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PSYCHOLOGICAL AND BIOLOGICAL FACTORS IN ACUTE CORONARY HEART DISEASE

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ABSTRACT

Psychosocial factors are thought to contribute to the long term development of coronary artery disease (CAD), to the triggering of cardiac events in people with advanced disease, and to adaptation following acute coronary syndromes (ACS). My thesis presents three studies addressing different aspects of the relationship between emotional factors and CAD, using different methodologies. They focus on the role of negative emotions in vulnerability to myocardial ischaemia in daily life, the influence of acute emotional triggers of ACS on long term quality of life, and the effect of depression following ACS on a particularly important aspect of adaptation, namely return to work.

The first study, called the Silent Ischaemia Study (SIS) investigated 88 out-patients with suspected CAD who underwent 24 hour ambulatory electrocardiogram (ECG) monitoring, together with saliva sampling and characterisation of daily life by a new method called the Day Reconstruction Method (DRM). The results indicated that in patients with definite CAD, depressed mood was associated with reduced high frequency and increased low frequency heart rate variability (HRV), suggestive of parasympathetic withdrawal. The cortisol slope over the day was flatter in more depressed patients with CAD. Episodes of transient ischaemia and/or arrhythmia were also associated with increased negative affect, but their incidence was low, primarily because most patients were medicated with beta blockers.

The second and third studies derive from the ACCENT (Acute Coronary Syndrome, Emotion and Triggers) study, exploring long term adaptation following ACS. Analyses showed that the likelihood of returning to work was negatively associated with depression immediately following ACS, independently of clinical and demographic factors, and that emotional triggers predicted elevated anxiety and poor mental health status at 12 and 36 months independently of covariates. In combination, these studies suggest that negative emotional status contribute both to the onset of acute cardiac events, and to adaptation following ACS.

PUBLICATIONS

Some of the research described in this thesis has been published, and other sections have been submitted for publication. In addition, some of the research described has been presented in conferences.

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*Depressed mood and heart rate variability in everyday life in patients with suspected coronary artery disease.

65th Annual Scientific Conference of the American Psychosomatic Society, Budapest, Hungary (March 2007)

* Biological pathways associated with depressed mood and positive affect in patients with suspected coronary artery disease. (Symposium: Connecting depression to the biology of cardiovascular disease risk)

Dedicated to my parents

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Chapter 1: Introduction

Cardiovascular diseases including coronary artery disease (CAD) are the largest cause of sickness and morbidity, and are the major cause of premature death and reduced quality of life for citizens of the European Union. CAD causes 114,000 deaths a year in the UK. Whereas mortality from CAD is falling rapidly, morbidity from CAD and other heart disease appears to be rising, especially in older groups. In those aged 65 years and older, morbidity has risen by a third since the late 1980's. CAD costs UK healthcare £3,500 million per year (British Heart Foundation statistics, 2005).

The term CAD encompasses a wide variety of cardiac diseases ranging from angina to myocardial infarction, and to subsequent complications like heart failure. To understand how such diseases occur, the pathophysiological changes of CAD need description. The term acute coronary syndrome (ACS) is usually used to describe two conditions, either a heart attack that is also known as myocardial infarction (MI), or unstable angina (UA). Coronary Heart Disease (CHD) occurs when a cholesterol plaque builds up in the walls of the coronary arteries. Over time, this may cause significant narrowing of one or more of the arteries. When the arteries narrow to more than 50 - 70%, the blood supply beyond the plaque cannot meet the oxygen demand of the heart on exertion. This lack of oxygen to the heart muscle usually causes chest pain known as angina, although about 25% of people will not actually experience pain. When the arteries become narrowed, in excess of 90-99%, patients may have angina at rest. This is known as unstable angina (UA). A person has an acute myocardial infarction (AMI) or heart attack when the flow of blood through their coronary arteries is reduced to such an extent that the heart muscle dies. This often occurs suddenly, when a coronary artery is occluded by a blood clot that forms in the artery, because of the rupture of one of these plaques. Physical or mental stresses in either daily life, or extreme events such as natural

disasters, or bereavement, can be triggers for rupture of a vulnerable plaque. Coaguability increases or vasoconstriction triggers complete the occlusion by thrombosis or clot formation.

The risk of acute coronary syndrome (ACS) is influenced by a range of factors. CAD risk is increased not only by established clinical factors such as hypertension, diabetes, and hypercholesterolaemia but also by genetics, lifestyle factors (such as smoking, obesity, and alcohol consumption), early life factors, and various psychosocial factors. Figure 1.1 illustrates how these various psychosocial factors interact with the environment to affect coronary artery disease and the possible biological associated pathways. A crucial observation for the research described in this thesis is that psychosocial factors are associated both with the long term development of CAD and with the triggering of acute cardiac events. There is some overlap between the factors involved (such as depressed mood), but they may be operating over different time scales in the two situations. Additionally, psychosocial factors influence adaptation and quality of life following ACS.

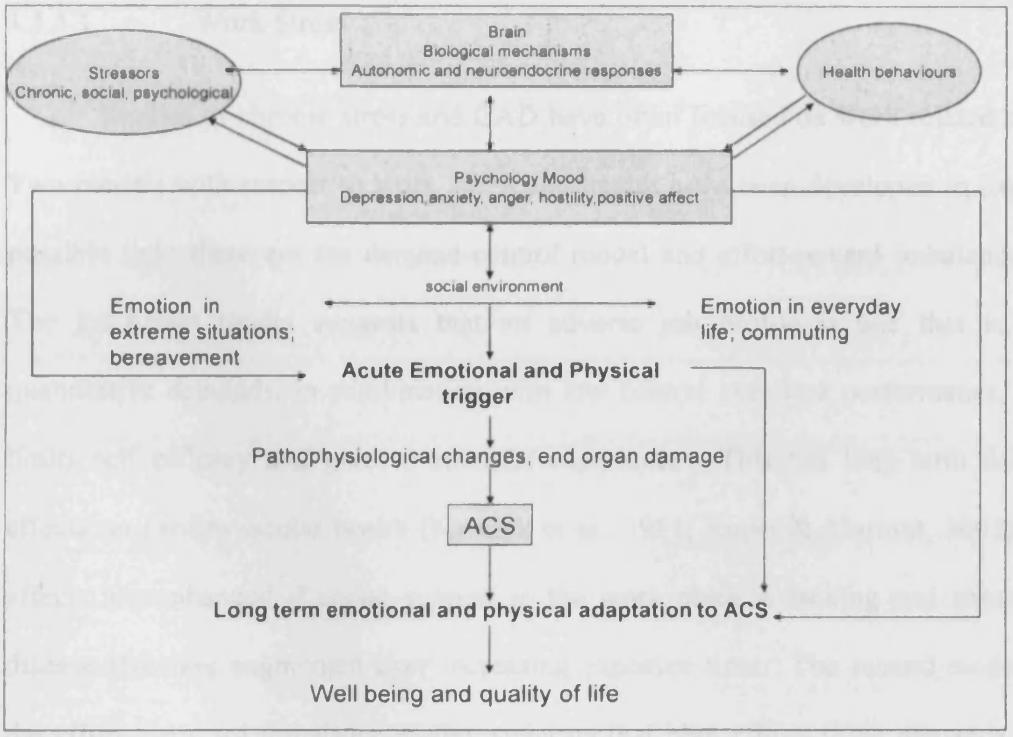
Psychosocial factors, including low socio-economic status, work-related, financial and marital stress, low social support, hostility, depression and anxiety, have all shown some association with an increased risk of coronary heart disease in prospective cohort studies (Kuper et al., 2002). Poor social support has emerged as a predictor of CAD and as an indicator of poor prognosis in patients with established disease (Berkman et al., 1979; Orth-Gomer et al., 2000). Marital stress may be especially predictive of poorer coronary outcomes for women (Orth-Gomer et al., 2000; Balog et al., 2003), and it has been well documented that cardiovascular and immunological measures increase in response to marital conflict (Miller et al., 1999). Associations between these psychological and social factors on the one hand and biological indices on the other

allow identification of those particularly at risk, although it is difficult to assess the direction of effects in cross-sectional studies (Kuper et al., 2002; Williams et al., 2002; Rozanski et al., 1999).

There is considerable evidence that emotional states, particularly negative affect, are associated with cardiovascular health outcomes. A variety of studies shows that depression, anxiety and hostility, lead to an increased risk of impaired cardiovascular outcomes and higher morbidity and mortality (Frasure-Smith et al., 1993; Frasure-Smith et al., 1995; Frasure-Smith et al., 2002; Lesperance et al., 2002; Mayou et al., 2000; Van Melle et al., 2004 and Kaufmann et al., 1999). Negative emotions (such as anxiety and hostility) may also be related to the risk of developing CAD (Kawachi, et al., 1994). Among psychological factors, depression has shown the most consistent association with CAD and particularly with angina (Aromaa et al., 1994; Penninx et al., 1998; Sesso et al., 1998). The evidence is less consistent for anxiety, hostility and Type D personality traits.

This chapter is divided broadly into four sections. The first section introduces the various psychosocial stressors affecting long term CAD development. Since many of the same factors also influence future morbidity in patients with established CAD, this literature is also reviewed. Additionally, I have highlighted research that throws light on mediating physiological responses. The second section will also examine how psychosocial factors, and in particular emotional responses, relate to the acute triggering of cardiac events. The third section examines how these factors relate to adaptation to CAD in the long term. The final section will conclude with the proposals for the new studies comprising the thesis.

Figure 1.1 Potential psychosocial pathways influencing both acute and long term coronary heart disease



1.1 Psychosocial factors and the development of cardiovascular disease

The principle research method used to investigate the role of psychosocial factors in the development of cardiovascular disease is the prospective observational cohort study. This involves measurement of exposure to the potential risk factor (e.g. work stress, depression) in a large sample of initially healthy participants. Other risk factors (age, gender, smoking, blood pressure, cholesterol, etc.) are measured at the same time. The cohort is then followed up for a period of years, during which time some individuals will develop CAD. Using multivariate statistics, associations between the psychosocial

factors and future disease can then be assessed, and the extent to which effects are independent of standard risk factors can be evaluated.

1.1.1 Chronic stressors

1.1.1 1 Work Stress

Studies of chronic stress and CAD have often focused on work related stressors. Two models with respect to work stress and health have been developed to explain the possible link; these are the demand-control model and effort-reward imbalance model. The job strain model suggests that an adverse job profile is one that is high in quantitative demands, in combination with low control over task performance, and this limits self efficacy and gives a stressful experience. This has long term deleterious effects on cardiovascular health (Karasek et al., 1981; Kuper & Marmot, 2003). These effects are enhanced if social support in the work place is lacking and stress related disease risks are augmented over increasing exposure time. The second model, called the effort – reward imbalance model, suggests that high efforts (high demands and / or high involvement) in the presence of low rewards (low pay, low esteem, few career opportunities and / or job insecurity), may have a hazardous effect on CAD risk (Siegrist, 1996, 2004). Several large prospective studies have found a consistent positive association between job strain and cardiovascular disease (CVD) morbidity and mortality (Kuper et al., 2003; Theorell et al., 1998), with low control being the most harmful to health (Schnall et al., 1994; Bosma et al., 1997, 1998).

Other studies show a significant association between effort-reward imbalance and CVD indices, including new cardiac events (Siegriest et al., 1990, Siegrist, 1996) and actual progression on coronary disease development in terms of atherosclerosis (Lynch et al., 1997). In the Whitehall II study, Bosma et al. (1998) found that both effort-reward imbalance in jobs and low job control were independent predictors of cardiovascular

outcomes, with a 1.56 – 2.38 greater risk of new coronary disease over a 5 year follow up period. Since then, researchers have combined information from the two job models and provided greater estimates of cardiovascular outcomes.

Recent studies have found a significant association between more generalised measures of work stress and CAD mortality (Matthews & Gump, 2002), as well as job insecurity, which is a component of the effort-reward imbalance model and the incidence of CAD (Lee et al., 2004). On average, job strain and effort reward – imbalance and other job stressors have consistently predicted adverse cardiac outcomes for men more so than for women (Lee et al., 2002; Orth-Gomer et al., 2000). Rosengren et al. (2004) in the INTERHEART case control study, which examined the association of a variety of psychosocial risk factors with the risk of an acute MI in 11,119 cases and 13,648 controls from 52 countries, showed that people with a myocardial infarction reported higher prevalence of permanent work stress (Odds Ratio (O.R) 2.14; 99% Confidence Interval (C.I) 1.73 – 2.64), after adjusting for age, sex, geographic area and smoking. When separate analyses was carried out on men and women, in contrast to men, work stress was not associated with acute MI in women ($p = 0.06$).

The majority of studies have controlled for potential confounders such as physical activity, smoking, body mass index (BMI), and socio-economic position. However, it is difficult to eliminate the co-factors associated with both stress exposure and physiological functioning. One way of overcoming this is by longitudinal follow up studies of specific biological mediators. Schnall et al. (1998) followed up 195 men for 3 years and analysed the relationship with job strain. Results suggested that those who reported high job strain at baseline, but not 3 years later, showed a significant reduction in cardiovascular indices such as ambulatory systolic and diastolic pressure, after

adjustment for age, BMI, smoking and alcohol consumption. This suggested that an improvement in chronic stress led to a decline in ambulatory blood pressure.

1.1.1.2 Financial stress

Financial strain is another chronic psychosocial stressor, and like work stress, has been associated with increased CAD risk. Perceived financial strain was predictive of myocardial infarction and cardiac death in the longitudinal 20 year follow up Framingham study of 749 women aged 45 - 64 years initially free of coronary disease (Eaker et al., 1993). It was also associated with CAD risk in the large epidemiological case control INTERHEART study (Rosengren et al., 2004). The literature also established that lower socio-economic position as expected, would be associated with financial strain as well as with poor residential area (Evans & Steptoe, 2002).

Steptoe et al. (2005) carried out a longitudinal study where the influence of changes in financial strain in relation to changes in ambulatory blood pressure and salivary cortisol were assessed. Data was analysed from 160 men and women aged 47 - 59 years at first assessment, in which the variables were repeated 3 years later. Results found that systolic blood pressure at 3 years follow up period, was lower in the improved financial strain group, than in the worse or no change group ($p = 0.029$) after adjustment for confounders. In addition, the cortisol awakening response was lower in men reporting improved financial strain ($p=0.048$), after adjustment for confounders.

Such studies on longitudinal data extend cross-sectional findings, by showing associations between favourable changes in chronic stressors like financial strain and reduced cardiovascular and neuroendocrine activation in everyday life.

1.1.1.3 Care giving stress

Caring for a family member with a chronic illness is generally regarded as a chronically stressful process with potentially negative physical health consequences for the carer. Informal caregivers are those who are not financially compensated for their services. They are usually relatives or friends who give assistance to persons who are having difficulties with activities of daily living due to physical, cognitive, or emotional impairments. A meta analysis by Vitaliano et al. (2003) combined results of 23 studies, to compare the health of caregivers with demographically similar non caregivers, examining across 11 health categories, and demonstrated a strong relationship between caregiving and stress hormones, antibodies and global reported health.

Chronic stressors, like care giving, are also associated with illness including cardiac disease (Cohen et al., 1997) and with disease progression (Everson et al., 1997). Caregivers undergo a burden resulting from the physical, psychological, emotional, social and financial problems experienced by families caring for impaired older adults (George & Gwither, 1986). Caregivers are more likely to be distressed, have clinical depression (Schulz et al., 1995) and engage in risky health behaviours. In addition, caregivers show other reactions, such as poor sleep, diet and sedentary behaviour (Vitaliano et al., 2002). The explanation as to how an increased risk of CAD may be linked to caregivers is two fold. One pathway appears to flow from chronic stressors to psychosocial distress and then onto activation of the hypothalamic - pituitary - axis (HPA) releasing cortisol, coupled with activation of the sympathetic adrenomedullary axis from which adrenaline and noradrenaline are secreted (Lovallo et al., 1997; Steptoe et al., 2000). These hormones stimulate peripheral activity leading to allostatic load or wear and tear from repeated arousal and inefficient control of physiological responses (McEwen et al., 2000) which may lead to pathophysiology (Niaura & Goldstein, 1992).

The second pathway is that stress in care giving may trigger risky health behaviours, such as excessive smoking. These two pathways may contribute to illness by increasing cardiovascular dysregulation (Kannel et al., 1986).

The impact of care giving is influenced by other psychosocial factors. For example, high levels of perceived social support among caregivers predict lower metabolic and cardiovascular risk (Vitiliano et al., 2002) and a lower CAD prevalence (Niaura & Goldstein, 1992). Two reports from the Nurses Health study show a strong association between care giving and incidence of CAD. Women caring for an ill spouse for 9 or more hours a week had almost twice the risk of incident CAD over 4 years. In addition, women who reported high levels of care giving for even healthy children or grandchildren also experienced an increased CAD risk (Lee et al., 2003).

1.1.1.4 Family stress

Another adverse psychosocial factor to influence CAD is family stress. There is increasing evidence that family discord and negative non-supportive relationships are associated with a heightened physiological stress response, which may contribute to CAD over time.

Much of the literature on marital discord relates to patients who have established CAD focusing on endocrinological and immunological correlates (Keicolt-Glaser et al., 1998), and on cardiovascular reactivity (Smith et al.,1998), as well as follow up studies of such patients focusing on recurrent cardiac events (Orth-Gomer et al., 2000). The literature on the association between marital distress and future CAD in initially healthy populations at baseline is more limited. In a large sample of initially healthy but high risk men, Matthews and Gump (2002) found that increasing levels of marital stress was associated with an increased risk of death from CAD.

A further study by Gallo et al. (2003) studied 393 healthy post menopausal women assessing marital status and quality, cardiovascular risk factors. Intima media thickness and plaque in carotid arteries and calcification in the coronary arteries of the heart was measured by electron beam computed tomography, as markers of atherosclerotic burden. These women were followed up for three years. The study found that women in highly satisfying marriages had the least atherosclerosis in both carotid arteries and aorta relative to women in low satisfying marriages.

1.1.2 Social Stressors: Social Support and Social Isolation

This section reviews the literature on the relationship between social relationships (namely social support and social isolation) and the long term health outcomes, in particular, as relates to cardiovascular disease.

There is much evidence for lack of social support being a significant psychosocial risk factor for CAD (Hemingway & Marmot, 1999; Berkman et al., 1995; Orth-Gomer et al., 1993; Kuper et al., 2002). Despite the clear evidence of a predictive association between social support and future CAD, there is ambiguity in precise measurement of social support. Different indicators of social support and isolation produce inconsistent effects (Irvine et al., 1999). Many different indicators of social support and isolation have been used in epidemiological studies, ranging from quantitative measures of network characteristics (membership of a club, marital status) to subjective measures of network support (perceived satisfaction with emotional or practical support).

There are several definitions of types of support. Briefly, *structural support* refers to the size, type, density and frequency of the network of people surrounding an

individual. A criticism of measuring support in this way is that the mere structure of a relationship does not necessarily describe the nature of the relationship. *Social integration* is defined as the participation in a broad range of relationships (Brissette et al., 2000) giving a sense of communality and identification of one's social roles. *Social isolation* is the flip side of social integration. It could be viewed that it is the negative aspects of the lack of these social networks, which acts as a psychological stressor and increases negative affect due to a sense of alienation and loneliness. This in turn increases neuroendocrine and cardiovascular responses (Uchino et al., 1996), suppresses the immune system, (Cohen et al., 1998) and affects health outcome. *Functional social support* refers to a social network's provision of psychological and material resources intended to benefit the individual's response to stress (House & Khan, 1985). One has to distinguish between functional support actually *received*, which is limited by its overlap with illness, distress or extent of need, from that of *perceived* functional support which is an individual's subjective appraisal of perception of available support if so needed.

There are several methodological issues related to an examination of the relationship between social support and cardiovascular function. These issues, as highlighted by Uchino et al. (1996), include assessing multiple functional dimensions of support and use of appropriate statistical controls. Many of the studies are correlational, with discrepancy in the literature due to potentially confounding variables of socio-economic status, lack of control for cardiovascular altering medications (e.g. beta blockers), age and gender (Shumaker et al., 1991).

Prospective studies of initially healthy individuals support the notion of social support as a predictor of the onset and progression of CAD. Kawachi et al. (1996) found in a study of 32,624 US male health professionals that social isolation was related to

increased cardiovascular disease mortality and deaths but was unrelated to other causes of death.

Orth-Gomer et al. (1993) in a longitudinal community based study, and Rosengren et al. (1993), have shown that low perceived emotional support is associated with an increased CAD incidence. Several studies have also shown an effect for structural support on initial cardiac events (Vogt et al., 1992) and cardiac mortality (House et al., 1982). However, other studies have found no significant effects of social integration on CAD incidence (Reed et al., 1983). There are mixed findings regarding social support and the incidence of CAD. This may be due to fact that although one may have greater social integration this can be accompanied by greater interpersonal problems. This is highlighted in a study by Medalie et al. (1976), in which a cohort of Israeli men revealed that those with greater social support in terms of numbers of ties had higher levels of family problems. This was associated with a greater risk of angina development. A significant inverse association was found between levels of emotional support and extent of atherosclerosis found by Blumenthal et al. (1987), which suggests that it is more the quality and level of social support than simply the network size that is important in cardiac health outcomes. The discrepancy in the findings from these studies may be thus due to the variability of measurement tools used. The majority of the studies show an effect for measures of structural support as predictors of CAD onset but we know little as to the specific dimensions of structural support used. In addition, few studies actually include a measure of perceived functional support, which limits the validity of conclusions made.

Socio-cultural factors such as gender, socio-economic status, as well as psychological factors like depression and personality are potential moderators of the effect of social support on CAD. Studies investigating gender specific effects of social

support suggest being married is more beneficial to health for men in terms of cardiovascular morbidity and mortality than for women (Kawachi et al., 1996; Matthews & Gump, 2002). Studies investigating socio-economic status give mixed results. Vitaliano et al. (2001) found that emotional support, but not tangible support, was associated with increased cardiovascular risk for low income patients only.

Low social support often co exists with established depression and both these factors have been implicated as predictors of CAD onset and progression. The effects of depression significantly interact synergistically with the effects seen with social support on CAD outcomes. Frasure-smith et al. (2000) found that high levels of perceived social support buffered the effects of depression on one year mortality in post AMI patients, such that depressed patients with high levels of social support were not at an increased risk relative to the non-depressed patients.

Social support influences health by several mechanisms. Cohen (1988) suggests that social support may be beneficial because it protects individuals from the deleterious behavioural and the physiological consequences of stress through two mechanisms: stress buffering and main effects. The critical factor in social support as a *stress buffer* is the perception that others will provide appropriate aid (Cohen, 1988; Uchino et al., 1996) thus bolstering one's perceived ability to cope with demands, and thereby lowering the stress level (Cohen & Wills, 1985). This in turn dampens the emotional and physiological responses to a cardiac event, or alters maladaptive behavioural responses (Wills & Cleary, 1996).

Cohen (2004) also suggests that the benefits of social support operate through *main effects*. Individuals who participate in social networks are subject to social controls that influence normative health behaviours as well engender feelings of responsibility for others and one's self. In addition, the positive psychological effects from close ties, in

turn directly motivate the individual in healthy practices and behaviours, including adherence to medication and lifestyle recommendations e.g. smoking (Doherty et al., 1983; Hartel et al., 1988).

Studies have indicated that the associations found between social support and CAD are linked to plausible physiological pathways. The reactivity hypothesis suggests that exaggerated cardiovascular activity to stressors may be a pathogenic mechanism in influencing the development of cardiovascular disorders (Matthews et al., 1986). Higher cardiovascular reactivity seen in situations of low social support (Gerin et al., 1995; Kamarck et al., 1995) may translate to gradual elevations in tonic blood pressure across an individual's lifespan (Light et al., 1992). Studies of conflictual relationships have been shown to produce heightened cardiovascular and neuroendocrine responses both in the laboratory and ambulatory studies (Holt-Lunstad et al., 2000). Individual differences in perceived support and experimental manipulation of perceived support are associated with reduced cardiovascular and neuroendocrine activity to stressors (Kiecolt-Glaser & Greenberg, 1984; Cohen et al., 1998; Uchino et al., 1996).

To conclude, despite mixed findings, overall studies show that structural and functional social support, social isolation and conflict all have a consistent impact on mental and physical health outcomes and especially so with CAD outcomes. However, the strongest effects observed are in prognosis post myocardial infarction rather than incidence (Seeman et al., 1996).

1.1.3 Negative emotions and cardiovascular health

There has been much research on how negative emotions play a role in the aetiology of cardiovascular disease in the form of large scale epidemiological studies

(Rozanski et al., 1999). Depression and anxiety predict CAD morbidity and mortality after controlling for traditional risk factors (Hemingway & Marmot, 1999; Kubzansky & Kawachi, 2000) whereas associations with anger, hostility and personality have more mixed findings (Krantz & McCeney, 2002). This section will review the key findings of the literature on depression, anxiety, hostility, and anger and the effect on cardiovascular disease risk and outcomes and highlight some of the limitations in the studies to date. I will discuss key pathophysiological mechanisms by which these psychosocial factors may influence CAD in chapter 2.

1.1.3 1 Depression

Both the presence of depressive disorder defined by clinical interview, and the presence of depressive symptomatology measured by questionnaire scales, has been studied as predictors of CAD. The Diagnostic and Statistical Manual of Mental Disorders criteria for major depressive disorder include nine criteria and for a diagnosis, an individual must have five of them, one of which must be depressed mood and symptoms lasting longer than 2 weeks, which impair daily functioning. Depression is not diagnosed in the context of grief, medication or direct physiological effects of a medical illness such as hypothyroidism.

