; Linden, Earle, Gerin, & Christenfeld, 1997) have argued that the speed of CV recovery from stress may be more relevant to the development or exacerbation of stress-related disease than CV reactivity. Brosschot et al. (2005) have similarly argued the importance of considering CV recovery as part of the overall concept of "prolonged activation" in response to stress rather than focusing exclusively on CV reactivity (Brosschot, Pieper, & Thayer, 2005). The present study examined relations between cognitive and somatic depressive symptoms on blood pressure, HR and HRV before, during and after several interpersonal stressors in a large sample of healthy adults. It was hypothesized that both somatic and cognitive depressive symptoms would be related to alterations in responses to stress including CV recovery from stress.

Methods

Participants

One hundred and ninety-nine adult men (n = 81) and women (n = 118) were recruited using advertisements in newspapers and community centers within

the greater Montreal area (Table 1). Exclusion criteria included: 1) utilization of mental health services within the past year; 2) current/known health problems (e.g. hypertension, diabetes, CVD) or use of medication capable of affecting CV, immune or neuroendocrine functions; 3) learning or cognitive disabilities rendering the individual unable to complete questionnaires or understand instructions and 4) current use of hormone replacement therapy. Individuals were screened by telephone to ensure they met these inclusion criteria. Similar numbers of participants were selected from three age groups (18-34 years, 35-44 years, and 45-65 years) to ensure a broad age range.

Procedure

Participants were scheduled for a laboratory appointment at 8:00 a.m. on a weekday at the Montreal Heart Institute. Participants were asked to abstain from drinking (other than water), smoking and strenuous exercise for 12 hours prior to testing. They were also asked to refrain from alcohol or drug use for the 24 hours preceding their appointment. Participants not having adhered to these instructions or exhibiting physical symptoms (e.g. cough, cold or headache) were sent home and a new appointment time was scheduled.

Participants were tested by a same-sex research assistant who had been trained to maintain a neutral tone and expression throughout the testing. Once written informed consent was obtained, electrodes for electrocardiogram monitoring were attached in a bipolar configuration to the lower side of the rib cage. A ground electrode was placed on the left hip. Sociodemographic, medical and psychological questionnaires were administered, followed by a 10-minute baseline period during which participants rested quietly. Testing included four

psychological challenges (a neutral reading task, two role-plays and a non-scripted debate), which were each preceded by a 5-minute taped autogenic relaxation procedure and a 2-minute preparation phase and followed by a 5-minute recovery period. The electrocardiogram was obtained continuously during laboratory testing. Systolic (SBP) and diastolic blood pressure (DBP) was measured using an AccutorPlus automated blood pressure monitor from Datascope using a standard inflatable cuff placed on the participant's non-dominant arm. This model uses an oscillometric method and has been recommended by the European Society of Hypertension (O'Brien, Waeber, Parati, Staessen, & Myers, 2001). A mean of two readings per period was used for analysis. Participants received $200 compensation for time and travel. The Research and Ethics Board of the Montreal Heart Institute approved this study.

Laboratory Tasks

Each task lasted 5 minutes. To ensure the stressful nature of the laboratory tasks, participants were videotaped during each task and the research assistant interacting with the participants maintained a neutral tone and demeanour throughout the laboratory session. The tasks, chosen based on an interest in hostility and defensiveness, had been shown to lead to significant affective and physiological reactivity in pilot testing or prior studies (Al'Absi, Bongard, & Lovallo, 2000; D'Antono, Moskowitz, Miners, & Archambault, 2005).

Neutral reading task. The first task involved reading a text on Antarctica's geography in front of a same-sex confederate. While it was intended to control for the effect of public speaking, it led to significant physiological arousal and was therefore considered a stressor.

Role-plays. As per a prior study (D'Antono et al., 2005), two role-plays manipulating hostile behaviour were administered following the reading task. Participants were required to imagine that he or she was a personnel supervisor providing feedback to an employee whose performance has been mediocre. In one condition, the script provided feedback using agreeable assertions while in the other, the script provided feedback using an equal number of quarrelsome assertions. The participant was asked to enact the script with a confederate who was acting as the supervisee to whom the participant provided the feedback. This procedure was repeated for the second script. The order was counter balanced across participants.

Debate. The final task involved a non-scripted debate on abortion. Participants argued from a partisan position and alternated speaking and listening for 1-minute periods with a confederate debating a position opposite to that of the participant. The participant began first, resulting in 3 minutes of active debate and 2 minutes of listening while the confederate spoke.

Measures

Sociodemographic variables. Data on sex, age in years, ethnicity, weight, height, marital status, income, and years of schooling were collected. Behavioural risk factors, such as daily tobacco and hours of physical activity, were reported by the participant.

Physiological variables. Heart rate (HR) and heart rate variability (HRV) were obtained using disposable electrodes and the Biopac acquisition system (AcqKnowledge 3.7.3 software). Signals were first filtered with a digital bandpass filter and a 1000-Hz sampling rate. Interbeat intervals were generated using a

peak detection algorithm, after which the series was screened by hand and corrected for artifacts. Spectral analysis of HRV was performed off-line using Fast Fourier Transformations of the interbeat intervals (RR) in MATLAB using published algorithms (Tarvainen, Ranta-aho, & Karjalainen, 2002; Tikkanen, 1999) and was characterized by the high frequency (HF; 0.15-0.40 Hz) and the low frequency components (LF; 0.04-0.15 Hz) as recommended by the Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology (1996).

Depressive symptoms. The Beck Depression Inventory-II (BDI-II) (Beck et al., 1996) was used to measure depressive symptoms. This widely-used questionnaire consists of 21 items scored from 0 to 3, with higher numbers indicating greater symptom severity. The BDI-II has an internal consistency of .837 (.007) and a test-retest reliability of .690 (.009) (Yin & Fan, 2000). The BDI-II has been shown to have good sensitivity (.82-.90) and specificity (.84-.89) for identifying major depression, defined using DSM criteria (Lustman, Clouse, Griffith, Carney, & et al., 1997). In the current sample, coefficient alpha for the total scale was found to be .88.

Somatic and cognitive depressive factors. Based on previous research, we anticipated a distinction between two symptom factors: a somatic factor and a cognitive factor. Responses to the 21-item BDI-II were subjected to principal component analysis using oblique rotation (promax) since the two factors were expected to correlate. The Kaiser-Meyer-Olkin measure verified the sampling adequacy for the analysis, KMO = 0.88, and all KMO values for individual items were > .79, which is well above the acceptable limit of .5 (Field, 2009). Two

components were retained based on the Scree Test. Combined, these two components accounted for 39% of the total variance, similar to what has been found by others (Martens et al., 2010). In interpreting the rotated factor pattern, an item was said to load on a given component if the factor loading was 0.40 or greater for that component, and was less than 0.40 for the other (Table 2). The correlation between the two factors was 0.64. Participants' mean score on the items from each factor was calculated and items that loaded on neither factor were excluded from subsequent analyses.

Affect and arousal. An affect grid was used to assess both the valence and intensity of affect (Russell, Weiss & Mendelsohn, 1989). The participant is presented with a 9 X 9 grid of squares and asked to indicate the extent to which he is feeling pleasure-displeasure on the horizontal axis and arousal-sleepiness on the vertical axis. The intensity of specific affects (e.g. anger, fear) was also measured using a 7-point rating scale from 1 (*not at all*) to 7 (*very much*).

Data Analysis

CV reactivity was defined as the difference between the mean SBP, DBP, HR, HF-HRV or LF/HF-HRV averaged across the four 5-minute laboratory stressors and the same variable averaged across the last 5 minutes of the 10-minute baseline resting period. CV recovery, on the other hand, was defined as the difference between the mean SBP, DBP, HR, HF and LF/HF-HRV averaged either across the first 2.5 minutes following each stressor ("short-term" recovery) or across the entire 5 minutes following each stressor ("long-term" recovery) and the same variable averaged across the 10-minute baseline resting period. Because of evidence suggesting that 2 minutes may not be long enough to detect HR

fluctuations of low frequency (Liao et al., 1995), however, LF/HF was only averaged across the entire 5 minutes following each stressor.

General linear models (GLMs) were conducted for each CV measure (SBP, DBP, HR, HF and LF/HF), examining the effect of total BDI score, somatic-affective symptom score and cognitive-affective symptom score. Model 1 examined each variable separately while model 2 included both factors simultaneously. Age, sex, body mass index and average number of hours spent exercising per week were included in all analyses as covariates as these factors have been associated with altered CV responses to stress (Cheng et al., 2003). Mean baseline and stress task values of the given variable were also included as covariates in the recovery analyses to ensure that any significant differences in recovery would not be due to differences in baseline or peak CV measures. For similar reasons, baseline and post-stress values were included as covariates in the reactivity analyses. Due to the known effect of respiration rate on HRV (Bernardi et al., 2000), respiration reactivity was also included as a covariate in the HRV reactivity analyses while respiration recovery was included in the HRV recovery analyses. Depressive symptoms-by-sex interaction terms were also included in both models to examine potential sex differences. All analyses were conducted using SAS v 9.2 (SAS Institute, Cary, NC).

Results

Participant Characteristics

Participant characteristics are shown in Table 1. Overall BDI-II scores ranged from 0 (no depressive symptoms) to 32 (severe depressive symptoms).

Cognitive factor scores ranged from 0 to 18 out of a possible 30 while somatic factor scores ranged from 0 to 14 out of 21.

Efficacy of the Stress Protocol

T-tests revealed that mean reactivity scores for SBP (t (1,198) = 20.83, p<.0001), DBP (t (1,198) = 20.45, p<.0001), HR (t (1,193) = 15.91, p<.0001) and LF/HF (t (1,193) = 10.24, p<.0001) were significantly greater than 0. HF reactivity, on the other hand, was significantly smaller than 0 (t (1,193) = -2.14, p=.033). Participants' recovery scores for SBP (t (1, 198) = 10.16, p<.0001), DBP (t (1, 198) = 8.16, p<.0001) and HR (t (1,195) = 8.02, p<.0001) and LF/HF (t (1,195) = 9.10, p<.0001) were also greater than 0. However, mean HF recovery scores were not (t (1, 195) = -1.11, p=.269) (Table 3). Since similar changes in physiological activity were observed across all tasks, reactivity and recovery scores were aggregated across laboratory tasks.

The stress tasks also induced a significant level of subjective arousal (F(1, 198) = 885.52, p<.001), negative affect (F(1, 198) = 53.14, p<.001), anger (F(1,198) = 150.14, p<.001), shame (F(1,198) = 28.95, p<.001), embarrassment (F(1,198) = 89.07, p<.001) and sadness (F(1,198) = 6.16, p<.02). However, there was no significant increase in fear or upset (Lévesque, Moskowitz, Tardif, Dupuis & D'Antono, 2010).

Reactivity

The results of model 1 are found in Table 4. In model 2, neither cognitive nor somatic factors were associated with CV reactivity. In all cases, the overall statistical model was highly significant (p's<.0001) and the R^2 for the overall model ranged from 0.3597 to 0.6744. Covariates significantly predicting CV

reactivity included baseline CV values (SBP, DBP, HR, HF, LF/HF), post-stress task values (SBP, DBP, HR, HF, LF/HF), age (DBP, HR), sex (DBP, HR, LF/HF), hours of exercise/week (HR) and body mass index (SBP, HR).

Recovery

Short-term (2.5 minute) recovery. The results of model 1 are found in Table 4. In model 2, neither symptom factor was associated with CV recovery, though the effect of the cognitive-affective factor on HR recovery remained a trend (β(SEM) = 1.39 (1.14), p = .071, partial η^2 = 0.0179).

Longer-term (5 minute) recovery. The results of model 1 are found in Table 4. The cognitive-affective subscale score was significantly associated with decreased HR recovery in model 2 (β(SEM) = 1.87 (1.11), p = .047, partial η^2 = 0.0217). There were no other significant effects. As with the reactivity analyses, the overall statistical models for all recovery analyses were highly significant ($p<.0001$) and the R^2 for the overall models ranged from 0.4031 to 0.6152. Covariates significantly predicting CV recovery included baseline CV values (SBP, DBP, HR, HF, LF/HF), stress task values (SBP, DBP, HR, HF, LF/HF), respiration rate (HF), sex (SBP, HF) and age (SBP, DBP).

Discussion

The primary objective of the current study was to compare somatic-affective and cognitive-affective depressive symptoms in their relationship with CV responses to psychological laboratory stressors in healthy adults. When examined separately, both types of symptoms were found to predict CV responses: cognitive-affective symptoms were associated with reduced HR reactivity and

recovery while somatic symptoms were associated with poorer SBP recovery. When both types of symptoms were included in the same statistical model, cognitive-affective symptoms but not somatic-affective symptoms were associated with reduced HR recovery. Both types of symptoms therefore appear to be associated with altered CV responses to psychological stress though cognitive-affective symptoms may be more strongly so.

These findings contradict research conducted in cardiac samples to some degree (de Jonge et al., 2006; Linke et al., 2009; Martens et al., 2010; Schiffer et al., 2009; Smolderen et al., 2009). The latter have found that somatic, rather than cognitive, depressive symptoms are most predictive of cardiac outcomes and autonomic dysfunction. However, our results are consistent with the only study to date that has examined the importance of cognitive versus somatic depressive symptoms in determining cardiac health in an adult community sample (Barefoot & Schroll, 1996). The reason for the discrepancy between the results found in healthy and cardiac samples is unclear. However, it seems unlikely that the current study's low rate of severe depressive symptoms is responsible, given that several studies of cardiac patients have found a relationship between somatic depressive symptoms and CV outcomes despite having similarly low rates (Hoen et al., 2010; Smolderen et al., 2009). Instead, it may be that at comparable levels of depression, cardiac patients have more somatic symptoms than healthy samples. The relationship between cognitive depressive symptoms and CV health may be obscured as a result.