Researchers assess depression with self-report questionnaires like the Beck Depression Inventory (Beck et al.,1988) or the Centre for Epidemiological Studies-Depression (CES-D) Scale (Radloff, 1977), and some depression reviews (Krantz & McCeney, 2002) have also included related but distinct concepts of vital exhaustion (lack of energy, irritability) and hopelessness (no reference to somatic symptoms of depression). In the studies of depression and CAD, the clinical manifestations of CAD include both cardiac death and acute coronary syndromes (as established by symptoms

together with ECG or biochemical changes and angina). In the systematic review by Hemingway et al. (2001), it is noted that studies that have separated angina from other outcomes reported stronger effects of depression on angina (Hallstrom et al., 1986; Sesso et al.,1998), suggesting possible reporting bias, as angina is the least amenable to objective verification. There are numerous cross-sectional studies establishing that depression is more common in CAD patients, but this does not establish the temporal relationships between depression and CAD development. This section examines longitudinal prospective follow up studies of initially healthy populations. Evidence relating depression following ACS with morbidity and mortality is described in section 1.3.3.

An important issue is that depression is often confounded with other determinants of CAD. For example, depressed patients may smoke more. Smoking may be a confounder in studies of depression and CAD, but it could also be a mediator of the association between depression and CAD. This issue has yet to be resolved in CAD research.

Epidemiological evidence for the effects of depression on CAD comes from population based, unselected, healthy samples of both men and women. One study by Anda et al. (1993) followed up 2,800 people for 12 years and found that depressed affect as reported by the General Health Questionnaire (GHQ), was associated with 50 - 60% excess risk of fatal and non fatal ischaemic heart disease after adjusting for cardiac risk factors. Barefoot and Schroll, (1996) followed up 730 healthy men and women in Denmark from 1964 to 1991 and found that a 2-Standard Deviation (SD) difference in depression score was associated with a relative risk (RR) of 1.71 ($p = 0.005$) and 1.59 ($p < 0.001$) for MI and death from all causes respectively, after adjustment for baseline variables. The author concluded that the graded relationships between depression scores

and risk, and the long lasting nature of the effect seen, suggested that depression was seen as a continuous variable, representing a chronic psychological trait, rather than an episodic psychiatric condition. The 'Precursors study' by Ford et al. (1998), evaluated 1190 male medical students and followed them up for 40 years. Those who reported clinical depression were at greater risk for subsequent CAD and MI than men without depression, with relative risk being 2.12 (95% C.I 1.24 – 3.63) and 2.12 (95% C.I 1.11 – 4.6) respectively. Of note, the increased risk associated with depression was present even for those who had an MI occurring 10 years after the onset of the first depressive episode. Pratt et al. (1996) reported that a diagnosis of major depression was related to a 4.5 fold increased risk of MI, and depressive symptoms as measured by the CES-D, predicted 70% excess risk of incident CAD in women and men (Ferketich et al., 2000). Ariyo et al. (2000) followed 4493 healthy patients at baseline for 6 years and found depression to be a statistically significant predictor of CAD but with a small effect size, with a hazard ratio of 1.15 for a 5 point increase in the 10 item depression scale (CES-D). Both meta-analyses by Rugulies (2002) and Wulsin et al. (2003) of community samples reinforce the conclusions that higher depression amongst healthy populations at baseline, conferred an average relative risk of 1.64 for cardiac death.

A more recent chapter by Steptoe (2006) reviewed 27 longitudinal observational studies published between 1964 and 2005, and pointed overall towards a positive association between depression and CAD although inconsistencies were present. Nicholson et al. (2006) carried out a meta-analysis of cohort studies measuring depression with follow-up for fatal CAD/incident myocardial infarction (aetiological) or all-cause mortality/fatal CAD (prognostic). Results revealed that in 21 aetiological studies, the pooled relative risk of future CAD associated with depression was 1.81 (95% CI 1.53-2.15) with adjustment reducing the crude effect marginally from 2.08 (1.69-2.55) to 1.90 (1.49-2.42). In 34 prognostic studies, the pooled relative risk was 1.80

(1.50-2.15) but after adjustment for left ventricular function result (available in only eight studies), this attenuated the relative risk from 2.18 to 1.53 (1.11-2.10), a 48% reduction. Therefore, the authors concluded that depression has yet to be established as an independent risk factor for CAD because of the incomplete and biased availability of adjustment for conventional risk factors and severity of coronary disease.

One important point to emerge from these is that the intensity of depression may be important. Studies that focused on the degree of depression found that the risk of CAD was higher amongst people seriously depressed, than amongst those who were only moderately depressed, suggesting a dose response association (Pratt et al., 1996; Penninx et al., 2001). Studies involving a clinical diagnosis of depression by interview, as opposed to questionnaire measures of depressed mood, have also found positive associations (Aromaa et al., 1994, Pratt et al., 1996).

There is a debate as to whether depression contributes to long term development of atherosclerosis, or to the clinical manifestations of the disease. Measurement of non invasive indices of atherosclerosis, such as the intimal medial layer of arteries, or presence of atherosclerotic plaque by either ultra sound scanning or electron beam scanning computer tomography (EBCT) of the heart has allowed studies to answer this question. In the Work Site Blood Pressure Study (Haas et al., 2005), depressed mood at baseline predicted carotid plaque 10 years later after adjustment for traditional cardiac risk factors. Another larger study of 4000 men and women in Rotterdam showed positive associations between depressive disorders and coronary artery and aortic calcification (Tiemeier et al., 2004). There also appears to be a relationship between subclinical atherosclerosis and other negative mood states like anxiety. Wolff et al. (2005) studied 726 healthy French men and women both at baseline and at 2 years follow up, and despite no development of CAD found that those with higher anxiety scores at

both time points had greater progression in carotid intima media thickness (IMT) over a four year period than less anxious women.

One other distinct possibility is that depression may act as an acute trigger for an acute cardiac event in vulnerable individuals and this issue is explored in section 1.2 on acute triggering of Acute Coronary Syndrome.

Finally, longitudinal studies do not necessarily show causation between depression and the associations found with CAD. The fact that associations between depression and CAD remain, despite studies taking into account the various lifestyle factors that may be associated both with CAD and depression, suggests that health behaviours are only partly responsible for the positive associations found between depression and CAD. It gives greater credence to biological processes as being important in mediating the impact of depression on CAD development. This is discussed further in chapter 2. Depression in relation to prognosis and adaptation to CAD is additionally explored further in section 1.3.

1.1.3.2 Anxiety

Anxiety has been defined as a state of emotional distress 'resulting from feelings of being unable to predict, control, or obtain desired outcomes' (Barlow, 2000). Researchers have used a variety of assessment tools including diagnostic interviews, diagnostic criteria or self-reporting rating scales to measure trait anxiety (Spielberger et al., 1983).

In general, psychological distress has been shown to give an increased risk of CAD in men that is unexplained by work characteristics, lack of social support or health behaviours. In a prospective occupational cohort study of London based civil servants, baseline psychological distress, as measured by General Health Questionnaire (GHQ),

was associated with an increased incidence of self-reported CAD at 5 years follow up (odds ratio = 1.83, C.I: 1.5 – 2.3) and ECG abnormalities (odds ratio = 1.51, C.I: 1.1 – 2.1) after adjustment for age, employment grade and follow up (Stansfeld et al., 2002). However, what has not been fully established is the question of what aspects of psychological distress are particularly associated with CAD risk. The GHQ screens for both depressive illness and lesser levels of anxiety and depression and the authors suggest that it may be the persistence of depressive or anxiety symptoms over long periods of time that may be more important in the development of CAD than in short episodes of a severe depressive illness.

Studies with community based samples suggest that anxiety disorders are associated with greater mortality (Kubzansky et al., 1997). Although several of the epidemiological studies suggest that high levels of anxiety increase CAD risk, most of the studies involve small samples, use a range of measures of distress and are limited to men. The issue of confounding is difficult when analysing the impact of anxiety and distress since risky health behaviours like smoking is often associated with such psychological states. Medalie et al. (1973, 1976) followed up an Israeli civil servant cohort and reported a strong or moderate association between anxiety and the incidence of angina. Phobic anxiety predicted a 2.45 fold greater risk of fatal CAD in 34,000 initially healthy male professionals (Kawachi et al., 1994). In the Normative Aging Study, men with two anxiety symptoms were shown to have an increased risk of cardiac death compared to those not anxious (Kawachi et al., 1994). In separate analyses of the same sample in a study by Kubzansky et al. (1997), men who reported high levels of worrying had more than a twofold increased risk of nonfatal MI after 20 years of follow up upon the same sample.

There are a few studies, which have found no significant risk associated with CAD and anxiety (Allgulander et al., 1991; Hippisley-Cox et al., 1998), but these studies were suboptimal in that traditional cardiac risk factors were not controlled for. In addition, they were not true prospective designs as these studies compared the number of cardiac deaths in a psychiatric sample with age and sex specific CAD mortality rates in the same geographical area.

One final point to note in these studies is the follow up period. It was found that studies with a longer follow up were less likely to find a positive association than studies with less extended follow up. This was demonstrated in the Northwick Park Heart Study in which Haines et al. (1987) showed that men with high levels of anxiety had nearly four times the risk of fatal CAD over 10 years after adjusting for traditional cardiac risk factors. This association between anxiety and fatal CAD disappeared when follow up was extended by another 10 years (Haines et al., 2001).

1.1.3.3 Type D personality

Personality is thought to have an impact on the cardiac disease process. Denollet et al. (1992) investigated coping styles in men with CAD and developed the type D or 'distressed' personality construct. The distressed personality is characterised by the joint tendency to experience negative emotions and to inhibit these emotions whilst avoiding social contact with others. Type D personality is defined by high scores on negative affectivity (NA) and social inhibition (SI) dimensions. NA is defined as the 'tendency to experience negative emotions' including anger, hostile feelings, depressed affect, and anxiety, while SI is defined as the 'avoidance of potential dangers involved in the social interaction, such as disapproval or non reward by others' (Denollet, 1998).

There is consistent evidence that type D personality is associated with cardiovascular disease outcomes in patients with existing CAD. Denollet et al. (1995)

showed in a prospective study of 268 men and 35 women with documented CAD, that type D personality was associated with a six fold increase in the likelihood of death from cardiac events two to five years post MI in men. In another longer prospective study by Denollet et al. (1996), it was shown that type D personality was associated with a four fold increase in mortality 6 - 10 years after a cardiac event, with a poorer outcome in post MI patients who had a decreased (<40%) left ventricular ejection fraction (LVEF) (Denollet et al., 1998). In all of these studies by Denollet, type D personality was shown was shown to be significantly associated with worse disease outcomes, even after controlling for traditional cardiac risk factors. However, symptoms of depression, anger, and anxiety did not add to the predictive power of the type D construct. Denollet et al. (1998), found that type D personality patients were likely to experience anxiety, depression and anger, therefore the inclusion of negative affectivity in the definition of type D personality may explain this null finding. NA and SI were also not predictive of outcome individually. It was only the joint presence of high scores on both dimensions that were linked to disease morbidity and mortality.

In a more recent study by the same group, (Denollet et al., 2006) they followed up 337 MI patients for 5 years, who filled out a general health questionnaire (psychological stress) and the type D personality scale, for adverse cardiac events (death, MI, revascularisation). Multivariate analysis revealed that left ventricular ejection fraction (LVEF) <40%, not having coronary artery by pass surgery (CABG) and type D personality were independent predictors of major adverse events (odds ratio 2.90, C.I 1.42-5.92; $p = 0.003$), whereas psychological stress was only marginally significant. This study concluded that type D reflected more than temporary changes in stress levels, as it predicted cardiac events after controlling for concurrent symptoms of stress.

Whilst many of the studies have suggested a potential link between type D and cardiac disease outcomes, there is yet, little established with regards to the specific biological pathways. Denollet et al. (1996) suggested that personality may be linked to CAD directly through pathophysiological mechanisms such as silent myocardial ischaemia, or platelet release and activation triggered by mental stress. A second way that type D personality may promote disease is through health related behaviours. The tendency of type D to inhibit behaviour in social interaction means they decrease the availability of social support. A third possible mechanism is an unknown third variable that is a primary cause of both personality trait and premature mortality. Type D personality could be a behavioural manifestation of an underlying biological variable, which predisposes the individual to cardiac outcomes associated with underlying genetic causes. There is evidence that negative affectivity and social inhibition can be due in part to genetic factors (Bouchard, 1994).

1.1.3.4 Anger and Hostility

Early literature in the 1950's and 1960's focused on the roles of anger, anger expression and hostility on CVD, and there was much research on type A coronary prone behaviours. Type A personality includes elements of impatience, hard driving goal orientated behaviour, irritation and anger. Initial work suggested that type A men and women had higher cholesterol and greater evidence of CAD compared to type B (Friedman & Rosenman, 1971), and a large prospective study of 3,100 middle aged men, established type A as a risk factor for CAD. Type A men were twice as likely to develop CAD in the subsequent 8.5 years as those who were not classified as Type A (Rosenman et al., 1975). Since then, subsequent literature regarding Type A behaviour have found it to be a weak and inconsistent predictor of CAD incidence with negative findings (Ragland et al., 1988). In a study by Johnston et al. (1987), type A behaviour as

measured by the Bortner questionnaire was found not to predict major ischaemic heart disease in 5936 men aged 40-59 years after an average of 6.2 years follow up.

Recently, more attention has been focused on anger and hostility as important components of type A behaviour, which have been found to predict CAD incidence as separate dimensions in epidemiological research (Smith, 1992).

Hostility is defined as cynical attitudes to others and the wider environment (Barefoot et al., 1989), and is considered an enduring personality trait. A popular measure of hostility is the Cook- Medley Hostility Scale (Cook & Medley, 1954) which is described in more detail in chapter 4. Anger is associated with subjective arousal, and has both situational and trait aspects. It is often assessed by a self-report inventory such as the Spielberger Trait Anger Scale (Spielberger et al., 1983). It is an emotion and part of a broader construct including hostility and aggressive behaviour (Smith, 1992). Hostility is one of the better defined and understood expressions of anger. Hostility may also be a more sensitive predictor of heart disease but it is unlikely that it is the only expression of anger that increases cardiac risk. A prospective study by Gallacher et al. (1999) assessed 2890 men using the Framingham scales comprising 'anger symptoms', 'anger in', 'anger discuss' and a new construct 'suppressed anger'. Results showed that both anger out and suppressed anger were predictive of incident of ACS, independent of physiological, psychosocial and behavioural risk factors. Neither of these constructs was similar to hostility suggesting the presence of mechanisms other than hostility by which anger predicts cardiac risk.

There have been many studies on selected and mixed samples investigating hostility and anger. These emotions have been measured with a variety of assessment tools in relation to CV morbidity and mortality, with both positive and negative findings (Hearn et al., 1989; Helmers et al., 1993; Barefoot et al., 1995). A large meta-analytic

review of 45 studies concluded that hostility is an independent risk factor for CAD and all cause mortality (Miller et al., 1996). After controlling for other risk factors for CAD, the widely used Cook-Medley Hostility Scale and other cognitive-experiential measures were most predictive of all-cause mortality (weighted mean r = .16) and, to a lesser extent, CAD (weighted mean r = .08). More recently, a case control study from the Multiple Risk Factor Intervention Trial showed that men at high risk of CAD who scored high on hostility, were more likely to die from CAD in the intervening 16 years, after adjustment for traditional coronary risk factors (Matthews et al., 2004). In the Normative Aging Study, each 1 point increase in hostility predicted a 6% increased risk of incident CAD over 3 years (Niaura & Goldstein, 2002). Kawachi et al. (1996) showed that men with high levels of anger had 2.5 times more coronary events after 7 years follow up. In the KIHD (Kuopio Ischaemic Heart Disease) study, hostility predicted a more than two fold increased risk of MI and CV mortality over nine years, largely explained by behavioural risk factors (Everson et al., 1997). In addition, some studies have shown hostility and anger to be associated with subclinical cardiovascular disease such as carotid atherosclerosis in both healthy post menopausal women (Matthews et al., 1998) and amongst middle aged men (Julkunen et al., 1994). Angerer et al. (2000) have also linked hostility to progression of atherosclerosis in serial coronary angiography, and higher levels of hostility were associated with greater coronary artery calcification 10 years later, in a subset of participants taking part in the CARDIA study (Iribarren et al., 2000).

However, Matthews et al. (1998), who assessed the thickness of arterial lesions of patients with known documented CAD, found no relation with anger whereas Kawachi et al (1996) found mixed results.

Overall though, evidence is strong, especially from methodologically sound population-based studies, that anger and hostility increase CAD risk in healthy populations. However, evidence is weaker in patients with documented CAD that anger and hostility are robust predictors of recurrent events and cardiovascular mortality (Hemingway & Marmot, 1999). Regarding hostility in CAD patients, only one study reported a significantly raised risk of CAD events associated with higher hostility (Chaput, 2002) with many other studies reporting null effects (Irvine et al., 1999, Kaufmann et al., 1999). Two studies measured trait anger in people with existing CAD, with fatal or non fatal MI as the outcome. Denollet et al. (1998), found higher trait anger significantly predicted occurrence of another MI whilst a second study found marginally significant positive associations (Mendes de Leon et al., 1996). Null effects were seen in other studies with regards to anger and its association with CAD in documented CAD patients (Welin et al., 2000; Ahern et al., 1990; Frasure-Smith et al., 1995, 1999, 2003). In common with the literature on anxiety, the research is limited to mainly men and especially Caucasian populations.

1.1.3.5 Overall conclusions concerning negative emotion and CAD

Consistent with previous reviews by Rozanski et al. (1999, 2005), there is a large body of evidence relating negative affect to CAD, with particular supportive evidence for depression and anxiety based on prospective studies in initially healthy samples. The effects seen are stronger for depression than anxiety. The evidence is far more mixed with respect to hostility and anger. However stronger evidence is emerging for hostility and anger expression rather than trait anger (Krantz & McCeney, 2002). The weaker findings may be due to difficulties of distinguishing reactive affective states after hospitalisation from trait anger, anxiety or personality effects. Overall, the evidence

supports the concept that depression and anxiety are likely risk factors for cardiac disease development.

1.1.4 Positive affect and cardiovascular health

Although the literature on negative emotion and its influence on health has been more extensively studied, there has been much more recent attention on the potential benefits of positive affect (PA) (Seligman & Csikszentmihalyi, 2000), defined as the feelings that reflect a level of pleasurable engagement with the environment (Clark et al., 1989) such as happiness, joy, excitement, enthusiasm and contentment. These can either be brief, known as *state* PA, which refers to short term bouts of PA in everyday life, or it can be more stable, enduring trait like feelings, referred to as *trait* PA. The latter is more likely to influence disease outcomes where underlying processes take time to develop i.e. the onset of chronic diseases like CAD. State PA is thought to influence the progression of ongoing disease events in a person with an underlying chronic illness.

There are two types of well being described: eudaimonic and hedonic. Eudaimonic well being is the realisation of one's true potential (Ryff, 1989) whilst hedonic well being describes the experiences of happiness and satisfaction. Optimal well-being is defined as being high on both eudaimonic and hedonic well being (Ryff et al., 2004). Mixed evidence exists for whether PA and negative affect (NA) are bipolar extremes of the same scale or orthogonal factors (Diener et al., 1984; Watson et al., 1988) i.e. are PA and NA bipolar ends of the same construct with benefits of PA reflecting an absence of NA or are the two affects mutually independent with PA providing benefits independent of NA? Ryff et al. (2004) explored whether the different types of well being have different biological correlates, and suggested that it is eudaimonic well being that may prompt reduced biological activation of the organism in terms of lower levels of daily salivary cortisol, pro inflammatory cytokines, cardiovascular risk profiles than states of happiness or contentment (hedonic well being).

These findings have implications for PA influencing CAD development and adaptation to CAD in the long term.

Regarding morbidity, both cross-sectional and prospective studies of PA support an association between higher PA and general good health of participants (Ostir et al., 2001; Cohen et al., 2003) after controlling for NA. For example, Ostir et al. (2001) assessed whether positive or negative affect, or both, predicted the risk of stroke in a 6-year prospective cohort study of an initially healthy population-based sample of 2478 older whites and blacks in North Carolina. Measures of depressive symptoms include questions about the presence of negative affect, such as sadness, as well as the absence of positive affect, such as happiness and optimism. Thereafter, interviews were conducted annually for 6 years. Results found that increasing scores on the modified version of the Centre for Epidemiological Studies Depression Scale (CES-D) were significantly associated with stroke incidence for the overall sample, (relative risk (R.R) = 1.04 for each one-point increase, 95% confidence interval (C.I) = 1.01-1.09), over the 6-year follow-up period, after adjusting for socio-demographic characteristics, blood pressure, body mass index, smoking status, and selected chronic diseases. The positive affect score showed a strong inverse association with the future incidence of stroke (R.R = 0.74, 95% C.I = 0.62-0.88) after controlling for NA affect scores and other known vascular risk factors for a stroke.

There have also been studies showing evidence of PA being associated with the development of CAD in initially healthy populations. Prospective studies have shown that positive beliefs (e.g. optimism) are associated with reduced risk of adverse cardiac outcomes in initially healthy populations (Kubzansky et al., 2001; Matthews et al., 2004). Kubzansky et al. (2007) carried out a prospective population based cohort study on 6025 men and women examining emotional vitality (characterised by a sense of

energy, positive well being and emotional self regulation) and incident CAD (non fatal and fatal events) from hospital records in a 15 year follow up. The results found that after controlling for age, gender, and race/ethnicity, those with the highest levels of emotional vitality had a risk ratio of 0.68 for CAD (95% C.I 0.58-0.78). After additionally controlling for standard cardiac risk factors and history of psychological problems, a significant effect of emotional vitality on CAD incidence was found, suggesting a 2-3% decrease in the risk of CAD for each unit increase on emotional vitality measure scale. The consistency of the association found between PA and CAD, after controlling for NA, suggests important and separate relationships between positive emotional factors and CAD.

Positive affect is also related to disease severity and physical functioning. The reporting of physical symptoms partly reflects underlying disease state but it is also influenced by psychological states and traits of patients (Cohen et al., 1991). Higher trait levels of PA and subjective well being (SWB) have been associated with fewer symptoms and better self-reported health amongst patients with coronary artery disease (Sullivan et al., 2001). Positive affect has been found to both mediate and moderate the effects of depression on physical health. Sullivan et al. (2001) carried out a prospective cohort study on 111 CAD patients examining both physical factors and psychological state or traits, which modify the relation between depression and physical health 5 years later. To examine the moderating effect on depression, the sample was divided into two groups on the basis of Hamilton depression scores. In the low depression group, there was no difference in physical health but in the higher depression group, patients reported much better physical health if they had higher levels of PA. PA had more marked effects on physical health in the presence of depression. Other prospective morbidity studies have found that PA trait benefits re-hospitalisation rates for coronary problems (Middleton & Byrd, 1996).

PA may influence CAD development in daily life by two possible mechanisms as proposed by Pressman and Cohen (2005). The first is the main effect model of PA in which trait PA influences health outcomes by mediating behaviours or physiological responses that create the long term risk and the second model is that PA may directly influence health by change in health practice: medication adherence, changing to healthy lifestyles etc.

Recurrent or prolonged activation of the arousal system (fight or flight response due to stress with attendant changes in blood pressure and heart rate) due to emotion can result in CAD (Krantz et al., 1981). Changes in state PA and associated acute changes in cardiovascular response in daily life could have implications for those with chronic cardiac disease where short term emotions may trigger an event such as a MI. The second mechanism proposed is the stress buffering model of PA in which individuals with high PA, experience less stress in the environment and when potential stressors are encountered, facilitates recovery from stress related activation by changes in cardiovascular or neuroendocrine response.

There are several within-person studies investigating whether periods of high PA are accompanied by changes in cardiovascular reactivity. Studies have shown that state daily PA of the individual to be associated with increased BP and not HR (Gellman et al., 1990; Jacob et al., 1999; Schwarz et al., 1994; Shapiro et al., 1997). Frederickson, (1998) experimentally demonstrated that positive emotions could shorten the recovery period of physiological indices after exposing subjects to a stimulus designed to elicit negative emotions. However, it appears that PA has possibly less of an influence on cardiovascular reactivity though, than NA. James et al. (1986) showed in a study that self-reported emotional arousal was associated with BP increases but in all cases, the

negative emotions of anger and anxiety were associated by larger increases in cardiovascular response than the positive emotions of happiness.

There have also been experimental studies in which state PA is manipulated in the laboratory using some kind of active PA manipulation such as using personally relevant stimuli like recall of past events (Sinha et al., 1992; Waldstein et al., 2000; Schwartz et al., 1981; Yogo et al., 1995) and all showed an increase in cardiovascular response measured. This pattern may have been due to the behavioural activation associated with task performance.

There are also studies examining between-person differences in PA and physiology. Happiness as a measure is an important positive emotion for health with direct influence on health related biology (Steptoe et al., 2005). Biological correlates of cardiovascular markers such as BP and HR, and neurohumoral markers such as cortisol output and the awakening cortisol response, are altered in response to stress or emotion. In the observational study by Steptoe et al. (2005), 228 healthy volunteers underwent measuring heart rate (HR) measurement, salivary cortisol measurement, a psychological distress measure questionnaire (GHQ) and assessment of PA by aggregating momentary experiences of happiness over a working day and leisure day. Findings showed that PA was inversely related to cortisol output over the day independently of age, gender, socio-economic position body mass and smoking. PA was also inversely related to heart rate in men only, which remained significant after additionally controlling for GHQ. PA was also seen to be related to the recorded ambulatory systolic BP assessed 3 years later (Steptoe et al., 2005).

1.2 Acute triggering of ischaemia and ACS

1.2.1 Introduction

In addition to chronic psychosocial factors and emotional traits playing a role in cardiac disease over a period, there are varieties of factors that may act more acutely in the triggering of ACS in susceptible patients. This section summarises key points of some of the literature related to the study of triggering of ACS, the methodology used and the current limitations we have in interpreting the findings from studies carried out so far. In particular, I shall highlight the role of timing of psychosocial factors related to CAD development, the causal sequence of emotional experiences, and discuss the role of acute emotional triggers of ACS.

The problem of why acute cardiac events such as myocardial infarction (MI) or sudden cardiac death occur *when* they do have been much researched. The key biological events underlying an acute coronary syndrome (ACS) are the disruption of coronary plaques by rupture or erosion, and the development of thrombus (Davies et al., 1996). The most angiographically severe lesions are not necessarily at the highest risk of rupture, and histological studies indicate that plaque rupture is a frequent event that only occasionally results in an ACS (Casscells et al., 2003). It is thought that some acute MI's are stimulated by triggers; these are external stimuli, activities or mental states that produce acute physiological changes, which promote pathophysiological responses (Servoss et al., 2002). A trigger can be defined as a stimulus or an activity that produces acute physiological or pathophysiological changes leading directly to onset of acute cardiovascular disease. (Strike et al., 2005; Tofler & Muller, 2006). There is no general agreement about how long before symptom onset the stimulus must occur to be regarded as an acute trigger, rather than a more general aetiological factor. Most research has

focused on a 1 to 2 hour period before the onset of symptoms, but there are possible triggers such as infection that have a longer time course. Triggering typically takes place against a background of long term coronary artery disease (CAD).

Systematic reviews of this literature indicate that emotional stressors may act as triggers (Strike et al., 2005). However, most of this work was carried out with acute MI, and not with the broader modern spectrum of ACS, that includes ST-elevation myocardial infarction (STEMI), non-ST-elevation MI (NSTEMI), and unstable angina (UA). Additionally, although there is quite extensive research on stress-induced myocardial ischaemia (Strike &Steptoe, 2003), research on triggering has not been directly linked with biological investigations of the same patients.

Emotional stimuli are part of a larger group of acute triggers that includes vigorous physical exertion, respiratory infection, drugs such as cocaine and marijuana, and heavy meals. (Smeeth et al., 2004; Willich et al., 1993; Mittleman et al., 1999; Lipovetzky et al., 2004). Triggering is also related to factors such as time of day, day of the week and season of the year.

Circadian variation in vulnerability to acute coronary syndromes (Muller et al., 1989) including transient ischaemia (Rocco et al., 1985; Mulcahy et al., 1988; Krantz et al., 1996) has been described, with a three-fold increase in risk of angina in the first hours after waking (Willich et al., 1987). This period of increased risk coincides with peak levels of the stress hormone cortisol, which then recedes over the course of the day, and with plasma catecholamines, heart rate, and blood pressure. These factors may contribute to a reduction in the ischaemic threshold early in the day. During such a period, subjective states of anger or anxiety, mental stress or intense physical exercise increase myocardial oxygen demand further. In the presence of coronary disease, these

changes may increase the risk of a transient ischaemic attack, with the potential for developing unstable angina or myocardial infarction.

The demands of everyday life and routines may superimpose their own circadian risk factor for ischaemia on CAD patients. Periods associated with commuting, or certain types of social interactions may place greater demands on the cardiovascular system if they are associated with negative subjective states. Interestingly, Willich and colleagues identified a smaller secondary peak in ischaemic incidence in the late afternoon (Willich et al., 1999). Therefore, it will be useful to assess the relative impact of emotional triggers against a background of biologically-mediated circadian changes in vulnerability to ischaemia.

1.2.2 Methodological issues in study triggering in the individual

The scientific study of acute emotional triggers in daily life presents particular methodological challenges. Since triggers are unpredictable, they are difficult to study *prospectively* in relation to emotion and involve identifying patients at high risk and monitoring their activities and feelings over an indefinite period in the expectation that a cardiac event might occur at some point. Acute psychological triggers of ischaemia such as anger, hostility, depression and anxiety occur against a backdrop of ongoing life events, situations and pressures, and personality traits (type D), coping methods (social support, positive affect) and long term affective states and are likely to be associated with them. Many of these experiences are internal and not open to objective verification.

Two broad strategies to investigate triggering are used. The first is to investigate the impact on ACS admissions of stressful events that affect large numbers of people, such as natural disasters, terrorist attacks, or sporting events. The advantage of this approach is that the stimulus is identified and timed objectively. A population-based

sampling frame can be used, and fatal as well as nonfatal cardiac events can be evaluated. Very often, however, the circumstances surrounding natural disasters or conflict are not well suited to systematic data collection.

Most of the events of ACS take place in individuals who are not exposed to large scale traumatic events. The second method is to collect data from patients after they have suffered an ACS or with suspected CAD, asking them about their experiences in the period before symptom onset. Data collection is retrospective. Information of this type is susceptible to memory loss or decay and retrospective biases concerning the social acceptability of the activities preceding onset (such as anger), and to the influence of patients' private beliefs about the causes of heart disease. Studies of the triggering of fatal cardiac events are difficult, unless the circumstances are witnessed by others, and the triggers of fatal events may be different from those for non-fatal ACS. Special methods of data collection and analysis have therefore been developed to minimize these limitations of interview-based studies.

1.2.3. Population-based studies

1.2.3.1 Earthquakes

Rates of cardiac events following earthquakes have been studied in the USA, Japan, Australia and Europe. Living through an earthquake is a devastating experience, but it is important to distinguish between the effects of stress and responses to sudden physical exertion (e.g. running away from buildings), direct injury or trauma. The impact of earthquakes on ACS onset has not been completely consistent. The most systematic analyses have been those of the Northridge Earthquake that took place in the Los Angeles area in January 1994 (Leor et al., 1996; Kloner et al., 1997). A postal

survey of more than 100 hospitals showed that admissions for acute MI increased from 149 in the week before to 201 in the week after the earthquake (Leor et al., 1996). Examination of the coroners' records for Los Angeles County found that sudden deaths from cardiac causes increased from an average of 4.6 per day in the preceding week to 24 on the day of the earthquake (Leor et al., 1996). Only three of these cases were associated with unusual physical exertion. A further analysis of all deaths in the county confirmed the increase CAD mortality, with no increase in deaths from other cardiovascular diseases or from non cardiovascular causes (Kloner et al., 1997).

Studies of the Hanshin-Awaji earthquake in 1995 in the Kobe region of Japan showed similar effects, with a large increase in the number of patients admitted with acute MI on the day of the event (Suzuki et al., 1995). Somewhat smaller increases in rates were recorded following earthquakes in Greece and Australia (Trichopoulos et al., 1983; Dobson et al., 1991). An exception to this pattern is the 1989 Loma Prieta earthquake in the San Francisco Bay area, which was not associated with increased ACS admissions (Brown et al., 1999). A possible explanation may lie in the timing of these events. The Northridge earthquake struck at 4:31 am on a Monday morning in winter, and the Hanshin-Awaji earthquake early on a Tuesday morning in winter. By contrast, the Loma Prieta earthquake occurred at 17:04 pm on a Tuesday in October. There is a greater susceptibility to acute MI in winter months, and from other information about timing of infarctions, a Monday morning in the winter is among the most lethal times for an event to take place (Barnett et al., 2005).

Given the unexpected nature of such disasters, there have not surprisingly been few studies of acute changes in the pathophysiological mechanisms underlying triggering. A major earthquake in Taiwan in 1999 happened by chance to take place as 15 patients with suspected CAD were undergoing holter monitoring (Lin et al., 2001).

Spectral analysis of R-R intervals showed a marked increase in the low to high frequency ratio for about 40 minutes after the earthquake, indicative of vagal withdrawal. ST-segment depression was measured in several patients, and was correlated with the increase in low frequency power. Parati et al. (2001) described a single patient who was undergoing ambulatory blood pressure monitoring during an earthquake in central Italy. There was a large increase in pressure and in heart rate, which persisted for an hour, and the next 6 hours were characterized by high blood pressure variability. Other acute effects that have been documented include increased blood viscosity, fibrinogen and D-dimer levels (Matsuo et al., 1998), an increase in deep negative T waves without Q waves, and abnormal cardiac sympathetic function as revealed with metaiodobenzyl guanidine imaging (Yamabe et al., 1996).

1.2.3.2 War and terrorist acts

Studies of the impact of war and terrorist acts have generated mixed results. Meisel et al. (1991) reported that the incidence of acute MI and sudden death increased in an area near Tel Aviv during the initial phase of the Gulf War in 1991. This finding was corroborated by a national survey in Israel, in which there was a 58% increase in total mortality on the day of the first missile strikes, largely attributable to acute MI and SCD (Kark et al., 1995). Studies in other war zones have produced mixed results, but the quality of data collected under such difficult circumstances is very variable (Mihatov et al., 1995; Dumitrascu et al., 1993).

It might be expected that traumatic events such as major terrorist incidents would have similar effects. A study of 200 patients with implantable cardioverter defibrillators (ICD's) in New York City showed an increase in serious arrhythmias following the attacks on September 11, 2001; the proportion of patients who experienced tachyarrhythmia more than doubled over the 30 days following the attacks in comparison

with other months (Steinberg et al., 2004). Another study involving ICD patients in Florida also showed a near threefold increase in ventricular tachyarrhythmia triggering defibrillator shocks in the 30 days following the attacks (Shedd et al., 2004). But studies of cardiac death and admissions to acute coronary care in New York City in the period surrounding September 11th have shown no excess rates (Chi et al., 2003). Similarly, the major riots and civil unrest in the Los Angeles area in 1992 led to a marked increase in traumatic deaths, but no change in cardiovascular mortality (Birnbaum et al., 1997).

1.2.3.3 Industrial disasters

A recent study investigated the impact on ACS of a major explosion in a chemical plant in Toulouse, France (Ruidavets et al., 2006). This induced an earthquake measuring 3.4 on the Richter scale, and destroyed 27,000 homes. A threefold increase in fatal and nonfatal ACS was recorded over the 3 - 5 days following the explosion in comparison with several reference periods. Impact was confined to a small district immediately surrounding the plant.

1.2.3.4 Festivals and public holidays

A controversial literature has emerged relating anniversaries and culturally significant dates with heightened cardiac mortality. Phillips and colleagues have argued that mortality is raised around Christmas and New Year, (Phillips et al., 2004) in the week following Passover among Jewish Americans, (Phillips et al., 1988) and on the 4th of the month (a superstitious date) among Chinese and Japanese Americans (Phillips et al., 2001). In the same vein, another study showed increases in cardiovascular mortality at the turn of the millennium (Poole et al., 2005). The reliability of these effects has been doubted, and it has been suggested that they may depend on the comparison periods used (Smith, 2002). It is also questionable whether these effects are driven by emotional responses, since other factors such as overeating, binge drinking, exposure to particulate

matter from domestic fireplaces, difficulties in obtaining medical assistance, and hospital staffing issues during holiday periods may contribute (Kloner et al., 2006).

1.2.3.5 Sporting events

Major sporting events can be very stressful for enthusiasts and supporters. An important match in the 1996 European soccer championship between France and the Netherlands resulted in a draw, and so proceeded to a penalty shoot out (sudden death) which the French won. Cardiovascular mortality during this exciting and much watched event was analysed in the complete Dutch population aged 45 or more (Witte et al., 2000). There was a relative risk of death from acute MI or stroke of 1.51 (95% C.I 1.08 - 2.09) on the day of the match for men compared with the five days on either side, with no effect on women. No such effect was observed among French men (Toubiana et al., 2001). A pattern of increased hospital admissions for acute MI in England on the day of the country's 1998 World Cup match against Argentina has also been described; this match again involved a penalty shoot out, and England lost (Carroll et al., 2002). Another study from the Netherlands failed to observe any increase in ACS on the days of other international matches (Brunekreef et al., 2002), while a more recent study of football matches played by teams from the North-East of England over a 5 year period demonstrated a small increase in deaths from acute MI and stroke in men on the days on which these teams lost (Kirkup et al., 2003). Two reports from French-speaking provinces of Switzerland showed higher rates of cardiac arrest and sudden cardiac death (SCD) during the 1998 World Cup compared with the periods immediately before and afterwards (Katz et al., 2005; Katz et al., 2006). The circumstances surrounding these deaths are not known, and it is possible that physical exertion, emotional stress, and alcohol consumption all contributed to triggering.

1.2.3.6 Problems of interpretation

The evidence from population studies of emotional triggering is mixed, but this is perhaps not surprising, since data are generally derived from opportunistic retrospective investigations of difficult circumstances in which the health services had more immediate priorities such as treating injuries. Definitions of ACS, the time frames of studies, and the selection of comparison conditions have also varied widely. Very few negative or null associations between stressful events and ACS have been published, suggesting that there may be bias towards publication of positive effects. More fundamentally, it is difficult in many cases to rule out alternative explanations of associations between disasters or traumatic incidents and ACS onset. These include concomitant behaviours such as vigorous physical exertion (escaping from disaster zones) or heavy eating and drinking (sporting events and festivals), exposure to toxins and pollutants (industrial disasters, war settings), and disruption of primary care and emergency services which might otherwise have prevented acute cardiac events. Nonetheless, the evidence is generally supporting of a positive relationship between exposure to population-level traumatic events and heightened rates of ACS and SCD.

1.2.4. Individual emotional experiences

Early research involved collating reports from patients soon after hospital admission. The incidence of *emotional* triggers varies widely between studies. For example, the Multicenter Investigation of Limitation of Infarct Size (MILIS) study involved 849 acute MI patients interviewed within 18 hours of symptom onset, of whom 18% reported emotional upset (Tofler et al., 1990). The pilot stage of the Triggers and Mechanisms of Myocardial Infarction (TRIMM) study included 224 acute MI patients, 35% of whom reported either emotional upset or stress within the preceding 24 hours

(Willich et al., 1991). By contrast, just 2% of the 1,114 patients in the Secondary Prevention Reinfarction Israeli Nifedipine (SPRINT) study reported mental stress as a possible trigger of MI (Behar et al., 1993). Combining results from a number of studies, Čulić et al. (2005) concluded that 6.8% of patients report emotional stress preceding the onset of MI.

There are two major difficulties with studies that simply enquire about the occurrence of triggers. First, patients' reports may be influenced by their attempts to make sense of their predicament. Patients and their families develop causal models of heart disease, with stress featuring prominently (French et al., 2001). These views will affect responses to enquiries about the triggering period. Second, control groups or control time periods are not tested. Emotional stress may occur frequently in patients' lives, and its association with ACS onset may be coincidental. Case-control methods can be used, but there are problems in identifying appropriate control groups (Maclure et al., 2000). General population comparisons have the limitation that healthy individuals are most likely to participate, leading to a healthy volunteer bias, and that controls are less likely to agree to be assessed on a stressful day. Data from individuals hospitalised for other health problems can be used, but will be affected by whatever caused their medical condition

The investigators in the Determinants of Myocardial Infarction Onset Study (Onset) have developed the case-crossover design, in which the critical time periods are compared with control times on a within-subject basis (Maclure et al., 2000; Maclure et al., 1991). This method involves questioning patients about possible triggers during the hazard period, and then in control periods. For example, an ACS patient might be questioned about emotional stress in the one hour preceding symptom onset, and also about the corresponding one hour that occurred 24 hours earlier (pair-matched interval

approach), or another time period such as the last week or the previous 12 months (usual frequency method). If a patient is habitually emotionally stressed, then he or she will report stress for both times. By comparing hazard and control periods, the relative risk that an episode of emotional stress is followed by an ACS can be computed. Most of the results described in later sections have used this method.

1.2.4.1. Anger

Studies of triggers based on interviews allow patients' emotional experiences to be defined in some detail. These analyses have identified anger as a possible trigger of ACS. The Onset study interviewed 1623 patients, 39 of whom reported being very angry or furious in the 2 hours prior to acute MI (an incidence of 2.4%) (Mittleman et al., 1995). The odds of ACS onset following acute anger relative to no anger in the pair-matched analysis were 4.0 (C.I. 1.9 - 9.4). This effect was independent of age, sex, cardiovascular risk factors, and the use of beta-blockers, although aspirin had a protective effect. Interestingly, the risk of anger triggering was inversely related to socio-economic status, so was more common in patients with little formal education. Anger was also assessed as a potential trigger in the Stockholm Heart Epidemiology Program (SHEEP). The absolute incidence of intense anger in the hour preceding onset was 1.2% (Moller et al., 1999), with a relative risk (compared with usual levels of anger) of 9.0 (C.I. 4.4 - 18.2).

Strike et al. (2006) tested the role of anger as a trigger not only of acute MI but of other forms of ACS in a cohort of 295 patients selected for their ability to recall the onset of symptoms, and excluding individuals with co-morbid conditions that might have affected mood and emotion. Episodes of anger, including arguments with neighbours, anger during commuting, and family conflict, were reported by 17.4%. The odds ratio

for onset of ACS after anger compared with no anger in the pair-matched analysis was 2.06 (C.I. 1.12 - 3.92). Anger triggering was again more common in socio-economically deprived patients, similar to the findings from the Onset study. Anger triggering was not related to cardiovascular risk factors, having a previous MI, or to the presence of premonitory symptoms, but was more common in patients admitted with ST elevation MI compared with non-ST elevation MI or unstable angina. A case-crossover study of patients who had suffered an ischaemic stroke also showed an association with anger in the two hours preceding symptoms (odds ratio 14.0, C.I. 2.8 - 253.6) (Moller et al., 2005).

1.2.4.2. Acute stress

The role of work stressors as acute triggers has been studied in a Swedish patient cohort (Moller et al., 2005). Using case cross over methods, it was found that work stressors such as having high pressure deadlines in the previous 24 hours were associated with substantial increases in risk (odds ratio 6.0, C.I. 1.8 - 20.4), in comparison with the period 24-48 hours before the MI. This finding is significant in view of the evidence that high job demands, either alone or in conjunction with low control, predict future CAD (Moller et al., 2005).

Other researchers have assessed general emotional distress. For instance, emotional upset was reported by 4.4% of patients in the 24 hours prior to onset in the TRIMM study, with a relative risk in a case-control analysis of 2.7 (C.I. 1.1 - 6.6) (Willich et al., 1993). Commuting stress resulting from exposure to heavy traffic has been evaluated in Augsburg, Germany (Peters et al., 2004). The odds of MI following exposure to traffic in the hour before onset of symptoms were 2.92 (C.I. 2.22 - 3.83).

1.2.4.3. Acute depression

Depression has not been widely studied as an acute triggering of ACS, although it is relevant both to the long term development of CAD and to prognosis following cardiac events (Nicholson et al., 2006). In a study by Steptoe et al. (2006), the occurrence of episodes of acute depressed mood prior to ACS symptom onset was examined. Discrete episodes of depression or sadness were reported by 18.2% of patients in the two hours before symptom onset. The odds of ACS following depressed mood were 2.50 (C.I. 1.05 - 6.56) in the case-crossover analysis. When analyses were limited to severely depressed mood, the odds were greater (5.08, C.I. 1.07 - 47.0). As with anger triggering, depressed mood in the hazard period was more common in lower socio-economic patients. It was unrelated to the clinical severity of the ACS, extent of coronary artery stenosis, or to a history of depression.

1.2.5. Methodological issues

The use of case-control and case-crossover designs has facilitated more valid conclusions to be drawn about emotional triggers, since these methods overcome many of the biases present in studying acute causes. Nevertheless, a cautious attitude to interpretation is still necessary.

The case crossover method involves questioning patients about possible triggers during the hazard period, and then in control periods. For example, an ACS patient might be questioned about emotional stress in the one hour preceding symptom onset, and about the corresponding one hour before the hour surrounding symptom onset and the hour after (pair-matched interval approach). An alternative approach can also be used in which another time is used such as the last week or the previous 12 months (usual frequency method). If a patient is habitually emotionally stressed, then he or she will report stress for both times. By comparing hazard and control periods, the relative

risk that an episode of emotional stress is followed by an ischaemic episode (characterised by ST depression on ECG or associated arrhythmia or change in heart rate or heart rate variability) can be computed. This method has several advantages in the analysis of transient events, since self-matching eliminates selection and individual reporting biases. Any differences in chronic cardiovascular risk profile between cases and controls are also eliminated, reducing the risk of residual confounding.

However, neither the case-crossover nor case-control designs involving hospitalised patients can completely eliminate reporting biases. Even though the same individuals provide information for hazard and control periods in the case-crossover design, ACS patients may emphasize emotional triggers in the presymptomatic period, as they develop their cognitive representation of the cardiac event (French et al., 2001). One method of addressing this issue is to seek verification of the patient's behaviour or emotional state from bystanders or relatives who witnessed the scene. To date, data have been derived almost completely from patients themselves.

In the case-crossover design, the control period is more distant in time than the hazard period, and may lack the salience of the hours preceding symptom onset. Memory for these control periods, even for a pair-matched period 24 hours earlier, may not therefore be as accurate as for the hazard period. This can result in an overestimation of relative risk. However, an analysis of patients with Ménière's disease involving repeated measures of stress showed that memory decay did not influence classification of exposure to triggers (Moller et al., 2004).

Another important issue is whether emotional triggers precede acute symptoms, or whether the patient experienced premonitory signs. The presence of premonitory symptoms may influence the hypothesised causal chain. For example, there are rapid increases in inflammatory markers such as IL-6 and C-reactive protein at the early stages

of ACS (Libby et al., 2002). Inflammation can induce acute negative emotional states, even when the inflammatory stimulus is relatively mild (Strike et al., 2004). Hence, it is conceivable some emotional "triggers" are actually secondary to the early stages of plaque disruption.

In summary, it remains unknown whether the initial experience of cardiac pain *then* triggers the ECG changes and subsequent emotional response or whether it is emotion itself that causes the cardiac symptoms and then the ECG changes. Closer examination of the mood and cardiac physiological changes surrounding the ischaemic episodes may elucidate this process.

1.2.6. Summary

To conclude, a range of studies suggests that behavioural and psychological stimuli may act as triggers of acute MI. There is less known about the physiological effects of emotional stresses and strains of everyday life that may affect moment to moment mood in susceptible individuals, which could contribute to the development of CAD, both acutely, and in the long term. The SIS study addresses this particular issue and the method of the study is described in chapter 4 with the results presented in chapters 5, 6 7 and 8.

1.3 Long term psychosocial adaptation and quality of life after ACS

1.3.1 Introduction

This chapter so far has described the various psychosocial factors that are thought to influence cardiovascular disease development, and some of the literature concerning psychosocial factors in the triggering of acute cardiac events. An additional issue is long term adaptation in survivors of acute cardiac events. This is important both for the patient and family. A crucial finding is that adaptation and later quality of life are not solely determined by clinical disease severity and treatment, but are also influenced by psychosocial factors.

The mortality rate for MI patients is relatively high during the first month, after which it levels off. This is related to a number of clinical factors such as myocardial contractility (Peterson et al., 1997), and presence of angina or arrhythmia (Bigger et al., 1994). The 1 year cardiac mortality rate is 18% for persons over the age of 75 years and increases with age (Aronow et al., 1998). Long term prognosis is also dependent on pre infarct cardiac risk factors such as diabetes (Sprafka et al., 1991). However, in addition to clinical factors, several psychosocial factors have been implicated in prognosis to CAD (Hemingway & Marmot, 1999).

Over the last decade, there have been significant advances in early recognition of MI and in medical treatment, and these have reduced early death, cardiac complications and recurrent episodes of disease. Reducing patient cardiac mortality has meant there is a growing recognition of the importance of outcomes following a myocardial infarction, such as physical symptoms, emotional distress and functional status (i.e. return to work).

The needs of people recovering after an acute cardiac event vary, with some having psychological problems and others needing risk factor management or lifestyle changes. In particular, a high degree of emotional distress may be seen whilst in the hospital coronary care unit (Cay et al.,1972), during early convalescence (under 3 months post MI) (Wiklund et al., 1984) and at follow up 1 year post MI (Mayou et al., 1978; Wiklund et al., 1984). Anxiety and depression post MI are still very common, have been associated with reinfarction and death, after adjustment for other cardiac risk factors (Laerum et al., 1988; Barefoot et al., 1999; Frasure-Smith et al., 1993, 1995), and are predictors of return to normal activity (Maeland et al., 1989). There is also more limited evidence that initial emotional distress at the time can predict outcomes for other aspects of quality of life (Petrie et al., 1996), lifestyle changes (Billing et al., 1997) and medication adherence (Maeland et al., 1989). Many patients post MI avoid physical activity (Wiklund et al., 1984) and a substantial number retire early or become unemployed (Mayou, 1979), with reduced social activities as a consequence as well.

There are a number of psychosocial influences (especially depression and anxiety that often co exists) on adaptation and prognosis in CAD, in various longitudinal, community based, prospective studies on cardiac patients, in terms of quality of life and well being, as well as the harder end points of cardiac mortality and morbidity. In my thesis, I am exploring both the psychosocial factors that may influence early development of CAD, and which physical or psychological factors at the time of an acute event may predict later adaptation to established CAD.