The psychological vs. physical nature of the stressors used in the current study may also explain why cognitive-affective symptoms were more strongly

associated with altered CV responses to stress compared to somatic-affective symptoms. While previous research has compared somatic and cognitive depressive symptoms in their association with ambulatory CV measures, this study examined the issue using interpersonal tasks. Such tasks may be more likely to elicit rumination, which refers to repetitively focusing on one's distress or the causes of the distress, in more depressed individuals. According to the "perseverative cognition hypothesis", proposed by Brosschot and colleagues, perseverative cognition, including anticipatory anxiety and rumination, may be key in linking stress and disease through prolonged activation of the endocrine, CV and immune systems (Brosschot et al., 2006; Brosschot et al., 2005). Rumination has been associated with depression (Nolen-Hoeksema, 2000) and reduced CV recovery following an emotionally laden task (Glynn, Christenfeld, & Gerin, 2002). Thus, rumination may be one mechanism through which cognitive-affective depressive symptoms might impact HR recovery more than somatic-affective symptoms. Given the nature of cognitive-affective depressive symptoms, it may be that a stress task eliciting greater sadness and depressed affect than the tasks used in the current study may have resulted in greater rumination and therefore a stronger relationship between cognitive-affective depressive symptoms and CV recovery.

The fact that overall BDI-II score was associated with the same CV parameters as the individual factors raises the question of how much is gained by separating depressive symptoms into cognitive and somatic factors. In a recent article, Carney and Freedland (2012) also question the factor approach, suggesting that the historically stronger effect of somatic symptoms on CVD may be due to

confounding factors such as the greater prominence of somatic symptoms in severe depression and reporting bias resulting from social stigma surrounding cognitive depressive symptoms. Furthermore, in interpreting the results of statistical models including both factors simultaneously, there is a possibility that a lack of significant findings might be due to a high correlation between the factors, preventing either effect from being significant. In the current study, the two factors were indeed highly correlated. Moreover, when examined separately, both symptom factors were associated with CV recovery. The inclusion of both symptom factors within one model may therefore not be appropriate. The high correlation between the two factors and the fact that both factors were associated with CV recovery when examined separately also suggests that it may not be advantageous to examine the two factors separately as opposed to examining the overall BDI-II score.

Consistent with past research, the overall BDI-II score was associated with impaired short-term HR recovery and long-term SBP recovery (Gordon et al., 2011). While the magnitude of these effects was small, other studies have found similarly modest associations between depressive symptoms and CV recovery following exercise (Hughes et al., 2008). The fact that the current study's participants were healthy may help explain the modest results since the nature of the sample examined (community vs. cardiac) has been found to be the most important factor determining the strength of the association between depressive symptoms and CV reactivity (Kibler & Ma, 2004). Still, it is worth questioning the importance of exaggerated autonomic activation as a mechanism linking depression and CVD. The only study to date examining the relative importance of

potential mechanisms in mediating the relationship between depressive symptoms and CVD events, (Whooley et al., 2008), found that HRV accounted for only 4% of the shared variance, suggesting that alterations in autonomic balance are less important relative to other mechanisms, such as health behaviors, accounting for nearly 50% of the variance. The current study's modest findings are consistent with this conclusion.

The negative association between cognitive-affective depressive symptoms and HR reactivity was somewhat unexpected given that depression has generally been associated with increased reactivity (Kibler & Ma, 2004). However, a growing body of literature suggests that depressive symptoms are, in fact, associated with reduced CV reactivity to both laboratory stress tasks (Phillips, 2011; York et al., 2007) and reward (Brinkmann, Schupbach, Joye, & Gendolla, 2009). While the reasons for this negative association are unclear, one potential mechanism proposed by York et al. (2007) may be related to decreased sensitivity (Charney et al., 1982) and density (Wood, Whiting, & Coppen, 1986) of adrenergic receptors.

This study has several strengths including diversity in age and socioeconomic status of the participants, increasing the generalizability of the results. As well, unlike the studies of cardiac patients, the participants of the current study were not taking any medications impacting HR or autonomic function. The analyses adjusted for body mass index and exercise, known to be related both to depressive symptoms and HR reactivity and recovery. The current study's use of interpersonal stressors also appears to be an important feature in that it seems to tap into mechanisms pertinent to depression, such as rumination,

that are not involved in physical stressors such as exercise. Furthermore, the stressors used in this study had good ecological validity, as most of the stressors encountered in daily life are recurrent, interpersonal in nature and mild to moderate in intensity. Limitations of the current study include its cross-sectional nature, making it impossible to infer causality. Also, the fact that the participants were French Canadian and Caucasian may limit the study's generalizability to other ethnic groups.

In conclusion, the current study found that among healthy adults, cognitive-affective depressive symptoms are more strongly associated with impaired HR recovery to psychological stressors than somatic-affective symptoms. These findings contradict studies in cardiac samples, which have found somatic symptoms to be most strongly related to CVD and markers of prolonged sympathetic activation. They provide evidence against the view that the depression-CVD relationship can be explained by an overlap in symptomology and highlight the importance of considering both types of depressive symptoms as risk factors for CVD.

Table 1

Participant Characteristics

	Mean (SD) or %
Women	59.4%
Age	41.1 (11.2)
Years of education	15.8 (3.3)
Caucasian	87.4%
Annual family income	
$29 999 and under	33%
$30 000 – 59 999	36%
$60 000 and over	31%
Hours of exercise/week	3.4 (3.9)
Body mass index (BMI)	24.8 (4.6)
Current smoker	20.6%
BDI-II score	8.4 (7.1)
BDI-II score < 14	76.1%
14-19	14.4%
20-29	8.3%
>29	1.1%
Cognitive factor score /30	3.2 (3.7)
Somatic factor score /21	3.4 (2.8)

Table 2

Factor Loadings of BDI-II Depressive Symptom Dimensions and Previous Dimensional Constructs Found in Depressed Outpatients

	Steer et al., 1999		Current Study	
BDI-II Symptoms	Cognitive	Somatic	Cognitive	Somatic
Sadness	0.39	0.46	**0.51**	0.07
Pessimism	**0.58**	0.10	**0.63**	0.06
Past failure	**0.71**	-0.15	**0.59**	0.08
Loss of pleasure	0.28	**0.50**	0.04	**0.67**
Guilty feelings	**0.60**	-0.03	**0.70**	-0.10
Punishment feelings	**0.52**	0.02	**0.54**	0.01
Self-dislike	**0.55**	0.00	**0.66**	0.00
Self-criticalness	**0.64**	-0.01	0.35	0.22
Suicidal thoughts	**0.44**	0.18	**0.68**	-0.03
Crying	0.35	0.20	0.32	0.31
Agitation	0.24	0.15	0.30	0.31
Loss of interest	0.24	**0.53**	-0.17	**0.85**
Indecisiveness	0.25	**0.46**	**0.45**	0.27
Worthlessness	**0.56**	0.23	**0.66**	-0.15
Loss of energy	-0.09	**0.85**	0.08	**0.67**
Changes in sleep	0.25	0.25	0.08	**0.41**
Irritability	0.24	**0.38**	-0.03	**0.62**
Changes in appetite	-0.10	**0.63**	**0.40**	0.20
Poor concentration	0.30	**0.41**	0.37	**0.42**
Fatigue	-0.15	**0.91**	0.23	**0.58**
Loss of libido	0.01	**0.40**	-0.11	**0.62**

BDI-II = Beck Depression Inventory-II

Table 3

Physiological data

	BDI<14	BDI≥14
N	137	43
Baseline		
SBP (mmHg + SD)	108.9 (11.8)	111.9 (12.9)
DBP (mmHg + SD)	68.9 (8.6)	70.6 (8.4)
HR (bpm + SD)	65.3 (8.6)	64.8 (8.9)
HF-HRV (m^2 + SD)	517.3 (884.2)	680.3 (1532.5)
LF/HF (SD)	2.0 (2.1)	1.5 (1.0)
Stress Period		
SBP (mmHg + SD)	120.9 (14.2)	123.8 (14.2)
DBP (mmHg + SD)	77.9 (10.6)	78.6 (10.6)
HR (bpm + SD)	71.6 (9.6)	69.9 (9.0)
HF-HRV (m^2 + SD)	387.9 (596.2)	462.0 (710.5)
LF/HF (SD)*	3.3 (3.0)	2.7 (2.3)
Short-Term Recovery Period		
SBP (mmHg + SD)	113.7 (12.3)	117.3 (13.2)
DBP (mmHg + SD)	71.3 (9.4)	72.9 (9.2)
HR (bpm + SD)	68.2 (8.6)	67.6 (8.4)
HF-HRV (m^2 + SD)*	419.6 (591.6)	735.0 (1526.3)
Long-Term Recovery Period		
SBP (mmHg + SD)	112.4 (11.9)	116.0 (12.4)
DBP (mmHg + SD)	71.2 (8.6)	72.7 (8.2)
HR (bpm + SD)	67.3 (8.5)	66.7 (8.0)
HF (m^2 + SD)	431.1 (571.8)	685.8 (1372.2)
LF/HF (SD)*	3.4 (1.9)	2.7 (1.2)

*$p<0.05$

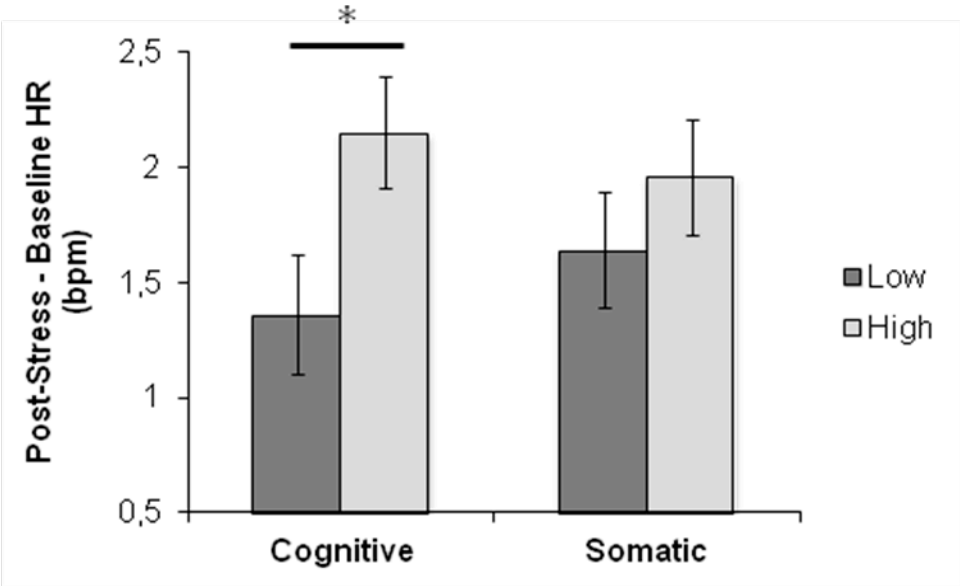
Table 4

Summary of GLMs for total BDI-II score, cognitive subscale score and somatic subscale score separately predicting reactivity and recovery adjusting for baseline CV values, mean post-stress CV values (in the case of reactivity), mean stress task CV values (in the case of recovery), age, sex, body mass index and number of hours of exercise/week

	Total BDI			Cognitive			Somatic		
	β	SE	p	β	SE	p	β	SE	p
Reactivity									
SBP	-0.06	0.10	.141	-0.36	1.88	.114	-1.69	1.95	.280
DBP	0.04	0.07	.668	0.51	1.40	.510	0.50	1.45	.855
HR	-0.11	0.06	.051*	-2.01	1.24	.045*	-1.62	1.28	.187
HF	0.89	5.88	.922	-9.99	117.11	.989	29.87	119.01	.893
LF/HF	-0.02	0.02	.433	-0.44	0.40	.288	-0.35	0.41	.688
Short-Term Recovery									
SBP	0.08	0.08	.059	1.51	1.61	.084	1.97	1.64	.035*
DBP	0.02	0.06	.334	0.73	1.18	.145	0.24	1.22	.714
HR	0.04	0.04	.047*	1.05	0.81	.029*	0.51	0.83	.224
HF	3.66	6.03	.194	128.86	122.58	.258	7.80	123.90	.204
Long-Term Recovery									
SBP	0.06	0.07	.043*	1.16	1.35	.050*	1.45	1.38	.049*
DBP	0.01	0.05	.398	0.35	0.93	.209	-0.06	0.96	.814
HR	0.04	0.04	.104	1.07	0.79	.050*	0.19	0.81	.453
HF	2.50	6.16	.138	103.15	125.57	.235	16.49	127.04	.197
LF/HF	0.02	0.02	.981	0.46	0.42	.484	-0.01	0.43	.637

*partial η^2 ranging between 0.0217 and 0.0258, indicating small effect sizes

Figure 1. Long-term heart rate recovery according to cognitive and somatic symptom scores, split at the median, with standard error bars, adjusted for age, sex, baseline heart rate, mean stress task heart rate, body mass index and hours of exercise/week. bpm, Beats per minute, N = 161, *p <.03



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References

Al'Absi, M., Bongard, S., & Lovallo, W. R. (2000). Adrenocorticotropin responses to interpersonal stress: effects of overt anger expression style and defensiveness. *International Journal of Psychophysiology, 37*(3), 257-265. doi: 10.1016/S0167-8760(00)00108-2

Barefoot, J. C., Brummett, B. H., Helms, M. J., Mark, D. B., Siegler, I. C., & Williams, R. B. (2000). Depressive symptoms and survival of patients with coronary artery disease. *Psychosomatic Medicine, 62*(6), 790-795.