1.3.2 Health related quality of life and psychosocial factors in cardiac patients

Health related quality of life (HRQL) is broadly defined by the impact of the disease and medical treatment on the patients overall functioning and well being (Gill et al., 1994). Health related quality of life measures are derived from questionnaires that

elicit from patients, the impact of their condition on their functioning, symptoms and quality of life. The World Health Organisation (Soc Sci Med. 1995) describes quality of life as 'an individual perception of their position in life, in the context of the culture and value systems in which they live and in relation to their goals, expectations, standards, and concerns'. It is a multidimensional global construct with three main domains: physical, physiological and well being. Several general and disease specific instruments, for example the SF36 questionnaire, have been developed to assess different aspects of health related quality of life in coronary patients with physical and mental health being their main components (Brown et al., 1989).

Differences in quality of life have been observed in presence of cardiovascular risk factors or clinical manifestations of disease (Rawles et al., 1992). Specifically, studies have shown that presence of angina, shortness of breath, congestive heart failure and consequent dysrythmias, co-morbidities, having a previous MI, surgery and revascularisation appear to be highlighted as predictors of poorer quality of life in follow up periods ranging from 3 months to 5 years (Failde et al., 2006; Nash et al., 1999; Wiklund et al., 1989; Heller et al., 1997; Brown et al., 1999). Many of the studies analysing predictors of poorer quality of life post MI have found physical functioning to be greatest affected in patients who have had an MI compared to those who have not (Van Jaarsveld et al., 2001; Mendes de Leon et al., 1996; Failde et al., 2006).

In the clinical management of post MI patients, the focus on adaptation is often on the optimal physical functioning of the patient, but in the long term adaptation to CAD, optimising general health, vitality, social functioning and emotional functioning is just as important (Brown et al., 1999). Increasingly, health related quality of life outcomes are now used as end points in randomised clinical trials of MI patients to evaluate the efficacy of medical or surgical treatments or post MI care (Strauss et al.,

1995). Finally, identification at the time of hospital admission of predictors of impaired quality of life would allow appropriate risk stratification on discharge for the clinician.

There have been several studies on the impact of MI on quality of life outcomes. These studies differed from each other by measuring particular dimensions of quality of life, focusing only on a single aspect of quality of life, i.e. physical function, social function, mental health scores (Wiklund et al., 1984, King et al., 1993), although recent studies have used composite measures of quality of life (Lim et al., 1993). Previous studies have had limitations in that they were cross-sectional in design (Medical Outcomes Study, Wiklund et al., 1989) or limited to selected patients enrolled in trials focussing on treatment or cardiac rehabilitation effects (Mayou et al., 1991; Beck et al., 2001) rather than on longitudinal community based samples. Additionally, very few studies have been carried out that evaluated baseline characteristics of the patients, or reported adequate clinical and non clinical data on relevant patients' characteristics (Heller et al., 1997) that could be associated with impairment or improvement of quality of life post MI.

Much of the literature has tried to identify the key clinical, demographic, and psychological characteristics of patients associated with changes in health-related quality of life following discharge after MI. Brown et al. (1999) carried out a cohort study on post MI patients over 4 years and compared them to community controls, to determine what factors were associated with a poor quality of life. The eight SF36 quality of life domain and overall scores were the main outcome measures. Results found that compared to age and sex matched controls, patients aged under 65 years showed impairment in all eight domains, the largest differences being in physical functioning (mean difference 20 points) and general health (mean difference 19 points). Multiple regression analysis revealed that impaired quality of life was closely associated with

inability to return to work through ill health, a need for coronary revascularisation, the use of anxiolytic medication, and a variety of clinical symptoms. The greatest impact on quality of life is seen in patients of working age. Impaired quality of life was reported by patients unfit for work, those with angina and dyspnoea, patients with coexistent lung disease, and those with anxiety and sleep disturbances. Similarly, Brink et al. (2005) found lower scores of quality of life for both physical and mental scores 5 months after MI. In contrast, Beck et al. (2001) analysed predictors of quality of life at 6 months and 1 year after an acute MI, in a prospective cohort study of 587 patients, and concluded that whilst age and psychosocial characteristics were associated with predictors of quality of life after MI, other clinical treatments or clinical characteristics had no effect. Although mean scores were slightly lower at 6 months than at the baseline, they did not actually change over the time course of follow up.

The follow up period over which the changes in quality of life are measured is also relevant, as are the distinct dimensions being measured. In the population based prospective study conducted by Mendes de Leon et al. (1998), which investigated changes in health-related quality of life outcomes following a MI from a population-based perspective. 2812 patients older than 65 years were followed up between 1982 and 1988. It was found that changes in quality of life were more significant in those who had a recent MI (under a year) compared to those whose MI had occurred more than a year before. In bivariate analysis, physical functioning declined more in MI patients than in the non MI group (26.4% vs. 11.9%, $p = 0.001$) as did social functioning (31.4% vs. 20.8%, $p = 0.06$). The effect of MI on both physical and social functioning was shown to be much stronger among the patients who had a recent MI (<1 year ago), than those whose MI had occurred more than a year before post MI assessment. Similarly, the study of 539 post MI patients by Wiklund et al. (1989) showed that quality of life scores were more favourable in participants at 5 years than at 1 year. At 5 years, there were

smaller impairments in the domains of energy, sleep, and mobility when compared with normative data. However, the patients in the study were originally selected for a beta blocker trial and therefore represented a selected population.

The effect of socio-demographic variables on quality of life in cardiac patients has been described by several authors, who have shown that women and patients of lower socio-economic status have poorer quality of life (Hemingway et al., 1997, Van Jaarsveld et al., 2002). Women showed a significantly lower quality of life compared to men, in a study by Emery et al. (2004), in which 536 cardiac patients (36% women) were followed up at 12 months. Heller et al. (1997) followed up 424 patients discharged from hospital after an MI or angina episodes for 6 months, and again found that poorer quality of life scores were predicted by sex and age. Age is another important predictor of quality of life (Beck et al., 2001; Nash et al., 1999). A more recent study by Failde et al. (2006) found that for each year of age increase, the physical function score (PCS) decreases by 0.2 points. This may be due to younger patients being treated more aggressively in hospital or having greater dissatisfaction with perceived disabilities. In the study by Brown et al. (1999), those aged under 65 years experienced a worse quality of life at 4 years follow up, than those of similar age who had no infarct. However, this difference was not seen in the over 65 year age group, perhaps due to lower expectations or due to existing co morbidities with advancing age. The importance of social support in predicting poorer prognosis post MI is supported in many studies (Ruberman et al., 1984; Case et al., 1992; Jenkinson et al., 1993; Welin et al., 2000; Emery et al., 2004). Employment and marital status as well as lifestyle factors such as smoking have also been shown to predictor poorer quality of life measures (Heller et al., 1997; Brown et al., 1998; Dias et al., 2005).

Considering the effect of psychological factors on quality of life, it has been shown that depression has an adverse effect on angina and quality of life. Studies of these relationships are more firmly established than the studies of effects that depression has on CAD mortality. Depression is associated with increased re-hospitalisation, more re-infarction, more angina, emotional instability, social impairment, delayed return to work and impaired quality of life (Cay et al., 1973; Wiklund et al., 1984; Maeland et al., 1987). In addition, even minor elevations in depressive symptoms significantly impair quality of life and may increase the risk of CAD in healthy people, let alone those with advanced cardiac disease (Davidson et al., 2004). Depression also predicts physical inactivity in post MI patients. Allan et al. (2007) conducted a study on 502 patients post MI assessing their level of depression, perceived behavioural control and exercise activity just prior to hospital discharge and followed up these patients at 12 months assessing the same factors. Results showed that depression and perceived behavioural control independently predicted fitness ($p < 0.005$) and regular exercise activity ($p < 0.005$) at 12 months, independent of age, gender, socio-economic status, illness severity and reported activity prior to hospitalisation.

Depression overlaps with other constructs. Patients who have undergone an MI exhibit both an increase in anxiety and/or depression scores, both initially after the MI and at a later date. These emotions have been shown to be related to much poorer quality of life measurements at follow up time points after the initial MI. Van Jaarsveld et al. (2001) studied 89 post MI patients and 119 heart failure patients who were selected from primary health care registers. An increase in anxiety was seen immediately after the diagnosis of MI, but at 6 months, an increase was also shown in depressive symptoms. Feelings of both anxiety and depression were higher at one year in the post MI and heart failure patients than pre morbid levels. Supporting this relation between anxiety seen after an acute cardiac event and later poorer quality of life is a study by

Wiklund et al. (1988). Wiklund et al. (1988) followed up 549 post MI patients after hospital discharge. Multivariate analysis showed that anxiety was closely associated with poorer quality of life with persistent anxiety inhibiting satisfactory resumption of daily functioning.

To conclude quality of life is an important measure of a patients' well being post MI, as advances in medical care mean that more patients are surviving the initial event to a greater age. Psychological disability is sometimes as great a barrier as physical impairment in the recovery from a physical illness.

1.3.3 Depression and prognosis in cardiac patients

Depression is disproportionately prevalent amongst cardiac patients, with much evidence to suggest that major depression occurs in about 15% of patients following an acute MI and minor depression in a further 20 % (Lett et al., 2004; Barefoot et al., 1997; Carney et al., 1997; Rozanski et al., 1999). This section outlines the evidence that depression and often co-existing anxiety states are related to CAD prognosis in terms mortality and morbidity.

Longitudinal prospective studies have been carried out in several populations, such as patients recovering from an MI, those with stable CAD and those awaiting surgery. A variety of measurements of depression have been used including the Beck Depression Inventory (BDI), the Zung self-report scale and the Centre for Epidemiological Studies Depression (CES-D) questionnaire. Some studies used clinical interview for assessment of depression. Additionally a variety of follow up time periods were used.

The majority of studies report that the presence of depression conferred 2.5 times the risk for mortality or non fatal cardiac events. In some studies, depression post MI

was associated with a three to four fold increase in risk of cardiac mortality, and this risk was not limited to major depression (Frasure-Smith et al., 1993, 1995; Ahern et al., 1990). These studies have also shown that the prognostic impact of depression is independent of other major prognostic factors, for example, severity of coronary atherosclerosis. In addition to the mortality risk associated with post MI depression, increased health care costs associated with readmission amongst depressed patients were also observed (Frasure-Smith et al., 2000). In the study by Frasure-Smith et al. (1999), 896 patients post MI were followed up, and at one year it was shown that elevated depressive symptoms, (as measured by the BDI), predicted cardiac mortality after controlling for other predictors of mortality. The impact of major depression appears to be as important as left ventricular dysfunction or a history of previous CAD (Frasure-Smith et al., 1993), and is a significant predictor of 1 year mortality in women as well as men, independent of other post MI risks (Frasure-Smith et al., 1999).

Similar results for the effect of depression on mortality were shown by Carney et al. (2003), when 358 depressed patients post MI from the ENRICHD clinical trial study were compared to 408 non-depressed controls in terms of prognosis. Six months post MI, it was found was that the depressed patients had more than twice the risk for all cause mortality. In a longer term study, Barefoot et al. (1996) followed up 1250 patients who had underwent diagnostic coronary angiography for 19.4 years, and showed that those with moderate to severe depression were at 69% greater risk for cardiac death and 78% greater risk for all cause death.

The findings of these studies contrasts with the study by Lane et al. (2000, 2001, 2002) which followed up 288 post MI patients and found that depression was unrelated to cardiac or all cause mortality at 4 months, 1 year and 3 year follow up. However, the discrepancy may be due to the small sample size or inadequate assessment of depression

in this study. Jenkinson et al. (1993) followed 1376 patients post MI for 3 years and reported no association between depression at the time of hospitalisation and all cause mortality. Although here the sample size was larger, one limitation is that depression was assessed using a non validated scale with only three items for depression. A higher prevalence of arrhythmia during ambulatory monitoring has been found amongst depressed CAD patients than in non-depressed CAD patients, which may partly explain the increased risk for cardiac mortality in depressed CAD patients (Carney et al., 1993).

There have also been studies assessing the association between depression and recurrent or new cardiac events, and not just all cause or cardiac mortality as a clinical outcome. Studies of patients with stable CAD have reported significant associations between depression and clinical outcomes. Carney et al. (1988) followed 52 patients post catheterisation over one year and found that those with major depression had more than twice the risk of having a cardiac event, after controlling for other risk factors.

There have been a number of studies comparing symptoms of both anxiety and depression as predictors of cardiac events and increased health care consumption post MI. In the study reported by Strik et al. (2003), both depression and anxiety predicted subsequent cardiac events but in multivariate analysis that tested both anxiety and depression and hostility, *only anxiety* was shown to be an independent predictor of cardiac events. In the literature, studies of anxiety and depression that predict clinical prognosis post MI have controlled for disease severity (Denollet et al., 1998). Other prognostic studies have shown that the clinical disease severity at follow up correlates with the level of depression or anxiety of the individual after controlling for confounders (Frasure-Smith 1995, 1999). Lesperance et al. (2002) showed that patients post MI had increased mortality rates as a function of the degree of depressive symptoms at one and five years after the MI. In the study by Denollet et al. (1998) a positive association was

shown between symptoms of anxiety and increased mortality post MI, whilst two other studies did not show this effect (Lane et al., 2001, 2002 and Mayou et al., 2000). Frasure-Smith et al. (1995) showed in a multivariate analysis of 222 patients with a previous MI, that depressive symptoms, anxiety and a major history of depression had an impact on outcome independent of each other. Specifically, an association between anxiety and recurrent cardiac events was seen but not between anxiety and mortality. Frasure-Smith and Lesperance et al. (2003) compared the effect of depression, anxiety, anger, stress, social support and self-reported health in prediction of mortality post MI, and only negative affect came out as uniquely predicting poorer outcomes.

Overall, findings from various studies are mixed. In populations with known CAD, there are several studies showing significant relations between depression and cardiac morbidity and mortality (Mendes de Leon, 1998, Welin et al., 2000; Lesperance et al., 2002; Sirois & Burg, 2003). However, there are also several studies showing no relation whatsoever between depression and CAD (Vogt et al., 1994; Wiklund et al., 1988; Legault et al., 1992; Irvine et al., 1999; Lane et al., 2000, 2001; Mayou et al., 2000). It may be that these prognostic studies which have negative findings do so because they have small sample sizes, low participation rates and/or short follow up intervals, which reduce the possibility of detecting effects, as noted by Carney and Freedland (2003).

However, the positive results found in prognostic studies may well have been because adjustments for confounding risk factors (e.g., disease severity) may not have been comprehensive, or the diagnosis of depression may have been confounded by the patients actual medical condition (Carney & Freedland, 2003). Another limitation in the literature is that majority of studies have not included racial or ethnic minorities.

Intervention trials examining the effects treating depression in cardiac patients with cognitive-behavioural therapy or pharmacotherapy, have not shown marked effects on coronary morbidity to date (Glassman et al., 2002; Mendes de Leon et al., 2006). But the strength of evidence relating depression to morbidity and quality of life, warrants continued research on understanding mediating mechanisms.

The evidence suggests that one has to keep an open mind on the causal link between anxiety and depression and subsequent cardiac morbidity and mortality post MI and although hard clinical end points are considered in assessing this link, new outcome measures such as quality of life have an increasingly importantly significant role in today's increasingly elderly population.

1.4 Studies described in this thesis

The broad aim of this thesis is to investigate the role of psychological factors in the development of CAD both acutely in everyday life in patients with suspected coronary artery disease as well as in the long term adaptation following ACS. My thesis presents three studies concerned with psychosocial factors in patients with suspected and advanced heart disease, focusing particularly on the role of negative emotions in vulnerability to myocardial ischaemia in daily life, the influence of acute emotional triggers of ACS on long term quality of life, and the effect of depression following ACS.

The largest study described in this thesis, called the Silent Ischaemia Study (SIS), evaluated the influence of emotional factors on cardiac health in daily life. Chapter 2 will review the literature on the physiological mechanisms proposed to account for the associations between psychosocial factors described in this chapter and CAD development and prognosis, in terms of transient myocardial ischaemia, autonomic and

neuroendocrine function. It is based on the propositions that transient ischaemic episodes, altered heart rate variability or an altered diurnal cortisol profile during everyday life can be induced by emotional stress, and that they are damaging because of their association with prothrombotic and inflammatory processes. Chapter 3 will discusses a number of methodological issues relevant to the SIS study, and the measurement of emotional experience and physiological function in everyday life of patients with CAD. In the light of the importance of depression in CAD development (summarised in Chapter 1.1.3), and its possible influences on the autonomic nervous system and neuroendocrine function, I have also analysed heart rate variability (HRV) and cortisol profile in relation to depressed mood

The method of the Silent Ischaemia Study is described in Chapter 4. The relationships between depression, mood in everyday life, and autonomic and neuroendocrine function, are described in chapter 5 and 6, while the psychophysiological correlates of acute ischaemic episodes are detailed in chapter 7. Chapter 8 describes the results of a 6 month follow up of this clinical sample, to assess progression in disease and functional recovery and to discover whether emotional and psychophysiological factors predict clinical outcomes and changes in health-related quality of life over this period.

The SIS study examined emotional and clinical factors at an *early* stage of CAD in which the patients were having cardiac symptoms and positive cardiac tests but had not actually had an ACS event yet. The second and third studies presented in my thesis explore the role of psychological experience in long term adaptation following ACS. Data were derived from the ACCENT (Acute Coronary Syndrome, Emotion and Triggers) study, an investigation carried out by the Psychobiology Group at UCL between 2002 and 2005. I was involved in collecting data, 12 and 36 months after the

patients in this study were initially hospitalised with an ACS. The focus of the analyses in chapters 9 and 10, is on the early emotional predictors of long term functional recovery, and quality of life following a cardiac event. Two issues are addressed: emotional predictors of return to work at one year after ACS, and the relationship between the acute emotional and physical triggers implicated in the ACS event and long term psychological and physical adaptation. The thesis concludes with chapter 11 which discusses the findings from all three studies in how mood may relate to CAD development and adaptation long term via psychobiological processes and what these new findings add to the existing literature. In addition, limitations of the current research and proposals of potential further work are discussed to add to the body of research.

Chapter 2: Mechanisms underlying the association between psychological states and CAD

2.1 Introduction

The literature presented in Chapter 1.3 strongly supports a relationship between mental stressors (such as negative affect) and CAD (both the development of CAD and the prognosis after CAD). This raises the question of what are the biological mechanisms through which negative emotions such as depression, anxiety, and anger/hostility exert their influence on CAD outcomes such as transient myocardial ischaemia (TMI), arrhythmias, angina, myocardial infarction (MI) or death from cardiovascular disease.

TMI is thought to be the one of the final pathophysiological effects of a variety of physiological responses. These include the activation of the autonomic nervous system (ANS), the hypothalamic – pituitary - axis (HPA), and a variety of other inter-related biological mediators that are activated by acute or more chronic emotional and physical stressors in daily life. TMI itself may act as a precursor for fatal cardiac arrhythmias, myocardial infarction and death. Figure 2.1 is adapted from Brotman et al. (2007), and illustrates the stress response as it relates to CAD. It highlights the psychobiological processes underlying the link between emotion and CAD that will be explored in this thesis.

The purpose of this chapter is to review the evidence for transient ischaemia in everyday life and in the laboratory, its clinical significance, and the influence of psychological states in daily life activity on TMI and the various biological mechanisms

that may be relevant. In particular, I will discuss the relationship between heart rate variability and cortisol profile and negative emotions in daily life.

2.2 The physiological response to stress and its effects on the cardiovascular system

Homeostasis is the feedback mechanism that maintains constant internal conditions in the face of environmental changes. There are three main stages of the stress response: first, there is an alarm reaction where the body responds to stress; second, there is resistance when the body attempts to restore itself to a steady level; and third, if the stress continues, exhaustion occurs, with the risk of a stress related disorder (Stansfeld et al., 2002). Allostasis refers to the process by which the body responds to, and maintains homeostasis during daily life challenges (Sterling et al., 1988). If a normal stress response occurs frequently, is not limited or the individual does not adapt to a repeated stressor, adverse metabolic consequences ensue including the development of CAD. 'Allostatic load' refers to the repetitive or continuous build up of stressors or stress response.

Although glucocorticoids and catecholamines are the two main hormones of the 'flight or fight' response activated by the HPA system, there are many other mediators including the autonomic nervous system and pro and anti-inflammatory cytokines (McEwen et al., 2008; Brotman et al., 2007).

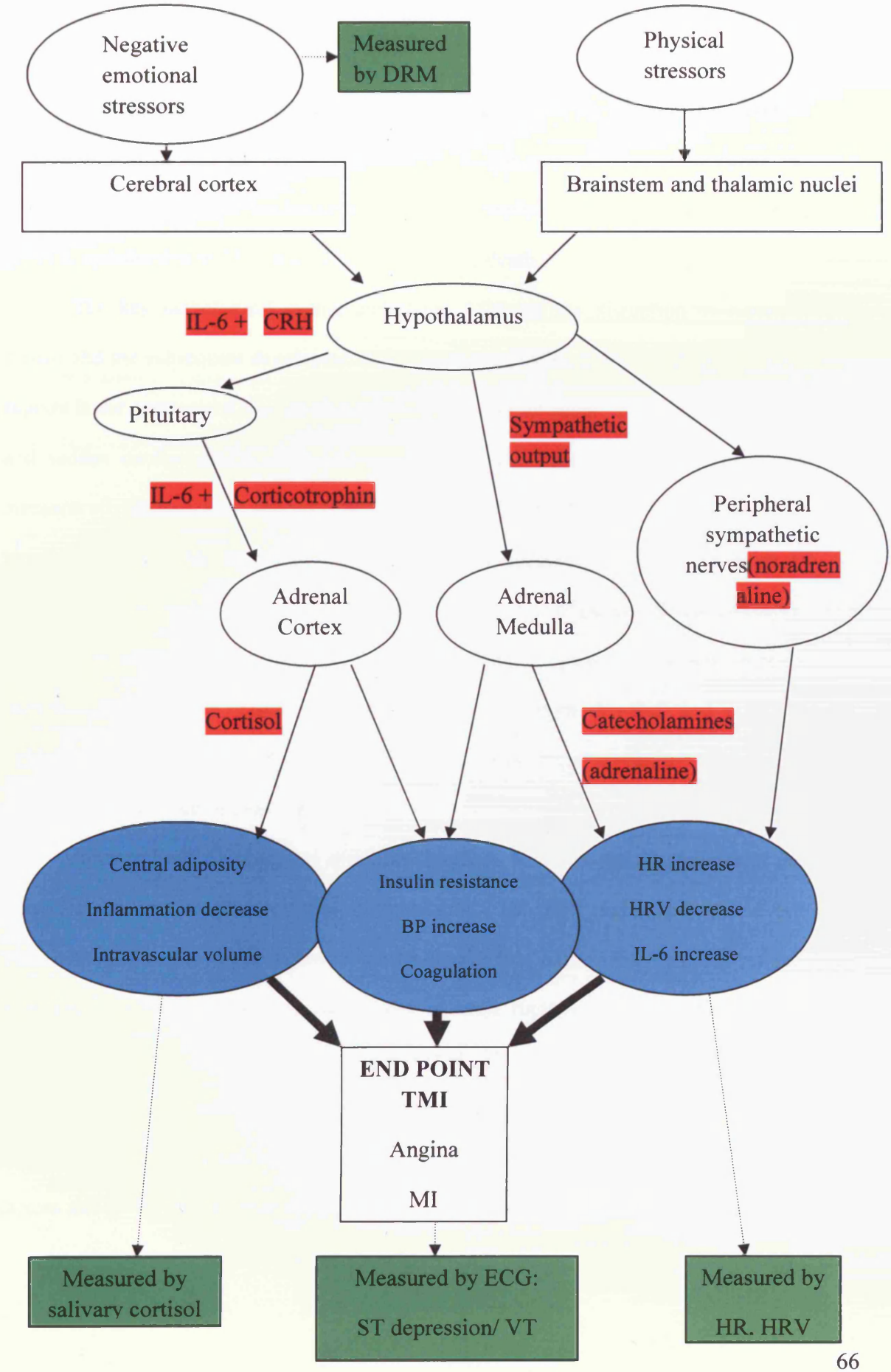
The main system that brings about activation of the stress response resides in the hypothalamus and brainstem (Tsigos et al., 2002). Afferents to the hypothalamus and pituitary gland that modulate the stress response come from many sources, including the

locus coeruleus and other noradrenaline-releasing brainstem nuclei, cortical input from sensory and daily life emotional (either positive or negative) triggers and inflammatory cytokines. The HPA is activated by corticotrophin-releasing hormone (CRH) from the hypothalamus, which prompts the release of corticotrophin from the pituitary, stimulating the production of glucocorticoids (cortisol) from the adrenal cortex and to a lesser extent, mineralocorticoids and adrenal androgens. Cortisol inhibits the release of gonadotrophins, growth hormone, and thyroid stimulating hormone, but importantly, in terms of cardiovascular effects, causes inhibition of inflammatory and immune responses, central redistribution of adiposity, reduced insulin sensitivity, and pressor effects (Girod & Brotman, 2004). The peripheral sympathetic nervous system, the other effector of the stress response, innervates tissues throughout the body, especially the heart, blood vessels, and adrenal medulla. It is the means by which the brain (and thus emotion) affects the heart and other body organs in response to acute stress (Tsigos et al., 2002). The adrenal medulla responds with systemic catecholamine release (adrenaline), whereas the sympathetic nerve terminals in the blood vessels predominantly release noradrenaline into the circulation. The sympathetic nervous system has not only direct cardiostimulatory effects (increases the rate and force of contraction of the heart via beta-1-adrenergic receptors) and pressor (blood pressure) effects (via alpha-1-adrenergic receptors), but also has metabolic effects (insulin resistance and lipolysis) and varied immunological effects (Goebel et al., 2000).