Barefoot, J. C., & Schroll, M. (1996). Symptoms of depression, acute myocardial infarction, and total mortality in a community sample. *Circulation, 93*(11), 1976-1980. doi: 10.1161/01.CIR.93.11.1976

Barth, J., Schumacher, M., & Herrmann-Lingen, C. (2004). Depression as a risk factor for mortality in patients with coronary heart disease: a meta-analysis. *Psychosomatic Medicine, 66*(6), 802-813. doi: 10.1097/01.psy.0000146332.53619.b2

Beck, A. T., Steer, R. A., & Brown, G. K. (1996). *Manual for Beck Depression Inventory-II*. San Antonio, TX: Psychological Corporation.

Bekke-Hansen, S., Trockel, M., Burg, M. M., & Taylor, C. B. (2012). Depressive symptom dimensions and cardiac prognosis following myocardial infarction: results from the ENRICHD clinical trial. *Psychological Medicine*, *42*(1), 51-60. doi: 10.1017%2FS0033291711001000

Bernardi, L., Wdowczyk-Szulc, J., Valenti, C., Castoldi, S., Passino, C., Spadacini, G., & Sleight, P. (2000). Effects of controlled breathing, mental activity and mental stress with or without verbalization on heart rate

variability. *Journal of the American College of Cardiology, 35*(6), 1462-1469. doi: 10.1016/S0735-1097(00)00595-7

Bosch, N. M., Riese, H., Dietrich, A., Ormel, J., Verhulst, F. C., & Oldehinkel, A. J. (2009). Preadolescents' somatic and cognitive-affective depressive symptoms are differentially related to cardiac autonomic function and cortisol: the TRAILS study. *Psychosomatic Medicine, 71*(9), 944-950. doi: 10.1097/PSY.0b013e3181bc756b

Brinkmann, K., Schupbach, L., Joye, I. A., & Gendolla, G. H. E. (2009). Anhedonia and effort mobilization in dysphoria: Reduced cardiovascular response to reward and punishment. *International Journal of Psychophysiology, 74*(3), 250-258. doi: 10.1016/j.ijpsycho.2009.09.009

Brosschot, J. F., Gerin, W., & Thayer, J. F. (2006). The perseverative cognition hypothesis: a review of worry, prolonged stress-related physiological activation, and health. *Journal of Psychosomatic Research, 60*(2), 113-124. doi: 10.1016/j.jpsychores.2005.06.07

Brosschot, J. F., Pieper, S., & Thayer, J. F. (2005). Expanding stress theory: prolonged activation and perseverative cognition. *Psychoneuroendocrinology, 30*(10), 1043-1049. doi: 10.1016/j.psyneuen.2005.04.008

Carney, R. M., & Freedland, K. E. (2012). Are somatic symptoms of depression better predictors of cardiac events than cognitive symptoms in coronary heart disease?. *Psychosomatic Medicine, 74*(1), 33-38. doi:10.1097/PSY.0b013e3182405ac4

Charney, D. S., Heninger, G. R., Sternberg, D. E., Hafstad, K. M., Giddings, S., & Landis, D. H. (1982). Adrenergic-Receptor Sensitivity in Depression - Effects of Clonidine in Depressed-Patients and Healthy-Subjects. *Archives of General Psychiatry, 39*(3), 290-294. doi: 10.1001%2Farchpsyc.1982.04290030030005

Cheng, Y. J., Lauer, M. S., Earnest, C. P., Church, T. S., Kampert, J. B., Gibbons, L. W., & Blair, S. N. (2003). Heart rate recovery following maximal exercise testing as a predictor of cardiovascular disease and all-cause mortality in men with diabetes. *Diabetes Care, 26*(7), 2052-2057. doi: 10.2337/diacare.26.7.2052

Christensen, N. J., & Schultz-Larsen, K. (1994). Resting venous plasma adrenalin in 70-year-old men correlated positively to survival in a population study: the significance of the physical working capacity. *Journal of Internal Medicine, 235*(3), 229-232. doi: 10.1111/j.1365-2796.1994.tb01064.x

Cole, C. R., Blackstone, E. H., Pashkow, F. J., Snader, C. E., & Lauer, M. S. (1999). Heart-rate recovery immediately after exercise as a predictor of mortality. *New England Journal of Medicine, 341*(18), 1351-1357. doi: 10.1097/00008483-200003000-00012

D'Antono, B., Moskowitz, D. S., Miners, C., & Archambault, J. (2005). Gender and communal trait differences in the relations among social behaviour, affect arousal, and cardiac autonomic control. *Journal of Behavioral Medicine, 28*(3), 267-279. doi: 10.1007/s10865-005-4663-0

de Jonge, P., Mangano, D., & Whooley, M. A. (2007). Differential association of cognitive and somatic depressive symptoms with heart rate variability in

patients with stable coronary heart disease: findings from the Heart and Soul Study. *Psychosomatic Medicine, 69*(8), 735-739. doi: 10.1097/PSY.0b013e31815743ca

de Jonge, P., Ormel, J., van den Brink, R. H., van Melle, J. P., Spijkerman, T. A., Kuijper, A., van Veldhuisen, D. J., van den Berg, M. P., Honig, A., Crijns, H. J., & Schene, A. H. (2006). Symptom dimensions of depression following myocardial infarction and their relationship with somatic health status and cardiovascular prognosis. *American Journal of Psychiatry, 163*(1), 138-144. doi: 10.1176/appi.ajp.163.1.138

Dozois, D. J., Dobson, K. S., & Ahnberg, J. L. (1998). A psychometric evaluation of the Beck Depression Inventory-II. *Psychological Assessment, 10*(2), 83-89.

Field, A. P. (2009). *Discovering statistics using SPSS* (3rd ed.). London: Sage.

Gerin, W., & Pickering, T. G. (1995). Association between delayed recovery of blood pressure after acute mental stress and parental history of hypertension. *Journal of Hypertension, 13*(6), 603-610. doi: 10.1097/00004872-199506000-00005

Glynn, L. M., Christenfeld, N., & Gerin, W. (2002). The role of rumination in recovery from reactivity: cardiovascular consequences of emotional states. *Psychosomatic Medicine, 64*(5), 714-726. doi: 10.1097/01.PSY.0000031574.42041.23

Gordon, J. L., Ditto, B., Lavoie, K. L., Pelletier, R., Campbell, T. S., Arsenault, A., & Bacon, S. L. (2011). The effect of major depression on post-exercise

cardiovascular recovery. *Psychophysiology, 48*(11), 1605-1610. doi: 10.1111/j.1469-8986.2011.01232.x

Heponiemi, T., Elovainio, M., Pulkki, L., Puttonen, S., Raitakari, O., & Keltikangas-Jarvinen, L. (2007). Cardiac autonomic reactivity and recovery in predicting carotid atherosclerosis: the cardiovascular risk in young Finns study. *Health Psychology, 26*(1), 13-21. doi: 10.1037/0278-6133.26.1.13

Hoen, P. W., Whooley, M. A., Martens, E. J., Na, B., van Melle, J. P., & de Jonge, P. (2010). Differential associations between specific depressive symptoms and cardiovascular prognosis in patients with stable coronary heart disease. *Journal of the American College of Cardiology, 56*(11), 838-844. doi: 10.1016/j.jacc.2010.03.080

Hughes, J. W., York, K. M., Li, Q., Freedland, K. E., Carney, R. M., & Sheps, D. S. (2008). Depressive symptoms predict heart rate recovery after exercise treadmill testing in patients with coronary artery disease: results from the Psychophysiological Investigation of Myocardial Ischemia study. *Psychosomatic Medicine, 70*(4), 456-460. doi: 10.1016/j.ahj.2006.02.00

Imai, K., Sato, H., Hori, M., Kusuoka, H., Ozaki, H., Yokoyama, H., Takeda, H., Inoue, M., & Kamada, T. (1994). Vagally Mediated Heart-Rate Recovery after Exercise Is Accelerated in Athletes but Blunted in Patients with Chronic Heart-Failure. *Journal of the American College of Cardiology, 24*(6), 1529-1535.

Joynt, K. E., Whellan, D. J., & O'Connor, C. M. (2003). Depression and cardiovascular disease: mechanisms of interaction. *Biological Psychiatry, 54*(3), 248-261. doi: 10.1016/S0006-3223(03)00568-7

Kibler, J. L., & Ma, M. (2004). Depressive symptoms and cardiovascular reactivity to laboratory behavioral stress. *International Journal of Behavioral Medicine, 11*(2), 81-87. doi: 10.1207/s15327558ijbm1102_3

Lake, C. R., Pickar, D., Ziegler, M. G., Lipper, S., Slater, S., & Murphy, D. L. (1982). High plasma norepinephrine levels in patients with major affective disorder. *American Journal of Psychiatry, 139*(10), 1315-1318.

Lévesque, L., Moskowitz, D. S., Tardif, J. C., Dupuis, G., & D'Antono, B. (2010). Physiological stress responses in defensive individuals: age and sex matter. *Psychophysiology, 47*, 332-341. doi: 10.1111/j.1469-8986.2009.00943.x

Liao, D. P., Barnes, R. W., Chambless, L. E., Simpson, R. J., Sorlie, P., & Heiss, G. (1995). Age, race, and sex-differences in autonomic cardiac-function measured by spectral-analysis of heart-rate-variability - the aric study. *American Journal of Cardiology, 76*(12), 906-912. doi: 10.1016/S0002-9149(99)80260-4

Light, K. C., Kothandapani, R. V., & Allen, M. T. (1998). Enhanced cardiovascular and catecholamine responses in women with depressive symptoms. *International Journal of Psychophysiology, 28*(2), 157-166. doi: 10.1016/S0167-8760(97)00093-7

Linden, W., Earle, T. L., Gerin, W., & Christenfeld, N. (1997). Physiological stress reactivity and recovery: conceptual siblings separated at birth?

Journal of Psychosomatic Research, 42(2), 117-135. doi: 10.1016/S0022-3999(96)00240-1

Linke, S. E., Rutledge, T., Johnson, B. D., Vaccarino, V., Bittner, V., Cornell, C. E., Eteiba, W., Sheps, D. S., Krantz, D. S., Parashar, S., & Bairey Merz, C. N. (2009). Depressive symptom dimensions and cardiovascular prognosis among women with suspected myocardial ischemia: A report from the National Heart, Lung, and Blood Institute-sponsored Women's Ischemia Syndrome Evaluation. *Archives of General Psychiatry, 66*(5), 499-507. doi: 10.1001/archgenpsychiatry.2009.27

Lustman, P. J., Clouse, R. E., Griffith, L. S., Carney, R. M., & Freedland K. E. (1997). Screening for depression in diabetes using the Beck Depression Inventory. *Psychosomatic Medicine, 59*(1), 24-31.

Martens, E. J., Hoen, P. W., Mittelhaeuser, M., de Jonge, P., & Denollet, J. (2010). Symptom dimensions of post-myocardial infarction depression, disease severity and cardiac prognosis. *Psychological Medicine, 40*(5), 807-814. doi: 10.1017/S0033291709990997

Miller, G. E., Ritchey, A. K., & Cohen, S. (2002). Chronic psychological stress and the regulation of pro-inflammatory cytokines: a glucocorticoid-resistance model. *Health Psychology, 21*(6), 531-541. doi: 10.1037//0278-6133.21.6.531

Nolen-Hoeksema, S. (2000). The role of rumination in depressive disorders and mixed anxiety/depressive symptoms. *Journal of Abnormal Psychology, 109*(3), 504-511. doi: 10.1037//0021-843X.109.3.504

O'Brien, E., Waeber, B., Parati, G., Staessen, J., & Myers, M. G. (2001). Blood pressure measuring devices: recommendations of the European Society of Hypertension. *British Medical Journal, 322*(7285), 531-536. doi: 10.1136/bmj.322.7285.531

Phillips, A. C. (2011). Blunted cardiovascular reactivity relates to depression, obesity, and self-reported health. *Biological Psychology, 86*(2), 106-113. doi: 10.1016/J.Biopsycho.2010.03.016

Poole, H., Bramwell, R., & Murphy, P. (2006). Factor Structure of the Beck Depression Inventory-II Patients with Chronic Pain. *Clinical Journal of Pain, 22*(9), 790-798. doi: 10.1097/01.ajp.0000210930.20322.93

Rugulies, R. (2002). Depression as a predictor for coronary heart disease. a review and meta-analysis. *American Journal of Preventive Medicine, 23*(1), 51-61. doi: 10.1016/S0749-3797(02)00439-7

Russell, J. A., Weiss, A., & Mendelsohn, G. A. (1989). Affect grid: a single-item scale of pleasure and arousal. *Journal of Personality and Social Psychology, 57*, 439-502. doi: 10.1037/0022-3514.57.3.493

Schiffer, A. A., Pelle, A. J., Smith, O. R., Widdershoven, J. W., Hendriks, E. H., & Pedersen, S. S. (2009). Somatic versus cognitive symptoms of depression as predictors of all-cause mortality and health status in chronic heart failure. *Journal of Clinical Psychiatry, 70*(12), 1667-1673. doi: 10.4088/JCP.08m04609

Smolderen, K. G., Spertus, J. A., Reid, K. J., Buchanan, D. M., Krumholz, H. M., Denollet, J., Vaccarino, V., & Chan, P. S. (2009). The association of cognitive and somatic depressive symptoms with depression recognition

and outcomes after myocardial infarction. *Circulation Cardiovascular Quality & Outcomes, 2*(4), 328-337. doi: 10.1161/CIRCOUTCOMES.109.868588

Steer, R. A., Ball, R., Ranieri, W. F., & Beck, A. T. (1999). Dimensions of the Beck Depression Inventory-II in clinically depressed outpatients. *Journal of Clinical Psychology, 55*(1), 117-128. doi: 10.1002/(SICI)1097-4679(199901)55:1<117::AID-JCLP12>3.0.CO;2-A

Steer, R. A., Ball, R., Ranieri, W. F., & Beck, A. T. (1999). Dimensions of the Beck Depression Inventory-II in clinically depressed outpatients. *Journal of Clinical Psychology, 55*(1), 117-128.

Steptoe, A., & Wardle, J. (2005). Cardiovascular stress responsivity, body mass and abdominal adiposity. *International Journal of Obesity, 29*(11), 1329-1337. doi: 10.1038/sj.ijo.0803011

Tarvainen, M. P., Ranta-aho, P. O., & Karjalainen, P. A. (2002). An advanced detrending method with application to HRV analysis. *IEEE Transactions on Biomedical Engineering, 49*(2), 172-175. doi: 10.1109/10.979357

Tikkanen, P. (1999). *Characterization and application of analysis methods for ECG and time interval variability data*. Oulu, Finland: University of Oulu.

Van der Kooy, K., van Hout, H., Marwijk, H., Marten, H., Stehouwer, C., & Beekman, A. (2007). Depression and the risk for cardiovascular diseases: systematic review and meta analysis. *International Journal of Geriatric Psychiatry, 22*(7), 613-626. doi: 10.1002/gps.1723

Vanheule, S., Desmet, M., Groenvynck, H., Rosseel, Y., & Fontaine, J. (2008). The factor structure of the Beck Depression Inventory-II: an evaluation. *Assessment, 15*(2), 177-187. doi: 10.1177/1073191107311261

Viljoen, J. L., Iverson, G. L., Griffiths, S., & Woodward, T. S. (2003). Factor structure of the Beck Depression Inventory-II in a medical outpatient sample. *Journal of Clinical Psychology in Medical Settings, 10*(4), 289-291. doi: 10.1177/1073191107311261

Whisman, M. A., Perez, J. E., & Ramel, W. (2000). Factor structure of the Beck Depression Inventory--Second Edition (BDI-II) in a student sample. *Journal of Clinical Psychology, 56*(4), 545-551. doi: 10.1002/(SICI)1097-4679(200004)56:4<545::AID-JCLP7>3.0.CO;2-U

Wood, K., Whiting, K., & Coppen, A. (1986). Lymphocyte Beta-Adrenergic-Receptor Density of Patients with Recurrent Affective-Illness. *Journal of Affective Disorders, 10*(1), 3-8. doi: 10.1016/0165-0327(86)90042-X

Yin, P., & Fan, X. (2000). Assessing the reliability of Beck Depression Inventory scores: Reliability generalization across studies. *Educational and Psychological Measurement, 60*(2), 201-223. doi: 10.1177/00131640021970466

York, K. M., Hassan, M., Li, Q., Li, H. H., Fillingim, R. B., & Sheps, D. S. (2007). Coronary artery disease and depression: Patients with more depressive symptoms have lower cardiovascular reactivity during laboratory-induced mental stress. *Psychosomatic Medicine, 69*(6), 521-528. doi: 10.1097/PSY.0b013e3180cc2601

Transition

The research described in manuscripts One and Two suggests that depression and depressive symptoms are associated with moderate levels of physiological hyperactivation in response to both physical and psychological stress. The study described in manuscript Three aimed to explore the effect of depression on markers of both ANS and HPA axis dysregulation together in the same study. As well, it aimed to address the question: do treatments for depression successfully dampen the prolonged physiological activation in depressed individuals? It did so by comparing depressed individuals taking and not taking antidepressant medication in terms of their physiological responses to a stressful diagnostic procedure.

Manuscript Three

Depression, Antidepressant Use, and Cortisol Following a Stressful Diagnostic Procedure in Medical Outpatients

Gordon, J. L., Ditto, B., Lavoie, K. L., Arsenault, A., Hayano, J., Bacon, S. L. Depression, antidepressant use, and cortisol following a stressful diagnostic procedure in medical outpatients. (In preparation)

Abstract

Depression has been associated with prolonged stress-induced activation of the hypothalamic-pituitary-adrenal (HPA) axis and the autonomic nervous system (ANS). However, the efficacy of antidepressants in resolving this is unknown. Fifty-two cardiac outpatients referred for a pharmacological stress test using dipyridamole were recruited: 10 depressed patients taking antidepressant medication, 17 unmedicated depressed patients and 25 non-depressed controls. Salivary cortisol was measured before, immediately after, and 1 hour following the stress test and participants wore a heart rate monitor throughout the test, allowing heart rate variability (HRV) to be measured. Questionnaires concerning medication usage and cardiovascular history were also completed. General linear models (GLMs) were used to compare the cortisol levels and HRV of three groups: non-depressed controls, unmedicated depressed participants, and depressed participants on antidepressants. Unmedicated, but not medicated, depressed participants exhibited significantly elevated cortisol levels in response to the procedure compared to controls. However, no significant findings were seen for HRV. These results suggest that antidepressant use may dampen stress-induced HPA activation in depressed individuals, which may have implications for their cardiovascular health.

Key words: Hypothalamic-pituitary-adrenal axis, Cortisol, Autonomic Nervous System, Heart Rate, Heart Rate Variability, Depression, Antidepressants

Depression is associated with an increased incidence of cardiovascular disease (CVD). In fact, meta-analyses suggest that in initially healthy individuals, clinical depression is associated with double the risk of CVD development (Rugulies, 2002) while depression in CVD patients is associated with double the risk of all-cause mortality (Barth, Schumacher, & Herrmann-Lingen, 2004). While the mechanisms behind this association are unclear, one pathway that has been proposed (Brosschot, Gerin, & Thayer, 2006; Joynt, Whellan, & O'Connor, 2003) is that depression is linked to CVD through prolonged activation of the biological stress systems: the autonomic nervous system (ANS) and the hypothalamic-pituitary-adrenal (HPA) axis.

There is considerable research supporting the link between depression and ANS dysfunction. Numerous studies have found both clinical depression (Carney et al., 2001) and self-reported depressive symptoms (Guinjoan et al., 2007) to be associated with reduced heart rate variability (HRV), an elevated resting heart rate (HR) (Dawson, Schell, & Catania, 1977; Lahmeyer & Bellur, 1987), impaired HR recovery after exercise (Gordon et al., 2011) and reduced baroreflex cardiac control (Watkins & Grossman, 1999), all indicating sympathetic dominance. Depression is also associated with altered CV responses to psychological and physical stressors. For example, depressed mood has been associated with a reduction in the high-frequency component of HRV, indicating decreased parasympathetic cardiac control, in reaction to a challenging speech task and a forehead cold pressor task (Hughes & Stoney, 2000). A meta-analysis of 11 studies has also found a moderate effect ($d = 0.37$) of depressive symptoms on exaggerated HR reactivity to laboratory stressors (Kibler & Ma, 2004). Similar

results have been observed in CVD patients (Sheffield et al., 1998; Thornton & Hallas, 1999).

Depressed patients are also known to exhibit signs of HPA axis dysregulation, including high waking cortisol levels (Vreeburg et al., 2009), non-suppression on the dexamethasone suppression test (Plotsky, Owens, & Nemeroff, 1998) and abnormal cortisol responses to psychological stressors. A meta-analysis of seven laboratory studies (Burke, Davis, Otte, & Mohr, 2005) found that although depressed and non-depressed patients exhibit similar baseline and stress cortisol levels, depressed patients exhibit much higher cortisol levels in the recovery period compared to the non-depressed controls ($d = 1.43$).

Whether antidepressants improve or worsen the HPA and ANS dysregulation seen in depressed individuals is unclear. With the exception of tricyclic antidepressants (TCAs), which are known to promote sympathetic dominance, the literature examining the effects of serotonin reuptake inhibitors (SSRIs) and serotonin and noradrenaline reuptake inhibitors (SNRIs) is conflicting. Considering SSRIs and SNRIs are currently the most widely prescribed antidepressants (Olfson & Marcus, 2009), understanding their potential health consequences is more important than ever. One meta-analysis in cardiac patients has found SSRIs and SNRIs to mildly dampen baseline sympathetic activation (Jiang & Davidson, 2005) while a second recent meta-analysis found they had no effect on ANS tone in non-cardiac samples (Kemp et al., 2010). However, several recent studies have found that they promote a shift towards sympathetic dominance, as indicated by an increase in sympathetically influenced QT variability, a decrease in baroreflex sensitivity (Koschke et al., 2009), lower

HRV, and lower respiratory sinus arrhythmia (Licht, de Geus, van Dyck, & Penninx, 2010; Licht et al., 2008). The use of an SNRI also increased HR while SSRIs mildly lowered HR (Licht, de Geus, van Dyck, & Penninx, 2010).

While the effect of antidepressants on baseline autonomic tone remains unclear, their effects on ANS responses to stress is even more uncertain given that only one study to date has examined this issue. This study assessed the effect of citalopram on HR responses to emotionally valent images in healthy participants (Kemp & Nathan, 2004). While participants' HR responses were found to differ according to the emotional valence of the images while taking a placebo pill, citalopram suppressed HR reactivity. While this study suggests that antidepressants may dampen one's ANS response to emotional stimuli, further research is needed to determine if this generalizes to depressed individuals facing more intense stressors.

In terms of antidepressants' effects on the HPA axis, a recent meta-analysis suggests that antidepressants, regardless of the type, lower cortisol levels in approximately 44% of depressed individuals who take them (McKay & Zakzanis, 2010), whether or not their depressive symptoms improve. However, whether antidepressants restore normal stress-induced cortisol responses is not well established. Only one study to date has addressed this issue by comparing 25 chronically depressed individuals on antidepressants and 25 non-depressed controls in terms of their cortisol responses to an orthopedic surgery (Kudoh, Ishihara, & Matsuki, 2000). Although the depressed participants exhibited significantly higher pre-surgery cortisol levels, their cortisol response during the surgery was blunted compared to the controls. While this suggests that

antidepressants may not be effective in restoring a normal HPA axis stress response in depressed individuals, more research is needed to confirm this finding.

The current study aimed to extend the current literature by measuring salivary cortisol and heart rate variability (HRV) in cardiac outpatients before, during, and after a standardized stressful diagnostic procedure. It was reasoned that the procedure in question provided an opportunity to examine the effect of a stressor that is well standardized. The current study also sought to assess the effect of antidepressants on stress-induced activation of the HPA axis and sympathetic nervous system by collecting information regarding medication prescription. It was hypothesized that 1) depression would be associated with exaggerated activation of the HPA axis and ANS both at baseline and following the procedure, as indicated by elevated cortisol, elevated HR and reduced HRV and 2) antidepressant use would reduce the strength of this association.

Methods

Participants

The current study was a planned sub-study of a larger project, the Research on Endothelial Function in Women and Risk for Cardiovascular Disease (REWARD) study. The primary objective of the REWARD study, which has been described elsewhere (Bacon et al., 2011), was to assess the utility of the forearm hyperaemic reactivity test in predicting CVD events in women relative to men. This study included a total of 1972 patients referred for pharmacological (dipyridamole) stress testing using single photon emission computed tomography (SPECT) imaging between February 2007 and October 2010 in the Nuclear

Medicine Service of the Montreal Heart Institute. The REWARD exclusion criteria included a serious comorbid medical condition for which the patient was not expected to survive the next 12 months, suspected or confirmed pregnancy, inability to understand and/or speak French or English, drug or alcohol abuse disorder and having a medical condition which impaired the patient's understanding of the nature, scope, and possible consequences of the study. The REWARD study was relatively non-invasive: it simply required that participants undergo a forearm hyperaemic reactivity test, lasting 15 minutes, as well as complete a blood test and questionnaire. The dipyridamole stress test to which participants were referred aims to screen for the presence of myocardial ischemia (a lack of blood flow to the heart) when heart rate is increased. In this way, it is similar to an exercise stress test but it uses a medication, dipyridamole, to achieve an increase in heart rate rather than exercise. It is specifically designed for patients with limited mobility and thus unable to complete an exercise stress test. The patients referred to such a test therefore tend to be older and in relatively poorer health compared to patients referred for an exercise stress test.

Recruitment for the current sub-study began near the end of REWARD (1534 of the 1972 participants had already been recruited). Once recruitment began, the eligibility of all REWARD participants who were identified as depressed, having both major depression according to a structured diagnostic interview called the PRIME-MD, and a BDI-II score ≥ 10, was assessed and eligible participants were recruited for the current sub-study. Each depressed participant was then matched with a control participant, identified as patients having no mood disorder according to the PRIME-MD, scoring <14 on the BDI-

II, not currently medicated for depression and matching the depressed individual for age, sex and myocardial perfusion imaging (MPI) dipyridamole test appointment time. This resulted in 54 sub-study participants: 29 depressed patients and 25 controls. Exclusion criteria for the sub-study included bipolar disorder, panic disorder, endocrine disorders affecting cortisol (e.g. cushings disease), regular night shift work, and steroidal anti-inflammatory use less than 12 months prior to the dipyridamole stress test. Participants were also asked to refrain from taking benzodiazepines within 24 hours prior to the dipyridamole stress test and to refrain from smoking or consuming caffeine within 8 hours of the test. Finally, two participants taking TCAs were excluded from the current analyses since TCAs may have different effects on ANS activity when compared to SSRIs or SNRIs. This left 27 depressed participants and 25 controls for the current analyses. It should be noted that due to technical difficulties with the HR monitor, HRV data were only available for 41 participants (20 depressed participants and 21 controls).