Thus, there are varied effects of both the HPA and the SNS on both the vasculature and metabolism. Both systems can increase blood pressure (BP), decrease insulin sensitivity, activate homeostasis and precipitate endothelial dysfunction - an early manifestation of atherosclerosis (Girod & Brotman, 2004; Curtis et al., 2002; Von Kanel & Dimsdale, 2000; Brotman et al., 2005). The physiological effects of mental stress on the heart are rapid (Bacon et al., 2006; Ghiadoni et al., 2000) and so the association of

daytime stresses and strains in daily life with transient myocardial ischaemia is likely to be seen in patients with stable coronary lesions (Gullette et al., 1997). The atherosclerotic process is influenced by the cross interactions between the hypothalamic-pituitary-adrenal axis, the sympathetic nervous system, and inflammatory mediators. This is further described in section 2.2.

Figure 2.1 Cardiovascular effects of stress and its measurement



2.3 Summary of the pathophysiological processes underlying acute triggering of ischaemia

In chapter 1, I described the literature relating to acute triggering of ACS both in population studies and studies of individuals. In this section, I will summarise the underlying interconnected mechanisms, which can potentially lead to the acute triggering of ACS, culminating in TMI, angina, a MI or cardiac death.

The key pathological events underlying ACS are the disruption of coronary plaque and the subsequent development of a thrombus (Tofler & Muller, 2006). Plaque rupture is the commonest type of disruption, accounting for some 70% of fatal acute MI and sudden cardiac deaths. Rupture occurs when the fibrous cap of the plaque is mechanically disturbed, or degraded by the action of matrix metalloproteinases released by macrophages. In other cases, injury is due to plaque erosion, as thrombus is superimposed on a plaque, which is intact except for the loss of the endothelial cell layer. Episodes of high haemodynamic shear stress may stimulate plaque disruption, so acute increases in heart rate, blood pressure, myocardial oxygen demand, and coronary vasoconstriction are all potentially important and may occur secondary to acute or chronic physical or emotional stressors.

Atherosclerotic plaques are dynamic structures in which the constituents of the lipid-rich core and the fibrous cap regularly change. The most angiographically severe lesions are not necessarily at highest risk of rupture. It is evident from histological and intravascular ultrasound imaging studies that episodic rupture is a frequent event that only occasionally results in an ACS (Naghavi et al., 2003). Two other factors therefore need to be taken into account. The first is the presence of a procoagulatory milieu. After plaque disruption, the local balance between circulating prothrombotic and thrombolytic factors will determine whether vessel occlusion takes place. The second is the presence

of a myocardium that is susceptible to ischaemia. Autonomic processes (as indexed by heart rate and heart rate variability) strongly influence outcome after plaque disruption, with sympathetic hyperactivity provoking potentially life-threatening ventricular tachyarrhythmias, while vagal activity is protective.

Physical exertion and emotional stress stimulate sympathetic nervous system activation, vagal withdrawal, pressor responses, catecholamine release, increases in circulating interleukin (IL)-6 and other inflammatory markers, together with platelet activation and prothrombotic responses (Steptoe et al., 2007). Emotional stress also induces coronary artery vasoconstriction in patients with CAD, particularly in regions of stenosis. Acute mental stress administered under controlled laboratory conditions induces transient myocardial ischaemia as defined by decreased ejection fraction, wall motion abnormalities or ST segment changes in around one third to one half of patients with CAD (Strike & Steptoe, 2003). Stress-induced haemodynamic responses, particularly increases in systemic vascular resistance, coronary artery vasoconstriction, and microvascular changes, may all contribute to transient myocardial ischaemia. These studies are discussed in detail in section 2.3.

Unfortunately, there is little direct evidence as yet, documenting the activation of pathways involved in mediating specifically emotional triggering of acute cardiac events in ACS. The emotions identified in the triggering literature certainly stimulate relevant biological responses in patients with CAD. For instance, anger recall elicits greater increases in vascular resistance in CAD patients compared with controls, (Jain et al., 1998) and vasoconstriction in stenosed vessels (Boltwood et al., 1993). Depressed mood is associated with reduced heart rate variability in patients following MI, (Carney et al., 2001) though relationships with inflammatory markers have been inconsistent (Schins et al., 2005; Lesperance et al.,2004). The only study to date that has assessed physiological responses to emotional stimuli in patients who have sustained an emotionally-triggered

cardiac event was our investigation of 34 male ACS survivors (Strike et al., 2006). 14 men had reported negative emotions (anger, stress or depression) in the two hours before symptom onset and 20 men had not. Haemodynamic variables and platelet activation were monitored in response to standardised mental stress tests. Both groups showed an increase in blood pressure in response to tasks, but the rate of post-stress recovery was slower in the trigger group. Systolic pressure remained higher at 30 minutes post-stress in the trigger than non trigger group. Additionally, the emotion trigger group showed significantly greater increases in platelet activation as indexed by monocyte-platelet aggregates; the acute response was larger, and activation persisted 30 minutes after stress in emotion trigger group. No differences were recorded in subjective distress between the groups. Patients who had experienced an emotional trigger therefore appeared to have heightened biological responsivity to emotional stimuli. If such responses coincided with plaque disruption, the result might be the development of an ACS.

2.4 Transient myocardial ischaemia

In this section, I assess the evidence for an influence of psychological factors on TMI in everyday life. The following issues were addressed:

1. How common is psychological stimulation of TMI in everyday life? What psychological states are the most common triggers? Are episodes likely to be silent or symptomatic?

2. Is psychological stimulation of TMI in everyday life more common among CAD patients with particular psychological or social characteristics such as depression or low socio-economic status?

3. What mechanisms are responsible for psychological stimulation of transient myocardial ischaemia? Are they the same mechanisms as physical exertion?

Studies that are discussed are those that examined the link between standardised mental stress tests in the laboratory and myocardial ischaemic responses and also those that additionally looked at ischaemic responses during the elicitation of emotion. Studies that examined the link between emotion in everyday life and ambulatory myocardial ischaemia (both silent and painful) are also considered.

Studies have been categorised as follows:

1. Experimental studies performed in a laboratory setting, relating psychophysiological responses to mental stress tasks with myocardial ischaemia monitored in everyday life.

2. Observational studies performed in a naturalistic setting evaluating myocardial ischaemia in everyday life.

Patients in some but not all the studies were off beta blocker medication for an average of 48 hours, calcium blockers for 24 hours and long acting nitrates for at least 6 hours. During a mental or exercise task an ischaemic response was defined on the ECG as horizontal or downsloping ST depression > 1mm or 1.5 mm upsloping below isoelectric baseline, measured at 0.08 seconds after J point and persisting for at least 60 seconds. Using radionuclide ventriculography, ischaemia was defined as new or worsening wall motion abnormality (WMA) during stress or Ejection Fraction (EF) not increasing by more than 50% (physical task) or >80 % (mental task).

2.4.1 Clinical significance of transient myocardial ischaemia (TMI)

The significance of silent and transient episodes of ischaemia has been under debate from the 1970's, in conjunction with increasing popularity of the use of ambulatory monitoring devices for clinical and research purposes. 30-35% medically treated patients with stable episodes (with evidence of fixed atherosclerotic coronary artery disease and exercise-induced ischaemia) will have such silent episodes during normal everyday life (Campbell et al., 1986). Silent ischaemia occurs more frequently than actual chest pain symptoms in patients with stable angina.

Early studies (Rocco et al., 1985; Deedwania &Carbajal, 1990), showed an increased risk of coronary events in patients with ambulatory silent ischaemia. Deedwania et al. (1990) in his study, showed that the presence of ambulatory silent ischaemia identifies a subgroup at increased risk of death with higher peak exercise heart rates (>120 beats/min) and concluded that silent ischaemia was an independent predictor of mortality. In fact, this is more recently supported in a study by Biagini et al. (2005), which looked at the long term outcome in patients with silent versus symptomatic ischaemia during dobutamine stress echo (DSE). They found that the hard event rate (cardiac death/MI) was significantly greater in patients with silent ischaemia when compared to those symptomatic on DSE, and that silent ischaemia was an important predictor of these hard events at mean follow up of 5.5 years (SD 3.3).

This contrasts with earlier studies. Mulcahy et al. (1988) assessed the significance of silent episodes of ischaemia in the absence of infarction, and the relationship with left ventricular function (LVF), as well as assessing short (1 year) and long term follow up (5 year) changes of LVF in patients with stable CAD on routine therapy with or without ECG evidence of transient ischaemia in daily life. This study concluded that in patients who do not suffer any intervening cardiac events, recurrent transient myocardial ischaemia does not result in gradual deterioration in LVF over 1-5

year period. In a larger, longer term prognostic study (Dargie et al., 1996), comparing stable CAD patients with TMI (silent or symptomatic) versus no TMI during daily life at baseline, there was no evidence of an association between the presence, frequency or total duration of ischaemic events on holter monitoring, either on or off treatment, and the hard end points of MI/death.

However, stress-induced myocardial ischaemia has been shown to predict adverse health outcomes in CAD patients (Strike & Steptoe, 2003). Sheps et al. (2002) assessed mortality over an average of 62 months following the psychophysiological testing of 196 CAD patients. All cause mortality was 16.2% in patients who had shown stress-induced transient ischaemia, compared with 6.6% in those who had not, independent of age, history of MI, baseline ejection fraction, and other clinical risk factors. However, it is not known whether these deaths were prompted by emotion-induced cardiac events or not.

2.4.2 Laboratory stress response and TMI

There is much evidence to directly show an association between mental stress-induced ischaemic changes and other haemodynamic variables in a laboratory setting, and the occurrence of ischaemic responses during daily living activities.

In a laboratory study by Krittayaphong et al. (1995), 42 men and women underwent 48 hour holter monitoring and a speech mental stressor task in the laboratory, with assessment of blood pressure (BP) and heart rate (HR) responses prior and during the test. Radionuclide ventriculography was also performed to assess ischaemic changes in the laboratory. This is one of the few studies reviewed in which 32 % patients were off medication, and the remainder continued their usual anti-anginal medication. 94% of episodes of ambulatory ischaemia were silent and there was a positive correlation

between ambulatory ischaemia and peak HR and change in HR during mental stress, but no correlation with blood pressure stress reactivity. This study concluded that HR responses during laboratory induced mental stress, together with average 24 hour heart rate, can predict the occurrence of ambulatory ischaemia.

A larger study by Blumenthal et al. (Blumenthal et al., 1995), showed that those patients who displayed mental stress induced ischaemia in the laboratory were more likely to exhibit ischaemia during daily life ($p < 0.021$), concluding that mental stress induced ischaemia (defined by new wall motion abnormalities on ventriculography) predicts daily life ischaemia, independently of exercise-induced ischaemia.

To determine further the relationship between mental stress induced myocardial ischaemia (MSIMI) in the laboratory and TMI during daily life and exercise, a database study (PIMI study) was carried by Stone et al. (1999). Results showed that 49.4 % of patients who displayed myocardial ischaemia in response to speech tasks in the laboratory also displayed ambulatory ischaemia during holter monitoring, compared with 34.9% of the remainder of patients who displayed no ischaemia in the laboratory. Additionally, the group of patients who developed ischaemia in response to mental stress showed higher cardiac ejection fraction (EF), cardiac output (CO) and lower systemic vascular resistance (SVR) during mental stress and were especially likely to exhibit daily life ischaemia. The study concluded that patients with daily life ischaemia have a heightened generalised response to mental stress, with a chronic state of sympathetic nervous system arousal, and a significant increase in systemic vascular resistance suggesting a propensity to coronary vasoconstriction. This notion of vasoconstriction is further supported by other studies. Legault et al. (1995) evaluated the relation of MSIMI to silent ischaemia on ambulatory monitoring. 46 patients underwent standardised standard mental stress tests, and exercise tests during which left ventricular EF was

determined using nuclear imaging. Life stress, type A behaviour and hostility were determined using standard interviews, and 48 hour ambulatory monitoring was performed. The proportion of those displaying ambulatory ischaemia was 68.4% in MSIMI positive group and 37% for MSIMI negative group, with EF response to mental stress being a significant predictor of ischaemia independent of LVEF to exercise ($p = 0.03$). Patients with MSIMI had longer duration and more frequent episodes of TMI. This study experimentally demonstrated an association between vulnerability to MSIMI and greater frequency of ambulatory ischaemia. It supports the theory that MSIMI may be due in part to vasoconstriction. However, life stress, type A behaviour and hostility were not associated with prevalence or severity of ambulatory myocardial ischaemia.

Gottdiener et al. (1994) showed that patients who exhibited MSIMI in the laboratory were susceptible to non-exertional ischaemia in sedentary daily activity independently of heart rate, and had a possible greater functional severity of CAD. Coronary vasoconstriction or abnormal vasomotor activity could possibly explain episodes of ischaemia, unrelated to increases in heart rate.

Several studies have shown that triggers of ambulatory ischaemia are heterogeneous (Barry et al., 1988), while other studies show heterogeneity among cardiac ischaemic and anginal responses to exercise, mental stress and daily life (Sheps et al., 1998). Given the diverse causes of ambulatory ischaemia, it is possible that different laboratory triggers (mental or physical) may be independently associated with the occurrence of ambulatory myocardial ischaemia. The results of these studies are summarised in Table 2.1.

Table 2.1 Studies of TMI and laboratory stress response

Authors	Design	Medication	Results
Krittayaphong et al. 1995 (n = 45)	48 hour holter monitor Speech mental stressor BP/HR/radionuclide ventriculography	32% Off 68% On	HR response during laboratory induced TMI and average 24 hour HR related to magnitude of ambulatory ischaemia from holter monitor
Legault et al, 1995 (n = 46)	Mental stress task Exercise test with radionuclide ventriculography. Standard interview and 48 hr holter	Off	23 patients (50%) had an ischaemic response to mental stress, which was associated with ambulatory ischaemia (13 of 19 with ambulatory ischaemia had mental stress-induced ischaemia vs 10 of 27 without ambulatory ischaemia, p = 0.04). MSIMI patients had longer total duration (31.4 +/- 57.0 vs 8.3 +/- 18 minutes, p = 0.06) and more frequent episodes of ischaemia (3.1 +/- 4.6 vs 0.9 +/- 1.9 episodes, p = 0.03).
Stone et al. 1999 (n = 196)	48 hr holter monitor	Off	58% MSIMI. Those who developed ischaemia to mental stress had higher EF, and lower HR and were more likely exhibit daily life ischaemia
Gottdiener et al, 1994 (n = 45)	48 hr holter monitor. Structured diary. 2 D echo (Regional Motion Wall Abnormality) after mental stressors and bicycle exercise	Off	Patients with MSIMI also have increased ischaemia during sedentary activities in daily life.
Blumenthal et al, 1995 (n = 132)	48 hr holter monitor and radionuclide ventriculography during exercise and mental stress testing.	Off	Patients with MSIMI in lab more likely exhibit daily life ischaemia (p <0.21). Also displayed larger diastolic BP (p <.006) and HR response (p <0.018). MSIMI predicts daily ischaemia independent of exercise induced ischaemia.

Since none of these studies have assessed psychological state in everyday life, they have not conclusively demonstrated whether emotional factors in everyday life stimulate ambulatory ischaemia. It is possible that those individuals displaying laboratory-induced MSIMI are more physically active, which is why they go onto display ambulatory ischaemia, or that they have more severe cardiac disease, or simply are more reactive

individuals in general with heightened haemodynamic responsivity (Blumenthal et al., 1995).

2.4.3 Relationship of TMI with psychological state

The most common method of evaluating the relationship between TMI and daily life psychological and physical stress has involved the use of diaries. In these studies, patients undergo ambulatory ECG monitoring, and also complete diaries of mood and activities periodically, so that associations can be investigated. Table 2.2 summarises the main diary studies.

The first such study was reported by Barry et al. (1988). This examined the relationship of physical activity and perceived mental state to myocardial ischaemia during 48 hour holter monitoring in daily life. A diary was introduced to the patient in which the 24 hours were divided into 5 minute intervals. Patients were asked to make an entry in the diary in blocks of time in the day, specifying the nature of activity and a note of mental activities. The time of ischaemic episodes, the duration of HR at the onset, and the number of episodes was recorded by the holter monitor. Results revealed that most ischaemic events occurred during usual physical and mental activities (36%). 26% of ischaemic events occurred during increased physical activity but with usual mental activity. 22% of ischaemic events occurred at high levels of mental stress and low physical activity. 10% occurred during sleep. Increasing mental or physical activity was associated with increasing duration of ischaemia per unit time ($p < 0.05$). This study concluded that the intensity of both physical and perceived psychological status, influenced ischaemic activity in daily life. These patients showed more frequent episodes (92%) of asymptomatic transient myocardial ischaemia in daily life and increasing intensity of physical or psychological state was proportional to the duration of

ischaemia. This supports the notion that external forces do influence transient ischaemia in patients with CAD. However, this study involved a tremendous respondent burden, with participants in effect having to account for their activities and mood every minute of the day in real time. It is not known whether patients completed the diaries at the time, or filled them in retrospectively at longer intervals.

In a larger study, Gabbay et al. (1996) assessed the potency of both physical and mental activities as well as emotions (anger and anxiety) as proximate triggers of ischaemia. This study again involved a continuous diary over the monitoring period. Patients were asked to make a new entry into the diary whenever their activity changed, and provided ratings of physical effort and mood. Patients made an average of two diary entries per hour.

Ischaemia was found to occur most frequently during moderately intense physical and mental activities. Participants spent the largest proportion of time engaged in low and moderate intensity physical and mental activity. But when the data were corrected for the time patients spent at each level of activation, the likelihood of ischaemia was greatest in intense physical ($p < 0.0001$) and stressful mental activity ($p < 0.03$). The percentage of ischaemic time was elevated and equivalent for high intensity physical and high intensity mental activities (5%) compared with that of low intensity (0.2%). Strenuous physical activity (e.g. effortful walking) and experience of intense anger were potent ischaemic triggers. Heart rates at the onset of ischaemia increased with the intensity of activity (either physical or mental) and with anger. This study concluded that mental activities appear to be as potent as physical activity in triggering daily life ischaemia. However, it was difficult to differentiate the effects of the two types of activity, namely physical and mental. There was a low frequency of reported intense emotion, possibly because the respondent burden of the study was so high. Simultaneous

occurrences of multiple activities during daily life make it difficult to specify independent behavioural triggers of ischaemia.

The reporting of chest pain does not necessarily imply that ischaemia is occurring and may depend on the type of trigger of the ischaemic episode or particular trait characteristics of the individual. Evidence of an uncoupling of angina and ischaemia was shown in the study by Krantz et al. (1994), evaluating daily life physical and mental triggers of painful and painless myocardial ischaemia in the same group of CAD patients recruited for the study by Gabbay et al. (1996). Results showed that 85% of ischaemic episodes occurred without chest pain, and 66% of angina pain reports were made in absence of ST depression. Painful ischaemia was triggered at significantly higher levels of physical activity ($p < 0.005$) (walking in 67% ischaemic episodes) and significantly higher levels of self-rated negative emotion ($p < 0.05$) compared to silent episodes.

Another study focused particularly on symptomatic ischaemic episodes in everyday life. Kinne et al. (1999) studied 64 patients with CAD, 45 of whom showed symptomatic ischaemia during exercise testing. They completed electronic diaries during holter monitoring, assessing pain and associated activities. Personality tests were conducted, suggesting that symptomatic patients were more neurotic and reported lower active coping than asymptomatic cases. There were no differences in the ECG characteristics of symptomatic and asymptomatic episodes, but interestingly, there was a significantly greater increase in heart rate in the 2 minutes before symptomatic episodes. This was associated with physical exertion and greater ratings of tension. However, it is possible that the greater subjective tension experienced during symptomatic episodes was a consequence of the pain and worry about having a bout of ischaemia, rather than being relevant to the triggering of the episode.

Silent episodes of ischaemia have been attributed to mental stress in the Barry et al. (1988) and Gabbay et al. (1996) studies, but the methods used do not allow for precise correlations between the onset of ischaemia and what the patients are doing or thinking at the time. The reason is that ischaemia may start during the intervals between diary ratings, so may not coincide with the reports of mental state. Freedman and Wong, (1998) carried out an investigation to determine the usual triggers of silent and symptomatic myocardial ischaemia in daily life, using a method that partly overcame this problem. 38 patients with stable coronary artery disease wore an ambulatory recorder for 48 hours. The device emitted a tone on detection of ischaemia and patients noted activities, feelings, and symptoms at the time. The analysis involved matching ischaemic episodes with perceived triggers. The results showed that 53% of episodes were silent (pain free). Triggers were defined as the activities occurring at the time of the ischaemic episode. Physical exertion was present for 56% of episodes, mental stress for 5%, and combined physical exertion and mental stress during 8%. Most of the episodes associated with mental stress were silent (69%), while most of those associated with physical exertion led to angina (65%). Ischaemic episodes in everyday life took place at lower heart rates than those elicited during exercise testing. This study concluded that daily life ischaemia is usually triggered by physical activity, and that mental stress alone is an uncommon trigger of silent or symptomatic ischaemia. However, the sample was very small, and the presentation of results made it difficult to deduce how many patients actually experienced ischaemic episodes.

The largest and most sophisticated study in this field was that published by Gullette et al. (1997). This examined the effect of mental stress on daily life ischaemia and tried to determine the relative risk of ischaemia triggered by specific emotions. 132 patients were recruited in a case crossover method in which the frequency of the presumed trigger during non-ischaemic or control hours is compared to the trigger's

frequency in the ischaemic or case hours. This approach eliminates confounding due to inter–individual differences, and there was no potential for recall bias. Data were collected prospectively. Patients wore holter monitors for 48 hours during which they also wore a signal device that prompted them to complete entries in a structured activity and mood diary an average 3.2 times an hour from 6 am to midnight. In the diary, patients were asked to record activities when prompted by programmed auditory signal, and were asked to wear a watch that synchronized with the monitors' internal clock so the time in diary corresponded to the time on ECG. The patients were also instructed to fill out self initiated diaries if they had any pain or intense emotion, recording time, posture, location, mental, physical activity, mood, symptoms and medication use. When prompted they recorded 2 positive emotions – happiness and feeling in control and 3 negative emotions - sadness, tension, frustration on a 5 point intensity scale. Occurrence of ischaemia was analysed without knowledge of the diary data.

Results showed a relative risk of myocardial ischaemia in the hour following negative emotion of 3.0 for tension, 2.9 for sadness, and 2.6 for frustration. The percentage of ischaemic hours was greatest during high levels of negative emotion (tension, frustration). The percentage of ischaemic hours was lower during high levels of positive emotions. The highest risk of myocardial ischaemia was associated with heavy activity and with specific emotions. Heart rate was found to be higher in ischaemic hours but was not significantly associated with negative emotion. This study concluded that mental stress during daily life including reported feelings of tension, frustration, and sadness, can more than double the risk of myocardial ischaemia in the subsequent hour (relative risk 2.2, 95% confidence intervals 1.1 to 5.4). Mental stress was a common trigger of ischaemia in daily life and in contrast, positive emotions such as feeling happy and in control were associated with a lower risk of ischaemia (relative risk feeling happy 0.6, 95% confidence intervals 0.3 to 1.1; relative risk of feeling in control 0.7 confidence

intervals 0.3 to 1.8). However, it can be seen that the size of the effect is smaller than that for negative emotions and the confidence interval is wider for positive emotions.

This study involved a method in which diary ratings were prompted around 3 times per hour. This made it difficult to determine the precise temporal sequence in relation to ischaemia, since ischaemic episodes could have occurred during the intervals between ratings. In addition, small numbers of women and ethnic minorities were used.

The studies of TMI in relation to psychological factors are summarised in Table 2.2. Limitations to the methodology of these studies will be discussed in chapter 3.

Table 2.2 Studies of TMI and psychological response

Authors	Design	Medication	Results
Barry et al. 1988 (n= 28)	48 hour holter. Patients kept 24 hour diary which was divided into 5 minute intervals and patients were asked to make an entry in blocks of time in the day and when ever physical activity changed and make note mental activities	Off	22 % ischaemic events at high level mental stress
Gabbay et al. 1996 (n= 63)	48 hour holter Structured self initiated diary (entry if mood or activity)	Off	Ischaemia greatest in intense physical activity ($p < 0.0001$) and stressful mental activity ($p < 0.03$) Level mental activity related to total minutes of ischaemia
Krantz et al. 1994 (n= 63)	48 hour holter, exercise test, radionuclide imaging at peak exercise 24 hour diary self-report	Off	Painful ischaemia triggered with higher levels self rated negative emotion. 85% ischaemic episodes without chest pain. Painful ischaemia triggered at higher levels physical activity ($p < 0.005$) and higher negative emotion ($p < 0.05$)
Gullette et al. 1997 (n= 132)	48 hour holter Signal device from monitor emitted to prompt diary entry at random points in the day in blocks of time	Off	98% ischaemic episodes without symptoms. Emotions (included tension, frustration, sadness) can more than double risk of myocardial ischaemia in subsequent hour. RR 2.2 CI 1.1 to 5.4

Authors	Design	Medication	Results
Freedman and Wong 1998 (n= 38)	48 hour holter Signal device from monitor emitted tone on detection of ischaemia and patient prompted to note activities, feelings and symptoms in diary at time of tone or in the preceding 5 minutes	On	Triggers of ischaemia: physical stress, 56% episodes; mental stress, 5% episodes; combined physical/mental stress, 8% episodes; no trigger, 31% episodes. Episodes associated with mental stress/no stress were more often silent (69% and 75% respectively) than those associated with physical stress (45%, $p < 0.01$). Combined mental/physical stress were usually symptomatic

2.4.4 Relationship of TMI with psychosocial factors

Results relating TMI with specific psychological characteristics are inconclusive at present. In a study by Carels et al. (2000), patients repeatedly monitored their levels of subjective tension in everyday life using diaries, and were categorised into high and low emotional responders. High responders were those who exhibit relatively large variations of self-reported tension levels. Those with a high emotional response had greater myocardial wall motion abnormalities on mental stress testing compared to the low responder group, and also had greater trait anxiety and depressive symptoms. There was no association of emotional responsiveness with hostility. In the study by Legault et al. (1995) described earlier, it was found that ambulatory myocardial ischaemia was not associated with life stress, type A behaviour, or hostility.

Depression is relatively common in patients with CAD and is associated with an increased risk of mortality and morbidity (Nicholson et al., 2006). A study by Jiang et al. (2003) evaluated the relationship between depression measured with the CES-D and myocardial ischaemia, both during mental stress tests and in daily life. A curvilinear association was seen, with more ischaemia as depression scores rose in the mild to

moderate range (<19), but less ischaemia as scores increased >19. There was no very compelling explanation of this pattern.

Taken together, these studies do not show a consistent pattern of associations between TMI and trait psychological factors, but the issue has not been very extensively studied.

2.5 Mechanisms underlying emotion-induced TMI in everyday life

2.5.1 Introduction

There are a number of important and potentially inter-related physiological mechanisms which underlie the association of negative emotions and other psychosocial factors on coronary artery disease development and progression. Depression related dysregulation of the ANS and HPA axis has been linked to hypercortisolaemia, elevated plasma and urinary catecholamines, impairment in platelet functioning, elevated heart rate and reduced heart rate variability (HRV) all of which have a negative impact on CAD prognosis (Carney et al., 1988, 2000; Rozanski et al.,1999).

Altered autonomic control appears to be positively associated with negative mood states such as depression (Carney et al., 2001). Negative mood states also promote arrhythmogenesis and findings relating to this will be discussed. In addition, psychosocial factors may influence cardiovascular function through dysregulation of the HPA axis, giving rise to a number of wide ranging effects, both in the short and long term. I will also discuss the possible haemodynamic mechanisms with regards to alteration in blood pressure and heart rate involved in transient ischaemia and mood. In addition, I will discuss the other relevant biological relevant mechanisms involving

haemostatic pathways in which platelet function, serotonergic function, fibrinogen and secretion of proinflammatory markers all play a significant role in the development of CAD.

In addition to direct physiological pathways, environmental, social and behavioural pathways (smoking, alcohol consumption, exercise) may also play an important role in the relationship of negative emotions increasing CAD risk. However, the main focus here will be on the physiological mechanisms through which psychosocial factors potentially affect TMI and CAD.

2.5.2 Autonomic Nervous System

One of the important mechanisms underlying the effects of emotion on morbidity and mortality in cardiac patients is neurohormonal dysregulation. Decreased parasympathetic and increased sympathetic nervous system activity predispose cardiac patients to myocardial ischaemia, ventricular tachycardia, ventricular fibrillation and sudden death (Carney et al., 1995; Glassman et al., 1998). These autonomic disturbances can be indexed by reduced HRV. Abnormalities of the ANS, associated with negative mood, could accelerate CAD progression and initiate cardiac events by altering cardiac autonomic tone, promoting the procoagulant and inflammatory processes and lowering the threshold of mental stress induced ischaemia. Studies have shown that low HR variability or excessive sympathetic activation analysed from ambulatory electrocardiogram (ECG) predict increased risk for developing coronary heart disease in healthy populations and increased mortality in cardiac populations (Stein et al., 1999). HR variability provides information on progression of focal coronary atherosclerosis beyond that obtained by traditional risk markers of atherosclerosis (Huikuri et al., 1999).

This section will review the literature concerning the definition of HRV and impaired cardiac vagal control in both healthy populations and patients with CAD. A central aim of my thesis is to examine whether there is a similar association between reduced HRV in stable cardiac patients who are depressed either as a trait measure or as measured on a moment to moment basis in the day.

The ANS has two major branches - the sympathetic system associated with energy mobilisation, and parasympathetic system, associated with vegetative and restorative functions. There is a circadian rhythm with increased sympathetic activity in the day and increased parasympathetic activity at night. The two branches are rapidly modulated in response to changing environmental demands and it is this organised variability that regulates energy; optimal functioning being associated with variability (Lipsitz et al., 1992). Autonomic imbalance is when one branch dominates over the other, typically when the sympathetic system is hyperactive and the parasympathetic system is hypoactive, and it is associated with various pathological conditions (Malliani et al., 1994). The heart is under tonic inhibitory control by the parasympathetic nervous system. Resting cardiac autonomic balance favours energy conservation by way of parasympathetic dominance over sympathetic influences. The parasympathetic system exerts a dominant inhibitory influence on resting HR (Katona, 1982). Resting HR can be seen as an index of autonomic imbalance (Levy et al., 1990) and a large positive dose response relationship between resting HR and all cause mortality has been seen (Habib, 1997). Additionally, an elevated HR has been shown to predict future CAD, independent of risk factors (Kannel et al., 1987).

Bork et al. (2000) have also shown that autonomic imbalance in the sympathetic direction is associated with metabolic, haemodynamic and trophic abnormalities, that contribute to elevated cardiac morbidity and mortality. Reduced HRV has been

associated with diabetes (Ziegler et al., 2001; Singh et al., 2000), hypertension (Liao et al., 1996; Singh et al., 1998), total cholesterol and LDL cholesterol (Christensen et al., 1999; Wannamethee et al., 1994), immune dysfunction and inflammation (Kiecolt Glaser & Glaser, 2002), as well as psychosocial stressors such as sedentary lifestyle (Rennie et al., 2003), substance abuse (Ingjaldsson et al., 2003) and smoking (Hayano et al., 1990). Increasing age has also been associated with reduced HRV (Antelmi et al., 2004).

Thus autonomic imbalance, especially decreased parasympathetic activity, may be a mediator between psychosocial stressors and increased cardiac morbidity and mortality.

There are multiple measures that can be used to index vagal activity. As described earlier, resting heart rate is under inhibitory control of the vagus, so can be regarded as a simple non-invasive measure of vagal function. The decrease in HR after termination of exercise is termed heart rate recovery. Faster HR recovery is associated with better health and decreased risk of mortality (Lauer et al., 2002). Abnormal recovery responses have been shown to be associated with an increased risk of all cause mortality in the long term (Cole et al., 1999, 2000) both in healthy people and cardiac patients (Shetler et al., 2001).

Heart rate variability (HRV) is defined as a measure of the cyclic variation in heart rate, and is a composite of numerous influences including blood pressure regulation and respiratory processes. Short term fluctuations of heart rate are mediated by cardiac autonomic activity. This can be assessed using frequency domain measures with power spectral analysis, or time domain measures. The heart is innervated by both sympathetic and parasympathetic vagal fibres which give rise to differing frequencies. By identifying these different frequencies and their association with branches of the autonomic nervous system, HRV can be used as a non-invasive tool for the assessment of cardiac autonomic

control. The spectrum of HRV frequency can be decomposed into a series of frequency bands, each of which have a particular physiological significance and reflect in part, different branches of pathways of the autonomic nervous system controlling the heart.

There are three distinct rhythms identified within the beat-to-beat modulation of the heart; a high, low, and a very low frequency component (Task force, 1996). The high frequency (HF) component consists of oscillations in frequency range of 0.15 – 0.4 Hz, which is mediated by vagal (parasympathetic) tone. The low frequency component (LF) has frequency oscillations between 0.04 and 0.15 Hz and is mediated by both sympathetic and parasympathetic influences. The ratio between HF and LF can be measured, and the higher the ratio, the greater the vagal tone. In 24 hour ambulatory ECG recordings, a very low frequency (VLF) component can be found with a frequency band of < 0.04 Hz which is possibly related to the renin-angiotensin system and other humoral factors. The exact underlying physiological mechanism underlying this component remains controversial.

It is commonly reported that LF and HF are highly and significantly correlated (Wang et al., 2005; Liao et al., 2002). Thus LF power reflects substantial parasympathetic influence. In addition, measures of baroreflex sensitivity (BRS), an index of responsiveness of the cardiovascular system to changes in blood pressure, are also useful indicators of vagal function.

HRV can also be assessed from calculation of the mean R-R interval and its standard deviation measured on short term (e.g. 5 minute) electrocardiograms. The smaller the standard deviation in normal to normal beat-to-beat (or R-R) intervals the lower is the HRV. There are many different types of arithmetic manipulations of R-R intervals, and time domain measures include standard deviation of normal mean R-R interval obtained over 24 hour holter recordings (called SDNN index) and the root-mean

square of the difference of successive R-R intervals (the RMSSD index). The various methods of expressing HRV are probably equivalent, with no evidence that one method is superior to another, providing measurement windows are 5 minutes or longer (Bigger et al., 1992). The measurement of HRV has been standardised (Task Force, 1996).

2.5.2.1 Studies of the relationship between HRV and mood and TMI in healthy and non-healthy populations

Three aspects of autonomic activity have been investigated in studies, namely the sympathoadrenal function (causing peripheral vasoconstriction and altered haemodynamic state), heart rate levels and control processes governing the balance between sympathetic and parasympathetic systems and baroreceptor reflex activity or control (BRC). There is evidence that resting heart rate in depressed individuals is higher than in non-depressed individuals without CAD (Moser et al., 1998). The relationship between depression and sympathetic nervous system activity can be measured by assessing urinary or plasma catecholamines in clinical cohort studies (Lake et al., 1982). Positive correlations have been found between urinary catecholamines and depression and anxiety after controlling for age, race and BMI (Hughes et al., 2004) in a healthy sample. Sympathetic activation can reduce the threshold for cardiac ventricular fibrillation but this occurs only in those with advanced CAD (Meredith et al., 1991).

The evidence relating sympathovagal balance, depression and CAD is quite mixed with a variety of different HRV indices measured and confounded often with the use of beta blocker medication for cardiac disease, which is used by those suspected of CAD and those who have well established disease. The findings are presented below in Table 2.3 which summarizes key studies highlighting issues such as beta blocker medication.

Table 2.3 Studies analysing the relationship between depression and HRV in non-CAD patients and CAD patients

Study Author Year	Study design	Beta blocker Yes/No	Time domain	Frequency domain	Results
Psychiatric patients					
Yeragani 1991 (n = 49)	19 Major depression, 30 panic disorder, 20 controls	No	PNN50, SDNN	LF, MF, HF	No association with major depression
Yeragani 1993 (n =21)	21 Phobic anxiety, 21 normal controls, examining depression and anxiety	No	SDNN	LF, MF, HF	No relationship with depression or anxiety
Rechlin 1994 (n = 80)	16 major depression, 16 panic disorder, 16 reactive depression, 16 amitriptyline with 16 normal controls, analysing depression and panic disordered	No	RMSSD	LF, MF, HF	Major depression had lower HF (0.6) vs 1.2 controls and RMSSD
Thayer 1996 (n = 34)	34 with anxiety disorder, 34 normal control, analysing anxiety	No		LF, HF	Anxiety associated with lower HF than in controls
Watkins et al., 1999 (n = 56)	Cross-sectional study of 56 major depression patients	No		BRC, RSA	Anxiety, but not depression associated with decreased baroreflex control
Moser et al., 1998 (n = 52)	Case-control cross-sectional study of 26 non medicated depressed females and 26 age and sex matched controls.	No	NN	RSA, HF	HR greater in depressed patients ($p < 0.03$) than control group in the absence of vagal tone changes

Study Author Year	Study design	Beta blocker Yes/No	Time domain	Frequency domain	Results
Healthy population					
Kim et al., 2005 (n = 3372)	Postmenopausal women aged 50 to 83 years were enrolled for 24-hour holter monitoring. CES-D Scale and the Diagnostic Interview Schedule were administered.	No	NN, SDNN, ASDNN, SDANN		All the time domain indexes of HRV were significantly lower in participants with depressive symptoms compared with those without depressive symptoms
CAD Patients					
Carney et al., 1988 (n = 77)	CAD patients in daily activities, 24 hr monitoring Examining depression	Yes	SDNN		No relationship to depression
Carney et al., 1995 (n = 19)	19 patients with CAD and depression with 19 age, sex, smoking matched controls. 24 h monitoring, examining depression		SDNN RMSSD pNN50		SDNN lower in depressed than controls 74 vs 94
Krittayaphong et al., 1997 (n = 42)	CAD patients with daily activities, 24 h monitoring, examining depression		SDNN		Lower SDNN amongst highly depressed and higher HR
Watkins et al., 1999 (n = 66)	CAD cross-sectional study, examining depression	Yes		BRC, RSA	Depression associated with decreased baroreflex control.
Carney et al., 2001 (n = 904)	CAD case control cross-sectional study, examining depression. 380 depressed MI and 424 non-depressed MI patientsunderwent holter monitoring.	Yes		LnULF, LnVLF, LnLF, LnHF	LnULF, LnVLF, LnLF was all significantly reduced in post MI patients with depression than in non-depressed MI patients .

Study Author Year	Study design	Beta blocker Yes/No	Time domain	Frequency domain	Results
Carney et al., 2005 (n = 678)	CAD case control cross-sectional study, examining 311 depressed MI and 367 non-depressed MI patients	Yes		VLF	VLF was lower in depressed MI patients. ($p < 0.001$)
Gehi et al., 2005 (n = 873)	CAD cross-sectional study of stable CAD patients	Yes	SDNN, SDANN	LnVLF, Ln LF, Ln HF,	No association between depression and any of HRV indices.
Stein et al., 2000 (n = 72)	Case control cross-sectional study of stable CAD patients and non-depressed controls	No	Average HR SDNN SDANN SDNNIDX RMSSD PNN50	HF, LF, LF/HF ratio, VLF, ULF RSA, Ln Total Power,	HR were higher and all HRV indices except RMSSD, ln HF and LF/HF ratio which were significantly reduced in moderately to severely vs the non-depressed group.

Table 2.3 abbreviations for HRV indices

Time Domain:

AVGHR, average heart rate in beats/minute; SDNN, standard deviation of normal-to- normal interbeat intervals; SDANN, standard deviation of 5 minute mean values of normal-to-normal interbeat intervals; ASDNN, average of all 5 minute standard deviations of normal – normal interbeat intervals; SDNNIDX, the average of standard deviations of normal-to-normal interbeat intervals for each 5 minute period; NIDX, normal-to-normal interbeat intervals for each 5 minute period, RMSSD, the root mean square successive difference of normal-to-normal interbeat intervals; pNN50, the proportion of successive normal-to-normal differences in interbeat intervals >50ms (percent); RSA,respiratory sinus arrhythmia (ms). BRC, baroreceptor reflex control of heart rate

Frequency Domain

TP, total power ($1.15x10^5$ – 0.4 Hz) for total 24 hour cycle; ULF ultra low frequency power, ($1.15x10^5$); VLF, very low frequency power, (0.0033-0.04 Hz), low frequency power (0.04-0.15 Hz), MF, medium frequency power (0.08 - 0.15 Hz), HF, high frequency power (0.15-0.4 Hz); LF/HF ratio, the ratio of low to high frequency power LnULF, log of ultra low frequency power, LnVLF, log of very low frequency power, LnLF, log of low frequency power, LnHF, log of high frequency power, Ln Total Power, log of total power

HRV is a significant independent predictor of mortality in high risk groups (Makikallio et al., 2001). In a study by Tsuji et al. (1994), the HRV data of an elderly subsample of participants of the Framingham Heart Study were analysed. All five frequency domain measures were significantly associated with all cause mortality, with log transformed LF power being the most significant index in multivariate models. The same has been shown in populations post MI, (Kleiger et al., 1987), the ATRAMI study (La Rovere et al., 1998), and in a study by Camm et al. (2004), which showed HRV to independently predict mortality after controlling for age, gender, LVEF, diabetes and beta blocker use. Reduced HRV has also been associated with development of atherosclerosis (Huikuri et al., 1999) and plaque rupture (Kennedy et al., 1997).

There are some contradictory findings with regards to emotional factors, like depression or negative affect and HRV. Rottenberg et al. (2007), in their meta-analysis, have described how some studies have shown that depressed patients have lower heart rate variability than non-depressed controls, whilst other studies reported no differences. It is important to take into account the confounding effects of medication, physical co-morbidities and sedentary lifestyles as well as a variety of psychiatric conditions like anxiety or panic disorders. These confounders may in part, explain the varied findings relating to HRV and emotion, in particular depression. This meta-analysis of 13 cross-

sectional studies revealed a small-to-medium effect size for depression in relation to HRV.

A study that characterised various other emotional states in CAD patients was carried out by Bacon et al. (2004) in which 135 patients were assessed to investigate the associations between mood and autonomic cardiac control in patients with CAD. Diary measures were taken every 20 minutes for 48 hours of holter monitoring, and within-person associations between mood and HRV were computed. Analyses showed that higher levels of negative emotions (e.g. anger, stress, sadness) were associated with decreases in high and low frequency power, whereas higher levels of positive emotions were related to an increase in low frequency power, independent of age, posture and medications. This finding was unexpected, since low frequency power is generally interpreted as indexing increased sympathetic over parasympathetic control, so an inverse association with positive emotions might have been anticipated. But the study does suggest that during daily life, negative emotion is associated with a reduction in vagal control and possibly an alteration in sympathetic control, transient alterations of which may contribute to acute triggering of cardiovascular events by emotional stress.

Vagal withdrawal can produce myocardial ischaemia and may be involved in ambulatory ischaemic events. A study by Kop et al. (2001) determined the time course of autonomic nervous system activity preceding ambulatory ischaemic events and showed how physical and mental challenges provoke transient decreases in high frequency component (vagal tone). The study analysed trajectories of HRV before, and after ischaemic events and examined the role of exercise and mental stress in pre-ischaemic autonomic changes. 19 patients with stable CAD and a positive exercise test and evidence of ischaemia on previous ambulatory ECG were studied. They all underwent 48 hour monitoring. Frequency domain HRV measures were assessed for 60

minutes before and after each of 68 ischaemic events and during non-ischaemic heart rate matched control periods. A validated diary system was used to evaluate patients' physical and mental activities throughout the day. Patients were instructed to complete a standardised page each time activities changed markedly. Mental and physical activity levels coinciding with onset of ischaemia were graded on a scale from 1-6. Cut-off points for activity levels were used to compare trajectories HRV occurring at low (scores<5) versus high (scores>5) activity levels. Patients also recorded episodes of chest pain and the use of glycerol trinitrate spray (an anti-anginal medication to relieve symptoms of chest pain). Activity levels were cross tabulated with concurrent ischaemic events as well as with non-ischaemic control periods.

Results showed that high frequency HRV decreased from -60, -20 to -10 minutes before ischaemic events ($p=0.04$) and further from -4, -2 minutes, until ischaemia. Low frequency HRV decreases started at -4 min ($p < 0.05$). Ischaemic events occurring at high mental activities were preceded by depressed high frequency HRV levels compared with events at low mental activity ($p=0.038$ at -4 minutes) whereas effects of mental activities were not observed during non ischaemic control periods. Heart rate variability measures remained significantly depressed for 20 minutes after recovery of ST segment depression, when events were triggered by high activity levels.

The study showed that decreases in HRV preceded myocardial ischaemia, as early as 10 minutes before the event and most pronounced in the 4 minutes before ST segment depression. Ischaemic events occurring at high mental activities were preceded by significantly decreased high frequency HRV levels, suggesting that vagal withdrawal can act as a precipitating factor for daily life ischaemia particularly in episodes triggered by mental activities, which is triggered by low heart rates.

Although majority of patients (12 out of 19) were monitored without discontinuation of beta blocker (which are known to affect HRV parameters), results suggested a similar pattern of vagal withdrawal in those off medication. Measures of vagal withdrawal were found to persist until 20 minutes after ischaemia. It is possible that TMI has sustained residual effects on cardiac vagal tone, independent of activity levels or that ambulatory ischaemia persisted longer than detectable ST segment depression. Vagal withdrawal associated with mental activities appears to be specific to ischaemic events because high mental activity levels were associated with HRV decreases in ischaemia but not in non-ischaemic control periods. Of note, the events were asymptomatic, hence not susceptible to confounders like perceived pain on the autonomic nervous system.

2.5.2.2 HRV and unstable CAD patients

Regarding the relationship between specific emotional states like depression and the relationship with HRV, the literature is varied and differs between those with unstable CAD and stable CAD. It has been shown by Carney et al. (2001) that depression is associated with reduced HRV in patients with a recent myocardial infarction. In this study, 380 acute MI patients with depression and 424 acute MI patients without depression were recruited, who participated in the Enhancing Recovery in Coronary Heart Disease (ENRICHD) clinical trial undergoing 24 hour ambulatory ECG monitoring after hospital discharge. (The clinical trial consisted of post MI patients who were depressed being randomly assigned to usual care or to cognitive behavioural interventions to determine the effects of treating depression and social isolation on reinfarction and mortality). In univariate analyses, 4 indices of HRV (log transformed domain indices HRV: Ultra Low Frequency, Very Low Frequency, Low Frequency and

High Frequency) were significantly lower in patients with depression than in patients without depression. Variables associated with HRV (age, sex, diabetes, present smoking) were then compared between patients with and without depression and potential confounds were identified. In the final multivariate model (in which variables were entered followed by depression status), all but one HRV index (high frequency power) remained significantly lower in patients with depression than those without. The conclusion was that greater autonomic dysfunction, as reflected by decreased HRV, is a plausible mechanism linking depression to increased cardiac mortality in post MI patients.

In another study on the same sample of patients (Carney et al., 2005), HRV indices were analysed from 311 depressed patients and 367 non-depressed patients enrolled in the ENRICHD trial. Results found that the log of very low-frequency (LnVLF) power, was lower in the depressed than in the non-depressed patients ($p < 0.001$). There were 47 deaths (6.1%) during a 30-month follow-up. After adjusting for potential confounders, the depressed patients remained at higher risk for all-cause mortality compared with the non-depressed patients (hazard ratio, 2.8; 95% confidence interval (C.I), 1.4-5.4; $p < 0.003$). When LnVLF power was entered into the model, the hazard ratio for depression was 2.1 (95% CI, 1.1-4.2; $p = 0.03$). The proportion of the risk for depression attributable to LnVLF power was 0.27 (95% CI, 0.23-0.31; $p < 0.001$). The authors concluded that low HRV partially mediated the effects of depression on survival post MI. HRV may therefore contribute to the understanding of possible biological mechanisms underlying depression's role, as a risk factor for mortality in cardiac patients.

2.5.2.3 HRV and stable CAD patients

Other researchers have found that depression is not consistently related to HRV in patients with stable CAD (Gehi et al., 2005; Stein et al., 2000). In a study by Gehi et al. (2005), a cross-sectional examination was made of the association between major depression (occurring in 22% participants) and 24 hour HRV in 873 out patients with stable CAD. Results showed no association between depression and HRV, as measured by time domain or frequency domain variables. Mean HRV was similar in participants with and without depression (all p values > 0.10), and participants with depression were no more likely than those without depression to have a reduced HRV (all p values > 0.10). The authors suggested that there may be a different pathophysiological basis to stable and unstable CAD, and that low HRV may be a mediator in depression and adverse outcomes in only unstable CAD.

Analysing the associations found between depression and reduced HRV further, De Jonge et al. (2007) carried out a study on the same dataset but divided patients according to cognitive and somatic symptoms of depression, to determine if depression that is associated with low HRV in post MI patients but not in stable CAD patients may be due to differential associations of somatic and cognitive depressive symptoms with HRV. They conducted a cross-sectional study of 863 stable CAD outpatients, with the severity of somatic and cognitive depressive symptoms determined using factor analysis of items of the Patient Health Questionnaire (PHQ-9). Time-domain (SDNN, SDANN) and frequency-domain (VLF, LF, HF) indices of HRV were derived from holter monitoring. Results found that in the unadjusted analyses, somatic symptom scores were significantly associated with HRV (r = -.09 for SDNN; r = -.08 for SDANN; r = -.08 for LnVLF; r = -.08 for LnLF; r = -.10 for LnHF). However, after adjustment for demographic variables, co-morbidities, and lifestyle factors, somatic symptom scores were no longer associated

with lower HRV. Cognitive depressive symptom scores were not associated with HRV in either unadjusted or adjusted analyses. These results suggest that individual symptoms of depression may have differential associations with HRV and highlights the heterogeneity of depression in CAD patients and the possible differential associations with prognosis.

These findings conflict with those found in patients with stable CAD undergoing elective angiography (Carney et al., 1988; Stein et al., 2000). Stein et al. (2000) found a lower HRV in 40 patients with depression compared with 32 patients without depression with documented CAD by angiography. Results revealed heart rates were higher and nearly all indices of heart rate variability were significantly reduced in the moderately-to severely depressed group versus the non-depressed group.

A possible explanation for the difference in results is the influence of medication. Medication used for treating angina, heart failure or hypertension improve cardiac vagal activity. Beta blockers like atenolol, are effective in increasing resting HRV measures of cardiac vagal activity and attenuate a stress induced reduction of vagal tone (Vaile et al., 1999). ACE inhibitors increase vagal inhibitory actions both peripherally and centrally (Potter et al., 1982). However, Gehi et al. (2005) found no evidence of an interaction between depression and beta blockers in analysis and no association of depression with HRV in the subset of participants not taking beta blockers. The majority of patients were also not taking antidepressants.

Possible confounding variables in the studies of HRV and depression are that studies have differed in relative proportions of male and female subjects in the samples, and there may also be differences in physical activity of the participants which may affect HRV results. Highly active individuals have been shown to have higher levels of HRV (Melanson, 2000). Other confounding variables may also be different diagnostic criteria

for depression used in the studies, the presence or absence of medication or a failure in matching appropriate control groups.