Procedure

Patients undergoing a dipyridamole stress test had their rest image collected on day 1 and the dipyridamole stress image collected on day 2. Dipyridamole is a medication causing rapid vasodilation, resulting in a rapid baroreceptor-mediated increase in HR and blood pressure. The dipyridamole stress test has been shown to induce peripheral sympathetic activation (Lucarini et al., 1992) and is associated with a high rate (45%) of adverse reactions, including headache, chest pain and nausea (Meyers et al., 2002). On day 1, patients were recruited for the REWARD study, asked to complete the Beck Depression

Inventory (BDI)-II and assessed using the mood and anxiety disorders modules of the PRIME-MD. They were also given a questionnaire package including questions regarding health and medication prescription, to complete at home and return on day 2.

Upon their arrival on day 2 of the test, patients were fitted with a heart rate monitor (Polar S810i, Polar Electro, United States), to be worn for the duration of their time at the hospital, and provided a saliva sample by placing a salivette (Salimetrics, State College, Pensylvania, United States) in their mouth for two minutes while sitting in a quiet area. They were also asked to report their emotional state using a visual analog scale (VAS) before being fitted with an indwelling catheter by a Nuclear Medicine technician and undergoing the dipyridamole stress test.

The dipyridamole test was carried out according to standard protocol. A total dose of .568 mg/kg of dipyridamole diluted in a 20 ml saline was infused at a regular rate over a period of 4 minutes. A maximum dose of 50 mg was used. A dose of 15 to 22 mCi of the radioactive tracer (Technetium Tc-99 m Tetrofosmin) was injected 6 minutes after the administration of dipyridamole. During recovery, 75 mg aminophylline was administered at the discretion of the attending physician, with 96% of the control group, 94% of the unmedicated depressed participants and 100% of the medicated depressed participants receiving it.

Immediately following the test, participants again completed the VAS and provided a second saliva sample while sitting quietly. They were then sent to the cafeteria to have a snack for approximately 45 minutes before having their stress images taken using a triple-head large field of view camera, which lasted

approximately 15 minutes. After the images were taken, participants again completed the VAS, provided a third saliva sample while sitting quietly and had the HR monitor removed.

Measures

Assessment of major depression. The PRIME-MD (Spitzer et al., 1994) is a structured psychiatric diagnostic interview designed to detect some of the most common disorders listed in the *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition* (DSM-IV) (American Psychiatric Association, 1994). For the present study, a graduate student in clinical psychology administered the mood and anxiety disorders modules of the electronic version of the PRIME-MD, which assess major and minor depressive disorder, dysthymia and bipolar disorder, as well as panic disorder, generalized anxiety disorder, and other anxiety disorder. Though the PRIME-MD takes between 10 and 20 minutes to administer, it has been shown to be of comparable reliability, sensitivity, and specificity as longer structured interviews such as the Structured Clinical Interview for DSM (SCID), particularly when used to diagnose major depression (Spitzer, et al., 1994). It has been used successfully in previous studies assessing the prevalence of psychiatric disorders in cardiac outpatients Gordon et al., 2011; Lavoie et al., 2010; Pelletier et al., 2009).

Depressive symptoms. The Beck Depression Inventory-II (BDI-II) (Beck, 1996) was used to measure depressive symptoms. This widely-used questionnaire consists of 21 items scored from 0 to 3, with higher numbers indicating greater symptom severity. According to a meta-analysis of 165 studies, the BDI-II has an internal consistency of .837 (.007) and a test-retest reliability of .690 (.009) (Yin

& Fan, 2000). The BDI-II has been shown to have good sensitivity (.76-.94) and specificity (.70-.92) in both medical outpatients and patients with stable coronary artery disease (Arnau, Meagher, Norris, & Bramson, 2001; Frasure-Smith & Lesperance, 2008).

Salivary cortisol. Saliva samples were obtained with the Salivette (Salimetrics, State College, Pensylvania, Unitesd States), allowing for quick and hygienic saliva collection. The exact time of the saliva collection was recorded. Following collection, the saliva samples were centrifuged at 3000 rpm for 15 minutes and subsequently frozen at -80°C until cortisol analysis.

Salivary cortisol concentrations were measured using a sensitive enzyme immunoassay kit (Salimetrics, State College, PA, USA) as specified in the kit instructions. Briefly, 25 μl of standard or saliva was incubated with assay buffer and conjugate in the antibody-coated well for 1 hour at room temperature. All assays were done in duplicates. After several washes, assay plates were incubated with the colour developing reagent for 30min at room temperature (protected from light). Three minutes after stopping the reaction, plates were shaken and the optical density of each well was read on a spectrophotometer set at 450nm and 492nm. The difference in optical density between the two wavelengths was used to calculate salivary cortisol concentration using the Assayzap software program (Biosoft Inc.). The limit of detection of this assay was 0.012 ug/dl for a range of 0.012-3 μg/dl. The intra- and inter-assay coefficients of variation were 2.14% and 14.00%, respectively.

Area under the curve with respect to ground (AUCg) and with respect to increase (AUCi) were calculated based on the recommendations of Pruessner and colleagues (Pruessner, Kirschbaum, Meinlschmid, & Hellhammer, 2003).

Heart rate variability (HRV). Although HRV data were collected throughout day 2, only the HRV data collected during the three saliva samplings (two minutes each) were used for analysis in this study. These time periods were chosen because they were not affected by posture or speech. HRV data was collected using a Polar S810i recorder, which collects beat-to-beat heart data. The interbeart interval data was extracted and stored on a computer. In addition to standard time domain measures, complex demodulation (Hayano et al., 1993; 1994) was used to examine time-dependent changes in the power of low frequency (LF) and high frequency (HF) components in HRV using two frequency bands, 0.04 to 0.15 and 0.15 to 0.45 Hz, respectively, as recommended by the Task Force of the European Society of Cardiology and North American Society of Pacing and Electrophysiology (1996). The ratio of LF to HF (LF/HF), which provides a potential proxy index of sympathetic relative to parasympathetic activation, was also calculated. Complex demodulation is a nonlinear time-domain method for assessing time-dependent changes in nonstationary oscillatory components within a predefined spectral region (frequency band) (Hayano et al., 1993). The results of complex demodulation analysis were averaged every 15 seconds.

Visual analogue scales (VAS). To measure participants' emotional state, they were asked to rate their levels of anxiety, fatigue, pain, stress, pleasure and discomfort during saliva collection by pointing to their level of emotion on a 10-

centimeter line spanning between “no emotion” and “extreme emotion”. Their position on the line was later measured to the nearest millimeter.

Data Management and Analysis

Natural logarithmic transformations were used for cortisol, HF, LF and VLF power due to violations of normality. General linear models (GLMs) were used to test the between-subjects effect of depression group, the within-subjects effect of time, and the interaction between depression group and time on each dependent variable of interest (i.e., cortisol, HR, SDRR, HF, LF, LF/HF and VLF power). Depression group consisted of three levels: 1) non-depressed, 2) depressed but not taking antidepressants and 3) depressed and taking antidepressants. Covariates, chosen a-priori, included age, sex, time of appointment, average level of anxiety on the VAS, statin prescription, antihypertensive medication prescription, benzodiazepine prescription, aminophylline injection, and history of CVD, defined as a having had a previous myocardial infarction, percutaneous coronary intervention (PCI), coronary artery bypass graft (CABG) or cerebrovascular event.

Two between-subjects GLMs were also conducted to test the effect of depression group on AUCg and AUCi. All analyses were conducted using SAS v 9.2 (SAS Institute, Cary, NC).

Results

Participant Characteristics

Participant characteristics, along with significant group differences based on Tukey post-hoc tests, are shown in Table 1. As expected given the nature of the test to which patients had been referred, participants were elderly and thus

relatively unhealthy: in fact, 96% of the participants either had a prior history of CVD or had a diagnosis of Type II diabetes, hypertension or hypercholesterolemia. Among the participants taking antidepressants, 40% were taking SNRIs and 60% were taking SSRIs.

Effect of Stress

Repeated measures analyses testing the main effect of time, including 3 levels: pre-test, immediately post-test and 1 hour post-test, revealed a main effect of time on cortisol levels ($F(2, 102) = 3.60$, $p = .031$). Planned comparisons revealed that cortisol levels at baseline and immediately post-test were similar (p=.237) but then mean cortisol significantly decreased from immediately post-test to one hour post-test ($p = .005$), returning to baseline levels (baseline vs. 1 hour post-test $p = .178$).

Unlike cortisol levels, HR and HRV data were available during the actual procedure. The following analyses therefore examined the effect of time, including four levels: pre-test (cortisol sample 1), during the test, shortly (within five minutes) post-test (cortisol sample 2) and 1 hour post-test (cortisol sample 3). A main effect of time was seen for HR ($F(3,123) = 14.15$, $p<.0001$) such that HR significantly increased during the procedure compared to baseline ($p<.0001$), then significantly decreased ($p = .014$) immediately following the procedure, with HR one hour post-procedure was similar to HR shortly post-test ($p = .163$). A main effect of time was also seen for SDRR ($F(3, 123) = 12.25$, $p<.0001$), HF ($F(3, 123) = 11.30$, $p<.0001$), LF ($F(3, 123) = 14.68$, $p< .0001$) and VLF ($F(3, 123) = 18.99$, $p<.0001$) such that all were significantly decreased during the procedure compared to baseline (p's ranging from <.0001 to .003), then increased (p's

ranging from <.0001 to .0003), returning to baseline levels (baseline vs. immediately post-test *p*'s ranging from .241 to .438) with the exception of VLF (baseline vs. immediately post-test $p = .001$) and remaining constant one hour post-test (*p*'s ranging from .322 to .591). However, no effect of time was seen for LF/HF ($F(3, 123) = 1.55$, $p = .205$).

In terms of emotions rated on the VAS, a significant effect time on self-reported anxiety ($F(2, 124) = 8.25$, $p < .001$) was found. While participants' anxiety remained similar at times 1 and 2 ($p = .418$), it significantly decreased at time 3 (1 hour post-test) (*p*'s <.001). The same pattern was observed for stress ($F(2, 124) = 3.20$, $p = .044$). A significant effect of time was also found for calm ($F(2, 124) = 5.68$, $p = .004$) such that level of calm was similar at times 1 and 2 ($p = .124$) but increased at time 3 ($p = .072$). No effect of time was seen for frustration, discomfort, pain, or fatigue.

Cortisol

Main effect of Depression Group. Mixed design GLMs revealed that depression group was associated with overall ln(cortisol) levels ($F = 8.15$, $p = .001$, partial $\eta^2 = 0.301$) (Figure 1). Based on Tukey-Kramer posthoc tests, the unmedicated depressed participants had elevated mean ln(cortisol) levels compared to controls ($p = .002$) while depressed participants taking antidepressants ($p = .990$) did not. Medicated depressed participants' mean ln(cortisol) level was also significantly lower compared to that of the unmedicated participants ($p = .007$). Next, independent groups design GLMs revealed that the effect of depression group was also significant for lnAUCg ($F(2, 50) = 8.00$, $p =$

.001, partial $\eta^2 = 0.291$). Tukey posthoc tests revealed that unmedicated depressed participants (geometric mean = 43.7 ± 17.6 μg/dl*min) exhibited elevated lnAUCg compared to non-depressed controls (19.6 ± 14.8 μg/dl*min) ($p = .002$) while medicated depressed individuals (18.2 ± 20.6 μg/dl*min) did not ($p = .949$). Medicated depressed participants also exhibited lower lnAUCg compared to the unmedicated depressed group ($p = .006$). A similar effect was seen for lnAUCi ($F(2, 51) = 7.20$, $p = .002$, partial $\eta^2 = 0.270$): unmedicated depressed patients (geometric mean = 8.9 ± 8.6 μg/dl*min) had significantly higher lnAUCi compared to controls (3.2 ± 7.2 μg/dl*min) ($p = .009$) while depressed patients taking antidepressants (2.4 ± 10.1 μg/dl*min) did not differ from controls ($p = .669$). Once again, the medicated depressed individuals had lower lnAUCi levels compared to the unmedicated depressed participants ($p = .004$).

Depression group X time interaction. No significant interaction between depression group and time of sampling was found ($F(4, 78) = 0.84$, $p = .503$).

Heart Rate Variability

Main Effect of Depression Group. Depression group was not significantly associated with HR ($F(2, 25) = 0.12$, $p = .885$), SDRR ($F(2, 25) = 0.46$, $p = .635$), lnHF ($F(2, 25) = 0.99$, $p = .384$), lnLF ($F(2, 25) = 1.68$, $p = .207$), LF/HF ($F(2, 25) = 0.57$, $p = .573$) or lnVLF ($F(2, 25) = 1.72$, $p = .200$),

Depression Group X Time Interaction. No significant interactions were seen for HR ($F(4, 50) = 0.94$, $p = .450$), SDRR ($F(4, 50) = 0.83$, $p = .515$), lnHF ($F(4, 50) = 1.76$, $p = .151$), lnLF ($F(4, 48) = 0.94$, $p = .447$), LF/HF ($F(4, 50) = 1.79$, $p = .146$) or lnVLF ($F(4, 50) = 0.42$, $p = .791$).

Discussion

The objectives of the current study were to examine the relationship between depression and HPA axis and autonomic responses to a stressful diagnostic procedure and to examine whether this relationship differed depending on antidepressant use. It was hypothesised that depression would be associated with exaggerated activation of the HPA axis and sympathetic nervous system but that these associations would be dampened by antidepressant use. These hypotheses were partially confirmed: while depression and antidepressant use was unrelated to HRV, unmedicated but not medicated depressed individuals exhibited elevated cortisol levels throughout the procedure. This result emerged despite significantly higher BDI-II scores among the medicated participants, suggesting that antidepressants may help dampen depression-related hyperactivation of the HPA axis even in the absence of complete symptom remission.

The fact that antidepressant use was associated with decreased cortisol release is consistent with the recent meta-analysis concluding that antidepressants significantly lower overall cortisol levels in depressed individuals, whether or not their depressive symptoms remit (McKay & Zakzanis, 2010). However, the current study expands upon these findings by suggesting that antidepressants may also help dampen stress-induced HPA axis activation. Since a main effect of depression rather than a time X depression interaction was found for cortisol, one might argue that the effect seen is unrelated to the stressor but rather due to elevated baseline cortisol levels among the depressed individuals. However, the inverted U-shaped pattern of cortisol release exhibited by the unmedicated depressed individuals provides evidence against this. With a larger sample size, a

significant time X depression group interaction would likely have been found. Antidepressants are believed to lower cortisol levels by increasing the expression and function of glucocorticoid receptors in the paraventricular nucleus of the hypothalamus, thus improving negative feedback within the HPA axis (Pariante, 2006). Evidence for this can be seen in the animal literature: one study by Barden (1999) found that antidepressant-induced improved dexamethasone binding was accompanied by increased glucocorticoid receptor mRNA in transgenic mice having disturbed glucocorticoid receptor function.

Given that antidepressants have been found to reduce ruminative thinking (Andrews, Parker & Barrett, 1998), another possible mechanism through which antidepressants might lower cortisol levels following a stressful task among depressed individuals is by decreasing post-event rumination. As part of the "perseverative cognition hypothesis", Brosschot and colleagues have proposed that perseverative cognition, including anticipatory anxiety and rumination, may be key in linking stress and disease through prolonged activation of the endocrine, CV, and immune systems (Brosschot, et al., 2006; Brosschot, Pieper, & Thayer, 2005). Rumination is associated with both depression (Nolen-Hoeksema, 2000) and reduced CV recovery following an emotionally laden task (Glynn, Christenfeld, & Gerin, 2002). Thus, if antidepressants reduced stress-induced rumination, they could also be expected to dampen stress-induced cortisol levels in depressed individuals. Support for this theory includes a recent study by our team finding that cognitive depressive symptoms, such as hopelessness, are more strongly associated with ANS activation following psychological laboratory stressors (Gordon, D'Antono, & Ditto, in press). However, participants' anxiety

scores on the VAS do not support this explanation: depressed participants on antidepressants, in fact, exhibited slightly higher anxiety scores compared to unmedicated depressed participants (Table 1). The medicated depressed participants also exhibited significantly higher BDI-II scores compared to the unmedicated depressed (score of 29 vs. 20), further suggesting that the effect of antidepressants on HPA axis regulation occured through physiological rather than psychological mechanisms. To explore this further, secondary analyses were conducted in which the analyses were repeated including a measure of trait rumination, measured using the Stress-Reactive Rumination Scale (Robinson & Alloy, 2003), as a covariate. However, the results remained unchanged.

The lack of an association between depression and HRV was somewhat surprising. However, this is not the first study to find no relationship between these variables - for example, one study of 873 outpatients with stable coronary heart disease found that depression was not related to 24-hour HRV (Gehi, Mangano, Pipkin, Browner, & Whooley, 2005). Similarly, another study found that depression was not related to 24-hour HRV in 83 post-MI patients after adjustment for basic covariates (Martens, Nyklicek, Szabo, & Kupper, 2008). The current study's null findings for HRV are also consistent with a recent meta-analysis finding that non-TCA antidepressant use is not associated with baseline HRV (Kemp, et al., 2010). However, considering the small sample size used in the current study, particularly for the HRV data, it is also possible that there was a lack of statistical power to detect an existing effect. The unadjusted HRV data (Table 2) appear to indicate that antidepressant may be associated with elevated HRV in response to stress.

The results of the current study must be interpreted in light of several important limitations. First, the cross-sectional nature of this study prevents drawing conclusions about causation. This is especially true given the many confounds that might have been at play in this heavily-medicated, relatively ill population. Second, a suboptimal saliva sampling schedule was used, in part due to the fact that the study protocol was designed to interfere as little as possible with standard hospital procedures. For example, the second saliva sample may have been collected too early to obtain peak salivary cortisol levels. Finally, although time of day was included as a covariate, the fact that participants were scheduled at all times of the day is suboptimal considering the evidence that cortisol responses to stress differ in the morning and afternoon (Burke, et al., 2005).

Though the dipyridamole stress test induced a significant increase in cortisol, this appeared to be mainly driven by the unmedicated depressed group as the two other groups seemed unresponsive to the procedure (Figure 1). It is unclear why this procedure did not induce a cortisol response in healthy controls. It may be that the procedure was not intense enough as a stressor. Alternatively, the lack of response may be related to the nature of the stressor since stressors with a component of social-evaluative threat have been found to most successfully induce a cortisol response (Dickerson & Kemeny, 2004). However, whatever the case may be, the fact that unmedicated depressed participants exhibited a cortisol response to a stressor that was benign to healthy controls and medicated depressed individuals may have important clinical implications. Elevated cortisol levels have been associated with several CV risk factors, including abdominal obesity,

hypertension, and insulin resistance (Whitworth, Williamson, Mangos, & Kelly, 2005). Furthermore, the size of the effect of depression on overall cortisol secretion ($\omega^2 = 0.291$) was quite large. This study therefore contributes to the hypothesis that hyperactivation of the HPA axis is a mechanism through which depressed individuals may be at greater risk of CVD (Joynt, et al., 2003) and seems to suggest that antidepressant use may help regulate HPA axis activation in depressed individuals. Furthermore, it is noteworthy that the cortisol-dampening effect of the antidepressants was evident despite the continued presence of severe depressive symptoms (i.e. BDI-II score of 29). In fact, the continued presence of such severe symptoms may be indicative of particularly persistent and treatment-resistant depression, making the results all the more impressive. These findings may indicate that SSRIs and SNRIs should be evaluated not only based on their depressive symptom effects but also their potential physiological benefits.

In conclusion, the current findings suggest that unmedicated severely depressed patients with or at high risk of CVD exhibit prolonged elevations in cortisol following a moderately stressful diagnostic procedure. However, this does not appear to exist among antidepressant users. While further research is needed to confirm these results, they suggest that even in the absence of symptom remission, antidepressants may help regulate the HPA dysfunction associated with depression.

Table 1

Participant characteristics

	Controls	Unmedicated depressed	Medicated depressed
Demographics			
N	25	17	10
Sex (% women)	56.0	52.9	30.0
Age (yrs ± SD)	64.5 ± 10.1	67.2 ± 11.9	63.1 ± 7.3
Caucasian (%)	100.0*	88.2$^{\#}$	60.0*$^{\#}$
High school diploma (%)	48.0	58.8	50.0
BDI-II score (± SD)	6.1 ± 3.4$^{\&\$}$	20.1 ± 6.9$^{\#\$}$	29.2 ± 14.3$^{\#\&}$
Anxiety time 1 (/10 ± SD)	1.7 ± 2.4	3.6 ± 3.1	3.5 ± 3.2
Anxiety time 2 (/10 ± SD)	1.6 ± 2.0*	2.6 ± 3.1	4.3 ± 3.1*
Anxiety time 3 (/10 ± SD)	0.5 ± 0.8*	1.8 ± 2.8	2.6 ± 2.7*
Cardiovascular Risk Factors and Events			
Body Mass Index (± SD)	29.7 ± 5.5	29.9 ± 8.1	30.8 ± 6.4
Current Smoker (%)	29.0	5.9	30.0
Type II Diabetes (%)	32.0	35.3	50.0
History of CVD (%)	40.0	35.3	40.0
Hypertension (%)	84.0	76.5	70.0
Hypercholesterolemia (%)	84.0	58.8	70.0
Past MI (%)	16.0	23.5	40.0
PCI (%)	32.0	17.6	20.0
CABG (%)	12.0	23.5	10.0
Stroke (%)	4.0	5.9	20.0
Medications			
Anxiolytics (%)	32.0	35.3	60.0
Ace inhibitors (%)	40.0	35.3	20.0
Beta-blockers (%)	44.0	41.2	60.0
ARBs (%)	40.0	17.6	20.0
Antihypertensives (%)	80.0	76.5	70.0
Statins (%)	80.0*	41.2*	70.0

BDI, Beck Depression Inventory; MI, myocardial infarction; PCI, percutaneous coronary intervention; CABG, coronary artery bypass surgery; ARB, angiotensin receptor blockers

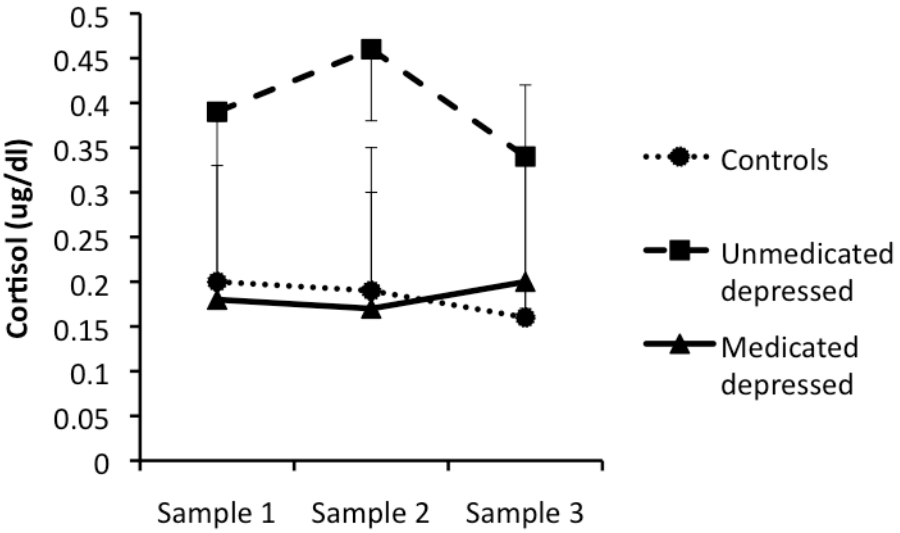
*$p<.01$ $^{\#}p<.001$, $^{\&, \$}$ $p<.0001$ according to Tukey post-hoc tests

Table 2

Adjusted geometric mean heart rate variability data before (time 1), immediately after (time 2) and one hour following (time 3) the stress test with standard errors.

	Controls (n = 21)			Unmedicated Depressed (n = 10)			Medicated Depressed (n = 10)		
	Time 1	Time 2	Time 3	Time 1	Time 2	Time 3	Time 1	Time 2	Time 3
HR (bpm)	66.6 ± 5.6	73.1 ± 6.1	75.5 ± 6.0	64.9 ± 5.6	71.5 ± 6.1	73.5 ± 6.1	66.2 ± 6.4	68.4 ± 7.0	72.9 ± 6.9
SDRR (ms)	27.4 ± 13.8	22.8 ± 13.9	31.6 ± 12.0	17.5 ± 13.9	10.6 ± 14.1	16.7 ± 12.1	17.6 ± 15.9	17.4 ± 16.1	19.9 ± 13.9
lnLF (ms^2)	5.2 ± 0.8	4.7 ± 0.7	5.7 ± 0.6	4.7 ± 0.8	4.0 ± 0.7	4.7 ± 0.6	4.0 ± 0.9	4.0 ± 0.8	4.3 ± 0.7
lnHF (ms^2)	4.8 ± 0.7	4.1 ± 0.7	4.7 ± 0.7	4.3 ± 0.7	3.4 ± 0.7	3.5 ± 0.7	3.7 ± 0.8	3.5 ± 0.8	4.0 ± 0.8
lnVLF (ms^2)	6.4 ± 0.6	6.6 ± 0.6	7.1 ± 0.5	5.6 ± 0.6	6.1 ± 0.6	6.4 ± 0.5	5.7 ± 0.7	6.0 ± 0.7	5.9 ± 0.6
LF/HF	1.1 ± 2.1	1.9 ± 1.1	3.6 ± 1.2	2.9 ± 2.1	2.7 ± 1.1	5.3 ± 1.2	2.6 ± 2.4	2.8 ± 1.2	1.6 ± 1.4

Figure 1. Geometric mean cortisol levels according to antidepressant use, with 95% confidence limits, adjusting for age, sex, time of saliva collection, self-reported anxiety, statin use, hypertension medication use, benzodiazepine use, history of cardiovascular disease and amino injection. N = 51



Author Notes

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Disclosures

None

References

Arnau, R. C., Meagher, M. W., Norris, M. P., & Bramson, R. (2001). Psychometric evaluation of the Beck Depression Inventory-II with primary care medical patients. *Health Psychology, 20*(2), 112-119. doi: 10.1037/0278-6133.20.2.112

American Psychiatric Association. (1994). Diagnostic and statistical manual of mental disorders (DSM-IV). 4th ed.