2.5.2.4 Conclusions about HRV

To date, it is well established in the literature that depression is associated with both long term aetiology of CAD (Nicholson et al., 2006), as well as acute triggering of cardiac events (Steptoe et al., 2006) and to prognosis and adaptation to CAD (Carney et al., 2003, 2005). It has also been shown that depressed patients post-AMI have a reduced HRV (Carney et al., 2001) and that it is the reduction in HRV that partly mediates the effects of depression seen on post-AMI mortality (Carney et al., 2005).

However, results are mixed and differ when examining cohorts of patients at different stages of CAD development. Depression has been shown to be inconsistently related to HRV in patients with *stable* CAD (Stein et al., 2000; Gehi et al., 2005). Depression has also been shown to be inconsistently related to HRV in people *without* CAD (Moser et al., 1998; Kim et al., 2005). Depression in patients with *advanced* CAD has been shown to be associated with impaired autonomic cardiac control, i.e. reduced heart rate variability (HRV).

What is still unclear, from the existing literature is exactly *when* this relationship between depression and HRV evolves in the cardiovascular disease process, or whether reduced HRV is related to concurrent mood states or only to trait measures of depressed affect. Study of the association between negative affect and reduced HRV may provide a potential biological mechanism linking both acute stress in daily life, and chronic long term stress to disease outcomes. A central aim of my thesis is to examine whether there is a similar association between reduced HRV in stable cardiac patients who are

depressed either as a trait measure as with the BDI measurement or as measured on a moment to moment basis in the day by the Day Reconstruction Method (DRM) which is described in Chapter 3.

2.6 Arrhythmia/Implantable cardioverter defibrillator discharge

Acute emotional stressors provoke a variety of serious cardiac arrhythmias which may induce TMI or more prolonged ischaemia, or sudden death. The effects of acute mental stress (anger recall and mental arithmetic) and physical stress (bicycle testing), on T wave alternans (TWA), a marker of cardiac electrical instability, were evaluated in a study by Kop et al (2004). This study consisted of 23 patients with CAD and implantable cardioverter defibrillators and 17 controls. The study concluded that mental stress testing can induce cardiac instability amongst patients with arrhythmic vulnerability, and at a lower HR than with exercise, but no significant association was found between TWA and the severity of ischaemia.

In contrast to the controlled laboratory task setting, the arrhythmogenic effects of extreme mental stress occurring in a terrorist attack setting was carried out by Shedd et al. (2004). They conducted an observational study to determine whether the World Trade Centre attacks in 2001 had an effect on the occurrence of ventricular arrhythmias amongst 132 patients in Florida with implantable cardioverter defibrillators (ICD's) who were far removed from the site of the attack. In the 30 days following the attack, a total of 14 patients (11%) had such arrhythmias, compared to 5 (3.8%) in the preceding 30 days, concluding a 68% increase in the frequency of life threatening ventricular arrhythmias requiring ICD treatment. This supports previous descriptive and epidemiological studies, which have shown a link between sudden cardiac death and

emotionally stressful stimuli such as those occurring in population catastrophies (Leor et al., 1996) as described in chapter 1.2.

Different types of emotion have a significant effect on arrhythmia. Whang et al. (2005) prospectively analysed data on 645 ICD patients with symptoms of depression and the associated risk of ventricular arrhythmias that resulted in ICD discharge in the Triggers of Ventricular Arrhythmia (TOVA) study. Results showed that of the 645 patients, those with moderate/severe depression (3.9%) had a more rapid 'time to first shock' for ventricular tachycardia (VT)/ventricular fibrillation (VF) compared with non-depressed patients (hazard ratio HR 3.2, 95% CI 1.1 to 9.9). Moderate/severe depression was also associated with the likelihood of any shock for VT/VF including recurrent episodes (HR 3.2; CI 1.2 to 8.6). This risk was associated with depression severity in the total population as a whole (p for trend=0.02) and more specifically, among patients with CAD ($p < 0.01$), even after controlling for multiple confounders. This study is consistent with findings of a previous study by Carney et al. (1993), in which depression (assessed by standardised psychiatric interview) was associated with VT episodes, detected by 24 hour ECG monitoring among 103 CAD patients, even after adjustments were made for beta blocker use.

Anger may be another mood state associated with fatal arrhythmia. Lampert et al. (2002) systematically evaluated whether emotional or physical stressors can trigger spontaneous ventricular arrhythmias in patients at risk, and if so, how frequently. 277 ICD patients were recruited and given diaries to record levels of mood states and physical activity during 2 periods preceding spontaneously occurring ICD shocks and during control periods 1 week later. Results were analysed in a case crossover approach. In the 15 minutes preceding shock, an anger level > 3 preceded 15% of the events compared with 3 % of the control periods ($p < 0.04$; O.R 1.83; 95% CI 1.04 to 3.16).

Anxiety also appears to have a role in abnormal cardiac autonomic control which increases the risk of potentially fatal arrhythmias and can also trigger rupture of plaques by triggering coronary vasospasm (Kubzansky et al., 1998). Some researchers have suggested that anxiety is associated with especially high rates of sudden death and the cardiovascular effects of anxiety result from chronic or intermittent sympathetic activity with arrhythmogenic potential (Rozanski et al., 1999; Albert et al., 2005).

Lane et al (2005) assessed emotional triggers in patients with apparently healthy hearts who had suffered a cardiac arrest (idiopathic ventricular fibrillation) in comparison with MI patients. Patients were interviewed systematically about the circumstances surrounding the cardiac events, and these accounts were rated independently by two experts for stress levels. The results indicated that in the 24 hours preceding a cardiac arrest or an MI, 36% of patients with ventricular fibrillation (VF) had experienced severe or moderate stress compared to 8% of MI patients. It is possible that the emotional stress needs to be particularly severe in intensity to actually elicit clinical events in patients who do not have underlying CAD. Limitations in this study were that although patients were instructed to focus on the period preceding shock, there is a possibility of recall bias, with patients attributing post shock feelings of anger to the pre shock periods as well. There is also the possibility that patients may have altered their behaviour during the control period 1 week after the shock.

Whether more benign ECG changes (minor ST depression) or heart rate variability changes are triggered by emotion remains unknown. Analysis of ST segment changes for ischaemic events is also relatively insensitive as a measurement tool. Radionuclide ventriculography and echocardiography are more sensitive, but impossible to use in everyday life studies. In the SIS study, the likelihood of arrhythmia occurrence was low, as our patients did not have advanced cardiac disease. However, in view of the

above literature, ECG recordings were analysed for ventricular tachycardia and autonomic changes as well as ST depression for transient ischaemic changes in relation to mood in the SIS study.

2.7 Neuroendocrine processes

Psychosocial factors such as mood can be related to CAD by stimulating biological systems through central activation of neuroendocrine response as well as autonomic responses.

2.7.1 Cortisol physiology and relationship to cardiovascular risk

Cortisol is a glucocorticoid hormone produced in the adrenal cortex both spontaneously and in response to acute stressors, and is evident in blood, urine and saliva. Steroid hormones have important effects on the brain altering excitability of nerve cells and in the aftermath of stressful experiences for example in the day, by modifying neurochemical and structural features of the brain (Lupien & McEwen, 1997). Figure 2.2 shows a diagram of the influence that cortisol release has on various cardiological, metabolic, haemostatic and immune parameters in the body, alteration of which may lead to CAD development and affect adaptation to CAD in the long term.

Figure 2.2 Glucocorticoid effects on various cardiovascular risk factors

(Girod & Brotman Cardiovasc Res, 2004)

As can be seen, cortisol is involved in a variety of pathophysiological processes contributing to atherogenesis including disturbed metabolism, abdominal adiposity and insulin resistance, prothrombotic responses and vascular inflammation (Girod & Brotman, 2004).

The measurement of salivary cortisol has become an important tool with which to investigate HPA axis function (Kirschbaum & Hellhammer, 1989). The HPA axis sustains life in stressful situations by increasing vascular tone, mobilising fuel, modulating inflammation and tissue repair processes, but chronic activation of this axis may override the short term physiological benefits of the stress response. Chronic tissue exposure to cortisol by chronic activation of HPA axis by mood states like depression

(Plotsky et al., 1998) lead to metabolic and vascular changes, which may in turn accelerate atherosclerosis (Colao et al., 1999).

Cortisol shows a natural diurnal pattern in healthy adults, which peaks at approximately 20 – 45 minutes after waking and then decreases through the day, reaching a nadir at night and in the early hours of the morning, before increasing once again. (Kirschbaum & Hellhammer, 1989). The HPA axis is highly sensitive to psychological stimuli (Mason, 1968). Due to the large diurnal variation in cortisol concentrations (morning peaks and evening troughs), single measures are generally unreliable. 24 hour urine collections of cortisol allow an integrated estimate of the average free (unbound) cortisol concentration that circulate over the course of the day, but finer temporal resolution is not possible and average concentrations do not necessarily represent the overall tone of the axis (Brotman et al., 2007).

There are studies showing consistent associations between cortisol patterns and mood in healthy patients. Some studies having found that some patients who are depressed show an abnormal circadian rhythm with blunting of the normal reduction in cortisol over the evening and hypercortisolaemia in the evening (Kirschbaum & Hellhammer, 1989). There are many studies reporting negative mood in medical conditions like Cushing's syndrome that are characterised by hypercortisolaemia (Kelly et al., 1983; Loosen et al., 1992). Some studies suggest an association between depression and elevated cortisol levels in the morning (Yehuda et al., 1996). Other studies suggest that evening levels of cortisol show the highest association with depression (Gold et al., 1988).

The increase in cortisol in the first 20-30 minutes after awakening is known as the cortisol awakening response (CAR). Evidence suggests that it is unrelated to the mean underlying level of cortisol activity throughout the rest of the day (Edwards et al.,

2001) with evidence for a genetic basis for the CAR, but not for the cortisol profile throughout the day (Wust et al., 2000), and thus implies that the CAR is under a distinct regulatory influence independent of the rest of the cycle (Clow et al., 2004). The CAR demonstrates a higher intra-individual stability than single measurements at pre-defined times. (Pruessner et al., 1997). The CAR has been associated with a wide range of psychosocial variables, stress and health but studies are inconsistent and it is unclear still whether health is associated with a larger or smaller CAR. Exaggerated increases in cortisol after waking have been associated with chronic stress (Steptoe et al., 2000). In addition, a larger CAR has been associated with depressive symptoms and a reduced positive affect (Pruessner et al., 2003; Steptoe et al., 2007) but also, a smaller CAR has been associated with patients suffering from chronic fatigue (Roberts et al., 2004).

Another aspect of the cortisol profile is the slope of decline over the day. This gradient is calculated as the difference between awakening and evening bed time values. A flatter slope has been found to be associated with depression (Weber et al., 2000) or stressful social experiences (Adam & Gunnar, 2001).

Salivary cortisol has proved to be an accurate reflection of plasma cortisol, and salivary sampling allows convenient assessment of diurnal patterns in a naturalistic ambulatory setting (Kirschbaum et al., 1989). It also allows assessment of the relationship between an individuals' affective state and neuroendocrine changes over time, in response to potentially stressful naturally occurring activities and situations in daily life subject to daily hassles and strains.

Earlier studies had measured a single daily cortisol measurement to represent the cumulative effects of stress in a day, as carried out in studies by Brantley et al. (1988); Lundberg et al. (1989), which showed in general, elevated cortisol levels to be associated with stress. Results measuring cortisol this way was inconsistent. No relationship were

seen between numbers of undesirable events in the day and between evening urinary or salivary cortisol levels in the study by Cummins and Gevirts, (1993).

Previous research has examined the impact of different daily stressors on mood and HPA activation using an ecological momentary assessment (EMA) design. EMA measuring stress and cortisol several times a day has distinct advantages over the end-of-the-day approach (Stone & Schiffman, 1994).

A variety of studies using momentary assessment, have shown that minor stressful daily events are associated with changes of mood in which positive affect (PA) decreases and negative affect (NA) increases to stress (Marco et al., 1993; Peeters et al., 2003; Van Eck et al., 1998). Also studies have examined the association between minor stresses (by subjective mood appraisal at time points) and demonstrated that daily stressors give rise to negative emotional responses which activate the HPA axis and increase cortisol levels or produce altered cortisol patterns (Van Eck et al., 1996; Peeters et al., 2003; Smyth et al., 1998;). Momentary mood states also predict within person variability in cortisol in daily life and the association between NA and higher cortisol is consistently evident (Harris et al., 2000; Peeters et al., 2003).

Van Eck et al. (1996) examined the daily impact of stressful daily events in 87 white collar workers over a period of 5 days. Stressful events were associated with an increase in cortisol secretion and stressful events that were ongoing at the time of assessment had a larger effect than those terminated early in the day. Smyth et al. (1998) extended this study to show that an increase in cortisol secretion was not only seen in response to a current acute stressor but also in anticipation of a stressor. Results suggested that affect may mediate the association seen between stress and cortisol, either by affect influencing the perception of daily events or being related to a heightened physiological effect of stress.

In the study by Peeters et al. (2003), patients with a major depressive disorder, assessed with the Beck Depression Inventory (BDI), were investigated by EMA in which self-reports of mood and events were assessed together with saliva sample. In contrast to healthy participants, the depressed group shows a blunted response to daily negative events.

A flattened slope has been found in association with work/home load stress in a sample of 156 healthy female adults (Adam et al., 2001). Another study by Adam et al. (2006) showed that feelings of tension and anger were concurrently associated with a flatter diurnal cortisol rhythm, mainly due to an increase in evening cortisol level.

Results for PA are less consistent and some studies show no association between PA and cortisol levels (Peeters et al., 2003) However, others have shown that positive affect, as assessed by EMA, to be inversely associated with cortisol levels over the day (Steptoe et al., 2005; Polk et al., 2005). To date, there is currently little in the literature which has related cortisol profile to mood, as assessed by the day reconstruction method (DRM; Kahneman et al., 2004), which may provide a more precise picture of daily life experience.

Marked gender differences have been found in relation to cortisol profile and mood. In the study by Polk et al. (2005), a sample of healthy 334 adults showed that trait NA was associated with a higher overall total cortisol concentration and a greater morning rise in men even after controlling for waking levels of cortisol. Women high in trait PA had low morning cortisol levels, resulting in a low flat rhythm, in contrast to the men where those low in trait PA had cortisol levels that did not decrease in the afternoon, resulting in a high flatter rhythm.

The choice of salivary cortisol as a physiological index is practical as it can be measured repeatedly in a non-invasive real life setting, and has shown intra individual

stability over time. Responses are however affected by gender, smoking, use of oral contraceptive and other factors (Schulz et al., 1998). It is also true that the study of cortisol dynamics in daily life means that much of the control possible in a laboratory is sacrificed in order to gain ecological validity. The statistical method of analyses of the cortisol profile in the SIS study is outlined in chapter 4.

2.7.2 Cortisol and relation to depression in CAD patients

Disturbed cortisol regulation is one of the mechanisms that may link depression with CAD. Heightened cortisol output is partly responsible for vascular endothelial dysfunction in depressed individuals (Broadley et al., 2005). There have also been studies linking elevated levels of cortisol with CAD. Troxler et al. (1977) found significant correlations between elevated morning cortisol of 71 male outpatients and moderate to severe coronary atherosclerosis as evidenced on angiography. Coronary artery calcification is associated with flattened cortisol profiles over the day in middle-aged adults (Matthews et al., 2006). A prospective association between cortisol and future CAD has been documented in middle aged men (Davey Smith et al., 2005), while acute cortisol elevation following ACS predicts adverse cardiac outcomes (Bain et al., 1989; Tenerz et al., 2003). Bain et al. (1989) studied cortisol levels in 20 post MI patients and 20 angina patients and found cortisol levels to be significantly elevated in patients within five hours of the onset of symptoms of an MI and concluded that early elevation of cortisol is sensitive (70%) and specific (85%) for MI, predicting MI in those with ischaemic chest pain. Raised cortisol concentrations also predict mortality in patients with chronic heart failure (Guder et al., 2007).

Evidence linking depression with cortisol directly in coronary artery disease (CAD) is more limited. A recent study showed morning cortisol levels in women to be

positively associated with the degree of stenosis found on angiogram (Koertge et al., 2002). Otte et al. (2004) found that elevated 24 hour urinary cortisol was associated with clinical depression in patients with established CAD, but studies of patients following ACS have been inconsistent (von Kanel et al., 2007; Whitehead et al., 2007). Von Kanel et al. (2007) measured morning serum cortisol and haemostatic factors: activated clotting factor VII, fibrinogen, von Willebrand factor antigen, and plasminogen activator inhibitor-1 activity in 285 women (56 +/- 7 years) between 3 and 6 months after an ACS. Results showed that a higher serum cortisol levels predicted higher fibrinogen (beta = .17, p = 0.001) and higher von Willebrand factor (beta = .16, p = 0.008), all independently of covariates. Cortisol showed crude correlations with vital exhaustion (r = .14, p = 0.022) and with depression (r = .13, p = 0.043) but did not mediate the relationship between any of the psychosocial variables and haemostatic factors. These results suggested that morning cortisol levels showed some independent association with prothrombotic activity in women with CAD, and that these increased cortisol levels might contribute to atherosclerosis via eliciting a hypercoagulable state. However, no significant relationship was seen with regards to mood.

In the study by Whitehead et al. (2007) salivary cortisol was assessed eight times over a 24 hour period in 72 patients within 5 days of admission for ACS and depression was measured with the Beck Depression Inventory (BDI), and type-D personality was measured with the Type-D Scale-16. Results showed a typical diurnal pattern for cortisol, with low levels in the evening, high levels early in the day, and the cortisol awakening response (CAR), which was measured as the difference in cortisol between waking and peak responses 15-30 minutes later, was found to average 7.58+/-10.0 nmol/l. In these results cortisol was not related to ACS severity or underlying CAD or to BDI scores, but the CAR was found to be positively associated with type-D personality independently of age, gender, and body mass (p=.007).

CAD patients have shown an altered cortisol profile in response to stress. Nijm et al. (2007) assessed 30 post ACS patients for urinary cortisol, saliva sampling and inflammatory markers (IL-6 and CRP), finding that CAD patients had higher 24 hour urinary cortisol secretion and a flatter slope. The study also found that these patients had a significantly blunted cortisol response to acute mental stress compared with controls.

In summary, there is much evidence of an association between various aspects of the cortisol profile (cortisol mean values, CAR, cortisol slope) with mood as assessed both by the BDI and by momentary assessment in healthy participants but findings have been inconsistent. There is more limited evidence directly linking depression with cortisol in cardiac patients. Depression is prevalent in CAD and altered cortisol profiles have been associated with various aspects of cardiac disease. Dysfunction of the HPA axis is a plausible biological mechanism underlying the association between psychological states and CAD.

2.8 Haemodynamic changes

A study by Deedwania and Carbajal, (1992) measured the heart rate (HR) and blood pressure (BP) changes preceding the silent ischaemic events during the daily life of 25 men with CAD. 92% of transient ischaemic episodes were silent, and 61% of these were preceded by an increase in the heart rate of 5 beats /minute or more. The silent ischaemic events showed a circadian pattern with 34% of the total events occurring between 6.00 am and noon. The increase in HR and BP paralleled the increase in silent ischaemic events during these hours. In the PIMI study, described in the previous section 2.3 (Stone et al., 1999), patients with daily life ischaemia had a heightened

generalised response to mental stress with a chronic state of sympathetic nervous system arousal and an exaggerated haemodynamic response to mental stress. In the ACIP study by Pepine et al. (1996), HR change was seen as the best independent predictor of TMI. The rise in heart rate increases cardiac oxygen demands and reduces supply due to a shorter period of time available for coronary blood flow. This probably reflects neurohormonal changes as a result of stressors in the patients' environment in everyday life. However, both vagal withdrawal or blood glucose changes and ischaemia itself could also contribute to increase in HR. Hostile emotions have also been associated with arterial constriction, increased BP and HR (Boltwood et al., 1993) and alteration in ventricular function as well as alterations in levels of catecholamines, cortisol and increased platelet aggregation (Rozanski et al., 1999).

2.9 Other mechanisms by which emotion may influence CAD development: platelet activation; serotonergic function; fibrinogen and pro-inflamammatory cytokines

Mechanisms that control coagulatory pathways that can result in the development of thrombi are of particular significance with relation to plaque rupture and a detailed review of the research is outside the scope of this thesis. However, as these mechanisms interact with other pathways relevant to the thesis, for the sake of completeness, they will be briefly described here.

Markovitz and Matthews, (1991) suggested that enhanced platelet reactivity to stress is a key mechanism by which stress can trigger ischaemic episodes in everyday life and contribute to CAD. Platelets are central in homeostasis, thrombosis and

development of atherosclerosis and ACS (Lefkovits et al., 1995). Depression is associated with increased platelet reactivity (Musselman et al., 1996, 2000). It has also been shown that CAD patients with depression have greater plasma concentration of platelet specific proteins, beta thromboglobulin and platelet factor 4, compared to non-depressed CAD patients (Laghrissi-Thode et al., 1997). In addition, serotonin is involved in mood and emotion regulation and studies have shown that depression is associated with serotonergic function in both the central nervous system (Meltzer et al., 1989) and in the peripheral circulating platelets (Owens et al., 1994). Most circulating serotonin is actually contained within the platelets, and secreted by them on activation at a site of endothelial injury. This contributes to platelet activation, smooth muscle proliferation, vasospasm and thrombus formation (De Clerck, 1991). Fibrinogen is important in the role of thrombus formation following activation of the clotting cascade, following endothelial injury or plaque disruption. Fibrinogen is a large plasma protein produced by the liver, and a structural component of thrombus once it has been enzymatically converted to fibrin, after activation of the clotting cascade. A raised fibrinogen level has been associated with increased risk of CAD (Kannel et al., 1987; Meade et al., 1993).

Finally, CAD is increasingly seen as a chronic inflammatory response to vascular endothelial injury (Ross et al., 1999). Depression may also contribute in triggering endothelial injury (Miller et al., 1999), triggering dysregulation of the neurohormonal system (Plotsky et al., 1998) or increasing susceptibility to infection by pathogens colonising the vessel wall (Sawayama et al., 2005; Smeeth et al., 2004). Interaction between platelets, leucocytes and endothelial cells stimulate pro-inflammatory, pro-thrombotic processes which contribute to plaque rupture and thrombosis in ACS (Freedman & Loscalzo, 2002). Negative mood or emotions can also adversely affect the inflammatory processes via the action of pro-inflammatory cytokines. This is a two way

process i.e. negative mood can affect cytokines and cytokines can influence mood. Penninx et al. (2003) showed in a study of 3000 adults, that depressed mood was associated with elevated C-Reactive Protein (CRP), inter-leukin 6 (IL-6) and tumour necrosis factor (TNF), after adjustment for confounders. Acute psychological stress has been shown to increase IL-6 by increasing inter-leukin 1 (IL-1) beta gene expression in peripheral blood cells (Brydon et al., 2005). The pro-inflammatory cytokines IL-1 and IL-6 stimulate the HPA axis, initiating a classic stress response resulting in elevated circulating glucocorticoids (Sapolsky et al., 1987). Cytokines induce behavioural and psychological expressions of stress, such as negative emotions, feelings of anhedonia and other recognised symptoms of depression. Depression and acute stressors may maintain the inflammatory response once initiated, by possibly diminishing the immune system sensitivity to glucocorticoid hormones that are responsible for terminating the inflammatory response (Carney et al., 2002).

2.10 Conclusion

To summarise the key points of this chapter which addresses the original questions proposed in the introduction, TMI is a common occurrence in everyday life (Deanfield et al., 1984) and associations have been shown with a variety of emotions (Gullette et al., 1997) and more so with negative emotions. Silent ischaemia is also common (Freedman and Wong, 1998; Deedwania et al., 1992), although of uncertain significance. Pathological ischaemic changes do not always occur with chest pain symptoms (Kinne et al., 1999), and there appears to be an inconsistent relationship between angina and ischaemia (Krantz et al., 1996).

TMI in daily life is more common in CAD patients with particular psychosocial characteristics. A significant association is found especially in patients with depression (Jiang & Blumenthal, 2003).

The principle biological mechanisms suggested so far to account for these associations are haemodynamic changes, heart rate variability (i.e. vagal withdrawal provoking ischaemia), arrhythmias and neuroendocrine changes.

Chapter 3 discusses the methodological limitations to some of the studies that have assessed TMI in daily life, together with important medication-related issues. It also describes the aims and hypotheses of this thesis, and its contribution to understanding the biological mechanisms underlying the association between mood and myocardial ischaemia.

Chapter 3: Methodological issues in the study of psychosocial factors and transient myocardial ischaemia in everyday life

3.1 Introduction

This chapter will describe the objective of the thesis in relation to the three new studies which I have carried out. In particular, I will discuss the methodological issues relevant to the SIS study. This will include highlighting some of the current limitations in interpreting the findings from the ambulatory studies relating to transient daily life ischaemia and physiological mediators previously described in chapter 2. I shall also address the medication issues that influence cardiac parameters and the reason why HRV and cortisol, in addition to ischaemic episodes, were examined in relation to mood in the SIS study.