Andrews, W., Parker, G., & Barrett, E. (1998). The SSSRI antidepressants: exploring their "other possible properties. *Journal of Affective Disorders, 49*, 141-144. doi: 10.1016/S0165-0327(97)00203-6

Bacon, S. L., Lavoie, K. L., Arsenault, A., Dupuis, J., Pilote, L., ... Vadeboncoeur, A. (2011). The Research on Endothelial function in Women And men at Risk for cardiovascular Disease (REWARD) Study: Methodology. *BMC Cardiovascular Disorders, 11*(50). doi: 10.1186/1471-2261-11-50

Barden, N. (1999). Regulation of corticosteroid receptor gene expression in depression and antidepressant action. *Journal of Psychiatry & Neuroscience, 24*(1), 25-39.

Barth, J., Schumacher, M., & Herrmann-Lingen, C. (2004). Depression as a risk factor for mortality in patients with coronary heart disease: a meta-analysis. *Psychosomatic Medicine, 66*(6), 802-813. doi: 10.1097/01.psy.0000146332.53619.b2

Beck, A. T. Steer, R. A. & Brown, G. K. (1996). Manual for Beck Depression Inventory-II. San Antonio, TX: Psychological Corporation.

Benedict, C. R., Shelton, B., Johnstone, D. E., Francis, G., Greenberg, B., Konstam, M. (1996). Prognostic significance of plasma norepinephrine in patients with asymptomatic left ventricular dysfunction. *Circulation, 94*(4), 690-697. doi: 10.1161/01.CIR.94.4.690

Brosschot, J. F., Gerin, W., & Thayer, J. F. (2006). The perseverative cognition hypothesis: a review of worry, prolonged stress-related physiological activation, and health. *Journal of Psychosomatic Research, 60*(2), 113-124. doi: 10.1016/j.jpsychores.2005.06.07

Brosschot, J. F., Pieper, S., & Thayer, J. F. (2005). Expanding stress theory: prolonged activation and perseverative cognition. *Psychoneuroendocrinology, 30*(10), 1043-1049. doi: 10.1016/j.psyneuen.2005.04.008

Burke, H. M., Davis, M. C., Otte, C., & Mohr, D. C. (2005). Depression and cortisol responses to psychological stress: a meta-analysis. *Psychoneuroendocrinology, 30*(9), 846-856. doi: 10.1016/j.psyneuen.2005.02.010

Carney, R. M., Blumenthal, J. A., Stein, P. K., Watkins, L., Catellier, D., Berkman, L. F. (2001). Depression, heart rate variability, and acute myocardial infarction. *Circulation, 104*(17), 2024-2028. doi: 10.1161/hc4201.097834

Cole, C. R., Blackstone, E. H., Pashkow, F. J., Snader, C. E., & Lauer, M. S. (1999). Heart-rate recovery immediately after exercise as a predictor of mortality. *New England Journal of Medicine, 341*(18), 1351-1357. doi: 10.1056%2FNEJM199910283411804

Dawson, M. E., Schell, A. M., & Catania, J. J. (1977). Autonomic correlates of depression and clinical improvement following electroconvulsive shock therapy. *Psychophysiology, 14*(6), 569-578. doi: 10.1111%2Fj.1469-8986.1977.tb01201.x

Dickerson, S. S., & Kemeny, M. E. (2004). Acute stressors and cortisol responses: a theoretical integration and synthesis of laboratory research. *Psychological Bulletin, 130*(3), 355-391. doi: 10.1037/0033-2909.130.3.355

Douglas, K. M., Taylor, A. J., & O'Malley, P. G. (2004). Relationship between depression and C-reactive protein in a screening population. *Psychosomatic Medicine, 66*(5), 679-683. doi: 10.1097%2F01.psy.0000138132.66332.85

Frasure-Smith, N., & Lesperance, F. (2008). Depression and anxiety as predictors of 2-year cardiac events in patients with stable coronary artery disease. *Archives of General Psychiatry, 65*(1), 62-71. doi: 10.1001%2Farchgenpsychiatry.2007.4

Gehi, A., Mangano, D., Pipkin, S., Browner, W. S., & Whooley, M. A. (2005). Depression and heart rate variability in patients with stable coronary heart disease: findings from the Heart and Soul Study. *Archives of General Psychiatry, 62*(6), 661-666. doi: 10.1001%2Farchpsyc.62.6.661

Glynn, L. M., Christenfeld, N., & Gerin, W. (2002). The role of rumination in recovery from reactivity: cardiovascular consequences of emotional states. *Psychosomatic Medicine, 64*(5), 714-726. doi: 10.1097/01.PSY.0000031574.42041.23

Gordon, J. L., Ditto, B., Lavoie, K. L., Pelletier, R., Campbell, T. S., Arsenault, A., & Bacon, S. L. (2011). The effect of major depression on post-exercise cardiovascular recovery. *Psychophysiology, 48*(11), 1605-1610. doi: 10.1111/j.1469-8986.2011.01232.x

Gordon, J. L., D'Antono, B., & Ditto, B. Cognitive depressive symptoms associated with delayed heart rate recovery following interpersonal stress in healthy men and women. *Psychophysiology*, in press. doi: 10.1111/j.1469-8986.2012.01397.x

Guinjoan, S. M., Castro, M. N., Vigo, D. E., Weidema, H., Berbara, C., Fahrer, R. D. (2007). Depressive symptoms are related to decreased low-frequency heart rate variability in older adults with decompensated heart failure. *Neuropsychobiology, 55*(3-4), 219-224. doi: 10.1159/000108381

Hayano, J., Taylor, J.A., Yamada, A., Mukai, S., Hori, R., Asakawa, T., Yokoyama, K., Watanabe, Y., Takata, K., & Fujinami T. (1993). Continuous assessment of hemodynamic control by complex demodulation of cardiovascular variability. American Journal of Physiology, 264(4 Pt 2), H1229-38.

Hayano, J., Taylor, J. A,, Mukai S., Okada, A., Watanabe, Y., Takata, K., & Fujinami T. (1994). Assessment of frequency shifts in R-R interval variability and respiration with complex demodulation. Journal of Applied Physiology, 77(6), 2879-88.

Hughes, J. W., & Stoney, C. M. (2000). Depressed mood is related to high-frequency heart rate variability during stressors. *Psychosomatic Medicine, 62*(6), 796-803.

Jiang, W., & Davidson, J. R. (2005). Antidepressant therapy in patients with ischemic heart disease. *American Heart Journal, 150*(5), 871-881. doi: 10.1016/j.ahj.2005.01.041

Jouven, X., Empana, J. P., Schwartz, P. J., Desnos, M., Courbon, D., & Ducimetiere, P. (2005). Heart-rate profile during exercise as a predictor of sudden death. *New England Journal of Medicine, 352*(19), 1951-1958. doi: 10.1056/NEJMoa043012

Joynt, K. E., Whellan, D. J., & O'Connor, C. M. (2003). Depression and cardiovascular disease: mechanisms of interaction. *Biological Psychiatry, 54*(3), 248-261. doi: 10.1016/S0006-3223(03)00568-7

Karlsberg, R. P., Cryer, P. E., & Roberts, R. (1981). Serial plasma catecholamine response early in the course of clinical acute myocardial infarction: relationship to infarct extent and mortality. *American Heart Journal, 102*(1), 24-29. doi: 10.1016/0002-8703(81)90408-7

Kemp, A. H., & Nathan, P. J. (2004). Acute augmentation of serotonin suppresses cardiovascular responses to emotional valence. *International Journal of Neuropsychopharmacology, 7*(1), 65-70. doi: 10.1017/S1461145703003894

Kemp, A. H., Quintana, D. S., Gray, M. A., Felmingham, K. L., Brown, K., & Gatt, J. M. (2010). Impact of depression and antidepressant treatment on heart rate variability: a review and meta-analysis. *Biological Psychiatry, 67*(11), 1067-1074. doi: 10.1016%2Fj.biopsych.2009.12.012

Kibler, J. L., & Ma, M. (2004). Depressive symptoms and cardiovascular reactivity to laboratory behavioral stress. *International Journal of Behavioral Medicine, 11*(2), 81-87. doi: 10.1207/s15327558ijbm1102_3

Koschke, M., Boettger, M. K., Schulz, S., Berger, S., Terhaar, J., Voss, A. (2009). Autonomy of autonomic dysfunction in major depression. *Psychosomatic Medicine, 71*(8), 852-860. doi: 10.1097%2FPSY.0b013e3181b8bb7a

Kudoh, A., Ishihara, H., & Matsuki, A. (2000). Inhibition of the cortisol response to surgical stress in chronically depressed patients. *Journal of Clinical Anesthesia, 12*(5), 383-387. doi: 10.1016%2FS0952-8180%2800%2900179-3

Lahmeyer, H. W., & Bellur, S. N. (1987). Cardiac regulation and depression. *Journal of Psychiatric Research, 21*(1), 1-6. doi: 10.1016/0022-3956(87)90004-5

Lavoie, K. L., Pelletier, R., Arsenault, A., Dupuis, J., & Bacon, S. L. (2010). Association between clinical depression and endothelial function measured by forearm hyperemic reactivity. *Psychosomatic Medicine, 72*(1), 20-26. doi: 10.1097%2FPSY.0b013e3181c2d6b8

Licht, C. M. M., de Geus, E. J., van Dyck, R., & Penninx, B. W. (2010). Longitudinal evidence for unfavorable effects of antidepressants on heart rate variability. *Biological Psychiatry, 68*(9), 861-868. doi: 10.1016/j.biopsych.2010.06.032

Licht, C. M. M., de Geus, E. J. C., Zitman, F. G., Hoogendijk, W. J. G., van Dyck, R., & Penninx, B. W. J. H. (2008). Association Between Major Depressive Disorder and Heart Rate Variability in the Netherlands Study of

Depression and Anxiety (NESDA). *Archives of General Psychiatry, 65*(12), 1358-1367. doi: 10.1001%2Farchpsyc.65.12.1358

Lucarini, A. R., Picano, E., Marini, C., Favilla, S., Salvetti, A., & Distante, A. (1992). Activation of sympathetic tone during dipyridamole test. *Chest, 102*(2), 444-447. doi: 10.1378/chest.102.2.444

Lustman, P. J., Clouse, R. E., Griffith, L. S., Carney, R. M., & et al. (1997). Screening for depression in diabetes using the Beck Depression Inventory. *Psychosomatic Medicine 59*(1), *24-31*.

Martens, E. J., Nyklicek, I., Szabo, B. M., & Kupper, N. (2008). Depression and anxiety as predictors of heart rate variability after myocardial infarction. *Psychological Medicine, 38*(3), 375-383. doi: 10.1017/S0033291707002097

McKay, M. S., & Zakzanis, K. K. (2010). The impact of treatment on HPA axis activity in unipolar major depression. *Journal of Psychiatric Research, 44*(3), 183-192. doi: 10.1016/j.jpsychires.2009.07.012

Miller, G. E., Stetler, C. A., Carney, R. M., Freedland, K. E., & Banks, W. A. (2002). Clinical depression and inflammatory risk markers for coronary heart disease. *American Journal of Cardiology, 90*(12), 1279-1283. doi: 10.1016/S0002-9149(02)02863-1

Mora, S., Redberg, R. F., Cui, Y., Whiteman, M. K., Flaws, J. A., Sharrett, A. R. (2003). Ability of exercise testing to predict cardiovascular and all-cause death in asymptomatic women: a 20-year follow-up of the lipid research clinics prevalence study. *Journal of the American Medical Association, 290*(12), 1600-1607. doi: 10.1001/jama.290.12.1600

Nolen-Hoeksema, S. (2000). The role of rumination in depressive disorders and mixed anxiety/depressive symptoms. *Journal of Abnormal Psychology, 109*(3), 504-511. doi: 10.1037//0021-843X.109.3.504

Olfson, M., & Marcus, S. C. (2009). National patterns in antidepressant medication treatment. *Archives of General Psychiatry, 66*(8), 848-856. doi: 10.1001/archgenpsychiatry.2009.81

Pariante, C. M. (2006). The glucocorticoid receptor: part of the solution or part of the problem? *Journal of Psychopharmacology, 20*(4 Suppl), 79-84. doi: 10.1177/1359786806066063

Peeters, F., Nicholson, N. A., & Berkhof, J. (2003). Cortisol responses to daily events in major depressive disorder. *Psychosomatic Medicine, 65*(5), 836-841. doi: 10.1097/01.PSY.0000088594.17747.2E

Pelletier, R., Lavoie, K. L., Gordon, J., Arsenault, A., Campbell, T. S., & Bacon, S. L. (2009). The role of mood disorders in exercise-induced cardiovascular reactivity. *Psychosomatic Medicine, 71*(3), 301-307. doi: 10.1097/PSY.0b013e3181988175

Plotsky, P. M., Owens, M. J., & Nemeroff, C. B. (1998). Psychoneuroendocrinology of depression. Hypothalamic-pituitary-adrenal axis. *Psychiatric Clinics of North America, 21*(2), 293-307. doi: 10.1016/S0193-953X(05)70006-X

Pruessner, J. C., Kirschbaum, C., Meinlschmid, G., & Hellhammer, D. H. (2003). Two formulas for computation of the area under the curve represent measures of total hormone concentration versus time-dependent change.

Psychoneuroendocrinology, 28(7), 916-931. doi: 10.1016/S0306-4530(02)00108-7

Ramage, A. G., & Villalon, C. M. (2008). 5-hydroxytryptamine and cardiovascular regulation.*Trends in Pharmacological Sciences, 29*(9), 472-481.

Robinson, M.S., Alloy, L.B. (2003). Negative cognitive styles and stress-reactive rumination interact to predict depression: a prospective study. *Cognitive Therapy and Research*, 27(3), 275-292. doi: 10.1023/A:1023914416469

Rugulies, R. (2002). Depression as a predictor for coronary heart disease. a review and meta-analysis. *American Journal of Preventive Medicine, 23*(1), 51-61.

Sheffield, D., Krittayaphong, R., Cascio, W. E., Light, K. C., Golden, R. N., Finkel, J. B. (1998). Heart rate variability at rest and during mental stress in patients with coronary artery disease: Differences in patients with high and low depression scores. *International Journal of Behavioral Medicine, 5*(1), 31-47. doi: 10.1207/s15327558ijbm0501_3

Spitzer, R. L., Williams, J. B., Kroenke, K., Linzer, M., deGruy, F. V., 3rd, Hahn, S. R. (1994). Utility of a new procedure for diagnosing mental disorders in primary care. The PRIME-MD 1000 study. *Journal of the American Medical Association, 272*(22), 1749-1756. doi: 10.1001/jama.1994.03520220043029

Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology. (1996). Heart rate variability:

standards of measurement, physiological interpretation and clinical use. *Circulation, 93*(5), 1043-1065. doi: 10.1161/01.CIR.93.5.1043

Thornton, E. W., & Hallas, C. (1999). Affective status following myocardial infarction can predict long-term heart rate variability and blood pressure reactivity. *British Journal of Health Psychology, 4*(Part 3), 231-245. doi: 10.1348/135910799168597

Vreeburg, S. A., Hoogendijk, W. J., van Pelt, J., Derijk, R. H., Verhagen, J. C., van Dyck, R. (2009). Major depressive disorder and hypothalamic-pituitary-adrenal axis activity: results from a large cohort study. *Archives of General Psychiatry, 66*(6), 617-626. doi: 10.1001/archgenpsychiatry.2009.50

Watkins, L. L., & Grossman, P. (1999). Association of depressive symptoms with reduced baroreflex cardiac control in coronary artery disease. *American Heart Journal, 137*(3), 453-457. doi: 10.1016/S0002-8703(99)70491-6

Whitworth, J. A., Williamson, P. M., Mangos, G., & Kelly, J. J. (2005). Cardiovascular consequences of cortisol excess. *Vascular Health & Risk Management, 1*(4), 291-299.

Yin, P., & Fan, X. (2000). Assessing the reliability of Beck Depression Inventory scores: Reliability generalization across studies. *Educational and Psychological Measurement,* 60(2)*, 201-223*. doi: 10.1177/00131640021970466

General Discussion

The research presented in the current thesis aimed to clarify several aspects of the relationship between depression and dysregulation of the HPA axis and ANS. More specifically, Manuscript One evaluated the relationship between major depression and post-exercise CV recovery among cardiac outpatients. This study improved upon previous literature in that it evaluated diagnosed major depression rather than continuous depressive symptoms measured with a questionnaire, which can be easily confounded with symptoms of CVD. Furthermore, both early and late CV recovery, which are differentially influenced by sympathetic withdrawal and parasympathetic activation, were measured. The fact that major depression was associated only with early recovery therefore provides evidence that the poor post-exercise recovery observed in depressed individuals is due to a dampened ability of the parasympathetic branch to reactivate.

Manuscript Two aimed to compare the relationship between two types of depressive symptoms, cognitive-affective and somatic-affective, and CV recovery following a series of interpersonal stressors. Previous studies had generally found somatic, but not cognitive depressive symptoms to be associated with alterations in cardiac autonomic control. However, CV recovery following exposure to interpersonal stressors, which are more likely to trigger the cognitive symptoms of depression, had not been examined. It was found that among healthy individuals, both somatic and cognitive symptom clusters were associated with CV recovery, though the effect of cognitive symptoms appeared to be somewhat stronger. This

study therefore provided evidence that the association is not limited to the somatic symptoms of depression.

Manuscript Three examined physiological reactions to a stressful diagnostic test. HR, HRV and cortisol levels were measured throughout the test, allowing for an evaluation of both the ANS and HPA axis activation. Three groups of participants were compared: non-depressed controls, depressed individuals taking antidepressants and unmedicated depressed participants. Independent of self-reported anxiety, the unmedicated depressed participants were found to have elevated cortisol levels throughout the procedure when compared to either the control group or the medicated depressed individuals. This not only suggests that depression-related hyperactivation of the HPA axis can be observed outside of a laboratory setting, in response to a well-controlled stressor but also that antidepressants may resolve depression-related HPA axis hyperactivation. Surprisingly, neither depression nor antidepressant use was found to be associated with HRV.

An important challenge in examining the relationship between depression and CVD is that there are several symptoms that both syndromes share in common (e.g. fatigue, sleep difficulties, lack of appetite). It has therefore been suggested that this overlap may help explain, at least in part, the correlation between the two disorders (de Jonge et al., 2006). This theory is consistent with research finding somatic depressive symptoms to be more strongly related to CVD compare to cognitive depressive symptoms (Bekke-Hansen, Trockel, Burg, & Taylor, 2011; Hoen et al., 2010). Since this theory posits that no causal link exists between depression and CVD, it would also help explain some findings

indicating that the risk of CVD remains elevated even when depression is effectively treated (Berkman et al., 2003). However, the current thesis suggests that this is not the case. First, in manuscripts One and Three, clinical depression is carefully diagnosed using a diagnostic psychiatric interview. A diagnostic interview based on DSM-IV criteria for major depression should be less likely to produce a false positive diagnosis of depression in a cardiac patient because the diagnostic criteria require that "depressed mood" or "loss of interest or pleasure" be present for at least two weeks, on most days for most of the day. Thus, a euthymic patient experiencing several severe somatic symptoms associated with poor CV health would not meet the criteria for depression. However, the same patient would potentially obtain an elevated score on a questionnaire such as the BDI-II and thus be considered "depressed" without actually reporting depressed mood or anhedonia. The fact that diagnosed major depression was associated with poor post-exercise HR recovery in Manuscript One and elevated cortisol and lower HRV in Manuscript Three therefore provides evidence that the relationship between depression and CVD is not solely due to an overlap in symptoms. That the cognitive symptoms of depression were more strongly associated with reduced post-stress HR recovery than somatic depressive symptoms in Manuscript Two provides even stronger evidence of this idea.

In Manuscripts One and Two, depression and depressive symptoms, respectively, were associated with markers of ANS dysregulation. However, these associations were of relatively small magnitude. In Manuscript One, the difference in the HR drop seen in depressed versus non-depessed individuals was 3.9 bpm. This is potentially clinically meaningful considering previous research

has found that a difference as small as 2.9 bpm differentiated participants who survived from those who died (Shetler et al., 2001). However, both the depressed and non-depressed participants exhibited HR recovery values that were above 12 bpm at 1 minute post-exercise, which has been identified as the cut-off for healthy recovery (Cole, Blackstone, Pashkow, Snader, & Lauer, 1999). It is therefore unclear whether the difference in recovery between the groups would translate to differential mortality rates. In Manuscript Two, the association between depressive symptoms and CV recovery following the laboratory stressors was also quite modest, with only 2% of the variance in HR recovery being accounted for by depressive symptoms. Finally, in Manuscript Three, the depressed participants did not differ from controls in terms of HR or HRV either at baseline or post-test.

As such, the overall conclusion of the current thesis appears to be that the relationship between depression and ANS dysregulation is relatively modest. It seems therefore unlikely that ANS dysregulation is entirely responsible for doubling depressed individuals' risk of CVD (van Melle et al., 2004). Of course, HPA axis dysregulation is another mechanism that appears to be at play. In Manuscript Three, the effect of depression on cortisol was quite strong among participants not taking antidepressants, with ω^2 reaching 0.297. Given the association between elevated cortisol levels and increased mortality (Vogelzangs et al., 2010), this is likely clinically significant.

However, there are other potential mechanisms through which depression is associated with CVD and mortality that were not assessed in the current thesis. In particular, poor health behaviours have been identified as promising mechanisms linking depression and CVD (Gordon et al., 2008; 2011). To date,

there have been only two studies aimed at determining the relative importance of physiological versus behavioural mechanisms linking depression and CVD. The first study of 1017 coronary heart disease patients found that smoking, medication non-adherence and physical inactivity accounted for 48% of the effect of depressive symptoms on the risk of CV events in the following 6 years. Physical inactivity (more pronounced in depressed individuals) accounted for the largest proportion of the variance (31.7%) (Whooley et al., 2008). Meanwhile, HRV accounted for only 5% of the variance and cortisol excretion accounted for 0.5%. A second similar study in 6576 healthy participants also found that smoking, physical inactivity and alcohol consumption accounted for 65% of the variance in the association between psychological distress and CVD (Hamer, Molloy, & Stamatakis, 2008). However, since this study measured psychological distress and not depressive symptoms, one should be cautious in generalising its findings to depression. Nonetheless, these studies seem to suggest that health behaviours account for at least half of the relationship between psychological variables and CVD. While further research is required to replicate these findings, they seem to be consistent with the findings of the current thesis. While ANS and HPA axis activity are likely factors that partially account for the association between depression and CVD and are theoretically interesting, they do not account for the entire relationship.

To date, intervention studies have failed to improve HPA (Taylor et al., 2009) and ANS (Carney et al., 2000) dysregulation or to reduce the risk of CVD among depressed individuals, even when depressive symptoms have been successfully treated (Berkman et al., 2003). The relationship between depression

and CVD is therefore clearly complex and not entirely understood, though the studies presented here have attempted to clarify certain aspects of it. Based on the findings presented in the current thesis, future interventions aimed at reducing the risk of CVD in depressed individuals will benefit from assessing signs of ANS and HPA axis dysfunction and perhaps prescribing antidepressants to improve cortisol regulation. However, considering ANS and HPA axis dysregulation likely do not fully account for the relationship between depression and CVD, other potential mechanisms, such as poor health behaviours, would also need to be targeted. Future intervention studies may therefore aim for a three-pronged approach: using psychosocial interventions to target depressive symptoms, prescribing antidepressants when HPA axis dysregulation is evident, and also using behavioural interventions targeting poor health behaviours, including physical inactivity, excessive calorie consumption, smoking and excessive alcohol use.

References

Bekke-Hansen, S., Trockel, M., Burg, M. M., & Taylor, C. B. (2011). Depressive symptom dimensions and cardiac prognosis following myocardial infarction: results from the ENRICHD clinical trial *Psychological Medicine*, in press.

Berkman, L. F., Blumenthal, J., Burg, M., Carney, R. M., Catellier, D., Cowan, M. J. (2003). Effects of treating depression and low perceived social support on clinical events after myocardial infarction: the Enhancing Recovery in Coronary Heart Disease Patients (ENRICHD) Randomized Trial. *Journal of the American Medical Association, 289*(23), 3106-3116. doi: 10.1001/jama.289.23.3106

Bigger, J. T., Jr., Fleiss, J. L., Steinman, R. C., Rolnitzky, L. M., Kleiger, R. E., & Rottman, J. N. (1992). Frequency domain measures of heart period variability and mortality after myocardial infarction. *Circulation, 85*(1), 164-171.

Cole, C. R., Blackstone, E. H., Pashkow, F. J., Snader, C. E., & Lauer, M. S. (1999). Heart-rate recovery immediately after exercise as a predictor of mortality. *New England Journal of Medicine, 341*(18), 1351-1357.

de Jonge, P., Ormel, J., van den Brink, R. H., van Melle, J. P., Spijkerman, T. A., Kuijper, A. (2006). Symptom dimensions of depression following myocardial infarction and their relationship with somatic health status and cardiovascular prognosis. *American Journal of Psychiatry, 163*, 138-144. doi: 10.1176/appi.ajp.163.1.138

Hamer, M., Molloy, G. J., & Stamatakis, E. (2008). Psychological distress as a risk factor for cardiovascular events: pathophysiological and behavioral mechanisms. *Journal of the American College of Cardiology, 52*(25), 2156-2162.

Hoen, P. W., Whooley, M. A., Martens, E. J., Na, B., van Melle, J. P., & de Jonge, P. (2010). Differential associations between specific depressive symptoms and cardiovascular prognosis in patients with stable coronary heart disease. *Journal of the American College of Cardiology, 56*(11), 838-844. doi: 10.1016/j.jacc.2010.03.080

Shetler, K., Marcus, R., Froelicher, V. F., Vora, S., Kalisetti, D., Prakash, M. (2001). Heart rate recovery: validation and methodologic issues. *Journal of the American College of Cardiology, 38*(7), 1980-1987. doi: 10.1016%2FS0735-1097%2801%2901652-7

van Melle, J. P., de Jonge, P., Spijkerman, T. A., Tijssen, J. G., Ormel, J., van Veldhuisen, D. J. (2004). Prognostic association of depression following myocardial infarction with mortality and cardiovascular events: a meta-analysis. *Psychosomatic Medicine, 66*(6), 814-822. doi: 10.1097%2F01.psy.0000146294.82810.9c

Vogelzangs, N., Beekman, A. T. F., Milaneschi, Y., Bandinelli, S., Ferrucci, L., & Penninx, B. W. J. H. (2010). Urinary cortisol and six-year risk of all-cause and cardiovascular mortality. *The Journal of Clinical Endocrinology and Metabolism, 95*(11), 4959-4964. doi: 10.1210/jc.2010-0192

Whooley, M. A., de Jonge, P., Vittinghoff, E., Otte, C., Moos, R., Carney, R. M. (2008). Depressive symptoms, health behaviors, and risk of cardiovascular

events in patients with coronary heart disease. *Journal of the American Medical Association, 300*(20), 2379-2388.