3.2 Problems in previous ambulatory studies

3.2.1 Diary methods to assess mental and physical activities in daily life

Previous studies have established a methodology for assessing the effect of everyday physical and mental stresses on ischaemia in CAD patients, most often using patient-completed diaries collected during a period of ambulatory ECG monitoring (Gullette et al., 1997; Gabbay et al., 1996; Krantz et al., 1999). These methods enable the relationship between episodes of ST segment depression and diary information on stress and physical activity to be examined. However, such designs have raised a number of methodological issues. Firstly, paper and pencil diary ratings of subjective states raise the problems of non-compliance and of participants filling in diaries

retrospectively later. A recent study revealed that participants faked entries on over 87% of diary cards in a study of chronic pain, and that use of an electronic diary raised actual compliance to 94% (Stone et al., 2003). Electronic diary methods which effectively 'time-stamp' patient responses seem to greatly enhance the validity of ambulatory studies (Bolger et al., 2003), but are quite cumbersome and intrusive, and may not be well understood by older patients.

A second problem with the diary methods that have been used to date, is that they may increase self-consciousness on the part of patients. If the person is required to indicate how they are feeling and what they are doing throughout the monitoring period, they may censor their activities, and endeavour to present a positive image to the investigators.

Assessment of mood has been traditionally based on retrospective self-report in the natural environment or laboratory-based studies but this cannot adequately assess the rather more complex and temporally dynamic psychological, behavioural, and biological processes in the natural environment of everyday life settings. Ecological Momentary Assessment (EMA) has been used as a methodology to overcome this problem (Stone et al., 1994, 2003). EMA involves repeated sampling of current mood and activities, and does not involve the more laborious assessments that have been used in most TIA studies. The EMA approach has allowed investigation of a number of research questions that include: (1) the comparison of retrospective data to momentary data; (2) evaluation of the psychophysiological processes in everyday life; (3) the relation of mood, symptoms and other disease processes to characteristics of the natural environment; and (4) examination of dynamic changes in psychosocial variables that may mediate improvement following treatment. With EMA employed to characterise daily life, assessments are collected at regular time points rather than continuously. It may not be

possible to determine the temporal sequence of events preceding an ischaemic episode over a relatively short monitoring period. Events may be missed and participant burden may lead to lack of compliance with the study. This also leaves the question as to what duration of negative emotions is required to increase the risk of an ischaemic episode, and whether specific mood states increase the risk of ischaemia independently of each other.

Measurements of positive emotions have varied as well. In a review of the literature by Pressman and Cohen (2005), the majority of the studies used simple self - report ratings or questionnaires to assess positive affect (PA). For example, the Positive and Negative Affect Schedule (PANAS; Watson et al., 1988) has separate 10-item scales for PA and negative affect (NA), rather than the two being bipolar ends of the same scale. Most of the studies in the review had a time frame examining general trait feelings rather than the current or moment – by moment mood state. Another measure is the positive affect scale derived from the CES-D (CES-D; Radloff, 1977), as utilized by Ostir et al (2001).

Steptoe et al. (2007) carried out an observational cohort study in which a sample of 716 men and women were assessed by measurement of both PA and NA by momentary sampling throughout the day, examining health-related psychosocial factors. It was found that PA was associated with greater social connectedness, emotional and practical support, optimism and lower levels of depression, independent of socio-demographic factors and NA. In a further study by Steptoe et al. (2007), 72 healthy men were assessed by testing the relationship between cardiovascular markers and neuroendocrine markers and affect measured by EMA and the PANAS questionnaire. The findings were that PA was inversely related to biological responses in the laboratory

and cortisol awakening responses, and those effects were stronger when PA was assessed by aggregating EMA samples rather than using the PANAS questionnaire.

The assessment of trait affect is often based on a single point of assessment, which can be influenced by momentary peak moods or recent moods (Frederickson & Kahneman, 1993). A better estimate of emotional experience is sampling mood at several time points across a period (Cohen et al., 2003), or sampling across multiple time points to distinguish frequency, peak periods, and intensity of emotions and activities (Stone & Schiffman, 1994).

In summary, there is evidence from the ambulatory studies in Chapter 2 that emotional states and the stresses of everyday life can stimulate transient myocardial ischaemia in patients with CAD. Only a few studies (Gullette et al., 1997; Kinne et al., 1999) have shown different types of emotional state to be differentially associated with ischaemia. These studies (Gabbay et al., 1996; Barry et al., 1988; Krantz et al., 1994) have highlighted how difficult it is to work out what proportion of patients show ischaemia specifically related to an emotional state, especially as levels of emotional arousal are typically quite low and subject to recall bias.

In addition, it is unclear whether people who fail to show emotion-related ischaemia do so because they are not actually susceptible (Strike et al., 2006) or because they do not experience sufficient arousal during the monitoring period. Accurate representation of the varying emotions during the day is a particular methodological issue in studies.

One last important point is that in order to assess the relative impact of mental stress and affective states on cardiac function, the effect of physical activity needs to be statistically controlled, as everyday physical activity has been associated with ischaemic episodes (Gullette et al., 1997; Gabbay et al., 1996; Krantz et al., 1994; Barry et al.,

1988). Actigraphy provides the means to partial out physical activity as an independent risk for ischaemic episodes. Some previous studies used diary records of physical activity, later rated by the experimenters for intensity (Gullette et al., 1997; Gabbay et al., 1996). Although experimenter ratings were validated against activity as rated by accelerometer (Patterson et al., 1993), the current availability of lightweight wrist-worn accelerometers which are well-validated against gold-standard measures of metabolic energy expenditure (Starling et al., 1999) really removes the need for detailed diary reports of activity in such studies. It also avoids the risk of patients interrupting normal daily activities by the need to regularly record physical activity. In the SIS study, participants wore an actiwatch to assess physical activity. The objective physical activity results have yet to be analysed and so are not presented in this thesis.

3.2.2 Medication issues

Patients with either suspected cardiac disease or established CAD are often on a range of cardiac drugs to limit the symptoms of angina, minimise risk factors like hypertension and confer prognostic benefit post MI. However, such medications will influence cardiac physiology and hence act as potential confounders in studies relating TMI with emotion. This section describes some of the literature regarding medication in studies on cardiac patients.

There are several inconsistencies in the literature regarding which medication or combination of medications is optimal in the prevention of myocardial ischaemia. There are also inconsistencies regarding the prognostic benefit of treatment of symptomatic versus asymptomatic angina. The studies are heterogeneous with a variety of confounders (age, sex, co-morbidities) to account for and the jury is out as to the optimal treatment of cardiac symptoms.

The question arises as to whether it is necessary to relieve all ischaemic activity or only that occurring with chest pain. Does the present use of anti-anginal medication neglect the early morning increases in TMI and are different dosages required to treat ischaemia adequately? Some studies have addressed the question of whether treatment responses can be improved by combination treatments versus monotherapy, taking into account the circadian pattern of myocardial ischaemia and irregular dosing by non-compliant patients. Effective treatment is important in the early hours of the day in view of circadian patterns of ischaemia. It has been argued that amlodipine, with its intrinsically long half life, either alone or together with a beta blocker, is likely to produce superior ischaemia reduction in clinical practice when patients frequently forget to take medication or dose irregularly (Deanfield et al., 1994, 2002). A brief summary of the major clinical trials regarding TMI in relation to medical therapy is outlined below.

A study by Davies et al. (1995) looked at the effects of the beta blocker agent atenolol, and the calcium blocker agent amlodipine, separately and together, on ischaemia both during treadmill testing and ambulatory ischaemia in the Canadian Amlodipine/Atenolol in Silent Ischaemia study (CASIS). The frequency of ischaemic episodes decreased by 28% with amlodipine ($p = 0.083$, not significant), by 57% with atenolol ($p < 0.001$), and by 72% with a combination of the two ($p < 0.05$ vs. both single drugs; $p < 0.001$ vs. placebo). This study concluded that there was evidence to suggest that ischaemia during treadmill testing was more effectively suppressed by the calcium blocker, amlodipine. This is supported by another study by Deedwania et al. (1999).

However, other studies argue that beta blocking agents alone are more useful. From the study by Davies et al. (1995), ischaemia during ambulatory monitoring was more effectively suppressed by atenolol than calcium blockers. This was supported by studies by Von Arnim et al. (1996) in The Ischaemic Burden Bisoprolol Study (TIBBS),

and Pepine et al. (1994) in the Atenolol Silent Ischaemia Study (ASIST). Another study carried out by Stone et al. (1990) compared the beta blocker, propranolol and alpha-1 receptor blocker, diltiazem as well as a calcium blocker, nifedipine, in the treatment of ambulatory ischaemia in 50 patients with stable angina. All of these medications were compared with a placebo each for 2 weeks in a randomised double blind crossover trial. Compared to the placebo, only propranolol was associated with a marked reduction in all manifestations of asymptomatic ischaemia. In contrast to the marked effects of active agents on ambulatory asymptomatic ischaemia, effects on exercise testing or angina were slight.

The findings of combination therapy are not conclusive. A large study by Fox et al. (1996) has shown no significant benefit in terms of exercise testing or in reduction of the total ischaemic burden from the combination of the two agents (atenolol versus nifedipine, a calcium channel blocker) when compared with each agent alone. Therefore, this suggests that no significant further benefit is gained from adding a second agent with a differing mechanism of action in patients with chronic stable angina. The question persists as to whether patients who show evidence of TMI should receive a beta blocker or calcium blocker, or indeed both, and to what exact prognostic benefit this may confer in patients with stable angina.

In the SIS study, patients who had cardiac symptoms and positive treadmill tests or myocardial perfusion scans, were put on a standard set of medication as per NICE (National Institute of Clinical Excellence) guidelines unless contraindications were present. These consisted of an antiplatelet agent aspirin, a statin for hypercholesterolaemia, an ACE inhibitor, and a beta blocker or calcium blocker agent as an anti anginal or antihypertensive agent, as well as a long acting nitrate depending on frequency or severity of angina symptoms experienced prior to the angiogram. The beta

blocking agent dampens down sympathetic activation, reducing the heart rate, providing symptom control and reduces the likelihood of ischaemia. Episodes of ambulatory ischaemia can occur when patients are sedentary and can be provoked by mental stress. Situations triggering emotional distress cause increases in heart rate (HR), blood pressure (BP) and possibly coronary vasoconstriction. Beta blockers, through their action on central nervous system, may be effective in inhibiting this response. However, this agent is also used to treat psychiatric disorders like panic attacks (Heiser & Defrancisco, 1976) and so may affect mood as well as cardiac ischaemia. When researching the effects of TMI, it would be ideal to include patients off such medication but this is often not feasible to do so. In view of the reduced likelihood of ischaemic episodes during the ambulatory monitoring of medicated patients in the SIS study, other physiological mediators linking emotion with daily stress were studied. These were the measurement of HRV and salivary cortisol, which are both easy to measure and have been used extensively in previous literature in studying emotional state and its influence on CAD.

3.3 Alternative techniques - The Day Reconstruction Method (DRM)

To overcome laborious diary methods and a possibly higher drop out rate of older less motivated and/or depressed subjects, I have adapted a new retrospective diary method for characterising daily life experience called the Day Reconstruction Method (DRM) as developed by Kahneman et al. (2004). This method assesses how people spend their time and how they experience various activities and settings of their lives by combining features of time-budget measurement and experience sampling. Participants systematically reconstruct their activities and experiences of the previous day by constructing a diary consisting of a sequence of episodes. Then they describe each

episode by answering questions about the situation and feelings experienced to provide an accurate picture of experience associated with activities. Evoking the context of the previous day is intended to elicit specific and recent memories, and in doing so, to reduce the error and recall bias that occur when general recollections are studied. Thus, instead of asking patients how they felt at different times of day, they are asked to recall the emotions associated with specific episodes of behaviour. This new method has the advantages of being more efficient, generating less respondent burden, without disruption of normal activities. It also provides an assessment of contiguous episodes over a full day rather than a sampling of moments.

We therefore investigated mood over the ECG monitoring period by having patients complete the Day Reconstruction Method (DRM) interview for the same period. The DRM also provided an opportunity to assess positive as well as negative affective states. Since negative and positive states have been associated with increased and reduced risk of CAD respectively (Burg et al., 2003; Kubzansky et al., 2007), I speculated that patients mood state over the study period would relate to TMI or altered patterns of HRV seen on the ECG or altered patterns of the cortisol profile.

3.4 Aims and hypotheses of the SIS study and ACCENT study

3.4.1 Aims

The three studies described in this thesis were carried out to: -

a) Evaluate the influence of emotional triggers on cardiac health acutely on a moment to moment basis in daily life.

b) Evaluate the influence of emotional acute triggers on the long term adaptation after an established coronary event or procedure, in terms of psychological adaptation and functional recovery.

c) Understand the psychophysiological basis for such effects.

3.4.2 Hypotheses

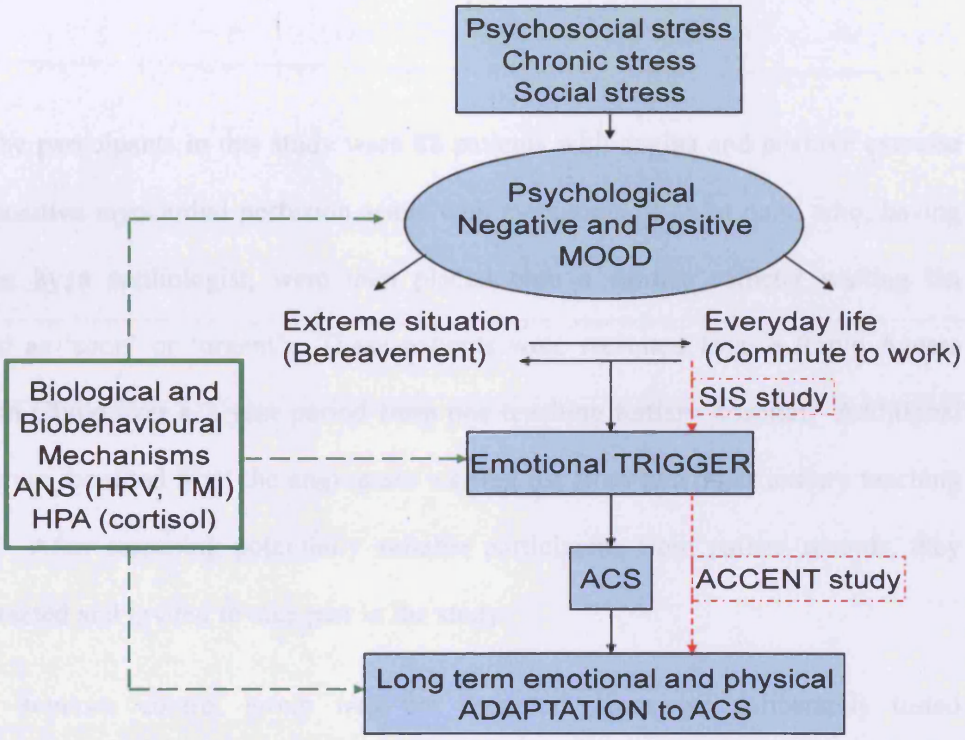
SIS Study

1. Episodes of silent myocardial ischaemia or arrhythmia triggered during ambulatory monitoring will be positively associated with negative mood states.
2. Trait measures of depressed affect as measured by validated scales and moment to moment negative mood states over the day will be associated with reduced heart rate variability. This hypothesis is tested using the DRM.
3. Episodes of silent myocardial ischaemia or arrhythmia triggered during ambulatory monitoring will be positively associated with lower cortisol awakening response.
4. Trait measures of depressed affect as measured by validated scales will be associated with flatter cortisol slopes over the day, and with an exaggerated cortisol waking response in patients with coronary artery disease.

ACCENT Study

5. Acute emotional state during hospitalisation for ACS will predict resumption of work 13 months later independent of both socio-demographic and cardiological variables.
6. Acute emotional triggers of ACS are predictive of poor longer term adaptation to ACS. Psychological and physical triggers, in the hours immediately before the symptom onset of ACS, will differentially predict mental and physical health adaptation 12 and 36 months later.

3.5 Diagrammatic representation of bio psychosocial model of how emotion may influence cardiac health both at the early and late stages of cardiac disease development. Figure 3.1



SIS study **:Silent Ischaemia Study**

ACCENT study **:Acute Coronary Syndrome, Emotion, and Trigger study**

Chapter 4: Method SIS study

4.1 Participants

The participants in this study were 88 patients with angina and positive exercise tests or positive myocardial perfusion scans with symptoms of chest pain, who, having been seen by a cardiologist, were then placed onto a cardiac catheter waiting list prioritised as 'soon' or 'urgent'. These patients were recruited from a Rapid Access Chest Pain Clinic over a 2 year period from one teaching tertiary hospital. Additional patients were recruited from the angiogram waiting list from two other tertiary teaching hospitals. After screening potentially suitable participants from patient records, they were contacted and invited to take part in the study.

A separate control group was not recruited, since we deliberately tested participants before their angiograms. I was confident that a proportion of patients (probably around one third) would turn out not to have CAD, so that I could make a comparison between patients with and without CAD using the single sampling procedure. Participants were deliberately tested before their angiograms were carried out so that I would be blind as to whether or not they had definite CAD.

CAD was subsequently documented by a positive angiogram and / or a history of myocardial infarction, coronary artery bypass surgery, or percutaneous coronary intervention (PCI).

We excluded patients with valvular disease, cardiomyopathy, congestive heart failure, Wolff-Parkinson-White syndrome, and uncontrolled hypertension as well as

those with severe renal, neurological, or pulmonary disease. Also excluded were patients with chronic disease, which would interfere with general mobility, or psychiatric disorders as well as those not fluent in English, which invalidates the interview procedure. The study was approved by the medical research ethics committees of Royal Free Hospital, St. Mary's Hospital, and University College Hospital, and all patients gave written consent.

4.2 Study design

Patients were contacted individually and recruited if they fulfilled the study criteria. Patients attended the study office on two consecutive mornings. On the first morning, physical measurements were taken, the ethical consent form was signed, and the patient was trained in collecting saliva samples. The holter monitor was also attached. On the second morning, the holter monitor was returned and saliva samples and diary collected, and the patient completed the DRM in an interview, which I conducted. This is described in a later section in this chapter in more detail. All patients remained on their regular medication.

4.3 Psychosocial measures

Socio-demographic data, clinical data, and psychological data were collected at the interview. All participants recruited to the study were also asked to fill out a background questionnaire in their own time and bring to the first session of the study.

4.3.1 Socio-demographic data

Socio-economic position was assessed at baseline using a number of measures contained in the interview (see appendix 3). Patients were asked for details of their level of educational attainment. This is an indicator of socio-economic position that is easily measured, applicable to people not in the active labour force as well as those in stable employment over time. The level of reported educational attainment was categorised into 7 groups; no educational qualifications, up to school certificate, CSE's, GCSE's, A level , Degree and Other but, for the purpose of statistical analysis, this was combined into 'Primary' and 'Secondary or above'. The participants' level of yearly income was classified into five categories; ranging from less than £10,000, to over £40,000. However, for the purposes of statistical analysis, groups were categorised into 'income above or below £20,000'. A deprivation index was also computed based on four criteria: living in a crowded household (defined as one or more person per room), not having access to a car or van, renting as opposed to owning their home, and being in receipt of state benefits. Participants were classified as low deprivation (negative on all items), medium deprivation (1 positive score) and high deprivation (2-4 positive items). The deprivation index gives a broader measure of social deprivation and access to resources and is based on the scale developed by Townsend (Townsend, 1990).

4.3.2 Clinical data

Clinical information was taken from the patients with respect to symptoms of chest pain, frequency, and cardiac investigations, such as an exercise tolerance test or a myocardial perfusion scan (otherwise known as a thallium scan), as well as established cardiac risk factors and current medications.

4.3.3 Psychological trait assessment

The study questionnaire was a compilation of standard psychometric instruments designed to assess different aspects of emotional experience and well-being together with measures of health behaviours. The use of these measures is well established and all have been previously employed in assessing cardiac patients. Psychological and psychosocial factors including depression, anxiety, social support, socio-economic status, financial strain, work-related stress and marital stress will be analysed in my thesis. Questionnaires were used at baseline and at 6 months follow up.

The measures used in the baseline questionnaire (see appendix 4) were:

4.3.3 i) Illness Attributions Questionnaire

Patients' beliefs concerning the causes of their heart problem and heart disease symptoms were measured using this questionnaire based on the major categories of causal attribution described by French et al. (2001) and Gudmundsdottir et al. (2001), and on the causal belief items from the Illness Perception Questionnaire (Weinman et al., 1996). It consisted of 16 items such as 'My illness is hereditary – it runs in my family', 'A germ or virus caused my illness', etc. Answers were scored as yes (2), maybe (1) and no (0). Scores could range from 0 – 32.

4.3.3 ii) Hospital Anxiety Scale (HADS anxiety)

The anxiety component is one of two 7 item self-report screening sub-scales taken from the Hospital Anxiety and Depression Scale (HADS), a well established measure of psychological distress in medical patients. The complete measure was originally developed to detect the presence of anxiety and depression in a clinical population of medical outpatients suffering from a wide variety of illnesses (Zigmond &

Snaith, 1983). HADS has been widely used in studies with patients following AMI as an index of outcome, and to assess quality of life and psychological well-being (Trzcieniecka-Green & Steptoe, 1996; Whitmarsh et al., 2003). In this study, only the anxiety sub-scale was used (HADS anxiety scale). This 7-item scale is scored from 1 (not at all anxious) to 3 (very often anxious), but with 5 items reverse scored. Total scores could range from 0 to 21. Higher scores reflect greater anxiety and patients were classified as being at least moderately anxious if their scores exceeded the recognised threshold of ≥ 8 (Zigmond & Snaith, 1983). HADS was developed for patients with physical illness and was found to be a reliable instrument for detecting severity of emotional distress in a review of validation data by Herrmann (1997).

4.3.3 iii) Medical Outcome Short Form 36 (SF36)

Health status and quality of life were measured using the SF36 health status measure, adapted for use in the UK (Ware & Sherbourne, 1992). The SF36 assesses 8 domains of health-related quality of life. There are 36 individual items, which are grouped into 8 multi-item subscales representing the 8 domains. These include physical function (limitations in physical activity due to physical health), role limitations due to physical problems (problems with work and daily activities due to physical health), bodily pain (severity), general health perception (evaluation of physical health and likelihood of improvement), vitality (energy level), social functioning (interference with social activities due to physical and emotional health problems), role limitations due to emotional problems (problems with work and daily activities due to emotional problems), and mental health (anxiety and depression). Each subscale is scored so that 0 represents the lowest (worst health) and 100 the highest possible (best health) level of function. Scores for the 8 subscales at baseline were calculated, and changes in the quality of life was measured by following the procedure advocated by Ware et al. (1994),

to calculate the physical and mental health status. This measure also contains 2 summary component scores; summary physical health status was calculated by averaging scores for the physical health domain subscales (physical function, role limitations due to physical problems, bodily pain and general health perception) while summary mental health status was calculated by averaging scores for the mental health domain subscales (vitality, limitations due to emotional problems, social functioning, and general mental health). The SF36 has been used in a number of studies investigating quality of life among cardiac patients (Brown et al., 1999; Fogel et al., 2004; Rumsfeld et al., 1999). In previous published studies, internal reliability statistics have exceeded the minimum standard of 0.70 recommended for measures used in group comparisons (Ware & Gandek, 1998).

4.3.3 iv) Life Orientation Test (LOT)

This questionnaire is a measure of positive outlook on life (Scheier & Carver, 1992). Optimism is measured by using the LOT, an eight item self-report measure (plus two filler items) assessing generalised expectancies for positive and negative outcomes. Participants were asked to indicate their degree of agreement with statements such as 'In uncertain times, I usually expect the best' using a 5 point scale ranging from 0 (strongly disagree) to 5 (strongly agree). Of the 8 scored items, 4 are worded in a positive direction and 4 are worded in a negative direction. Total optimism scores equalled 32 with higher scores indicating greater optimism. Cronbach's alpha was 0.82 (Scheier et al., 1994). The benefits of optimism have been associated with rapid recovery after cardiac procedures surgery and improved quality of life in cardiac patients (Scheier et al., 1989).

4.3.3. v) Beck Depression Inventory (BDI)

Depression was measured using the second edition of Beck Depression Inventory (BDI), a standard measure of depressive symptoms (Beck, et al., 1988). This is a 21 item self-report instrument that assesses severity of depression symptoms over the past week, by asking participants to rate the severity of symptoms ranging from no symptoms (0) to severe (3). BDI scores can range from 0 to 63; BDI scores of 10 or greater indicate symptoms of mild to moderate depression (Ziegelstein et al, 2000). The BDI has been used in a number of studies of patients with cardiac disease and is considered a valid measure of depression (Buchanan et al., 1993; Crowe et al., 1996; Frasure-Smith et al., 1997). A meta-analysis of studies (including cardiac patients) focusing on the psychometric properties and internal reliability of the BDI yielded a mean coefficient alpha of 0.81 for non-psychiatric participants (Beck et al., 1988).

In addition to the set of psychosocial measures outlined here that comprised the baseline questionnaire, there were four other additional measurements used in the follow up questionnaire at 6 months.

The additional measures used in the follow up 6 month questionnaire (see appendix 6) were:

4.3.3.vi) *Social Network*

These were measured using the Social Network Index developed by Cohen et al. (1997) as an index of the diversity of social interactions. Participants were asked about the frequency of their interactions within a typical fortnightly period with 12 sets of contacts (e.g. children, friends, work colleagues). Greater values represented more diverse social networks, and scores could range from 0 to 12 (higher scores indicating

larger social networks). For the purposes of analysis, participants were categorised into three groups; small social network (0 to 3 social contacts), medium social network (4 to 5 social contacts) and large social networks (6 or more).

4.3.3 vii) Social Support

Social support was assessed using a scale previously shown to predict survival in elderly patients following myocardial infarction (Berkman et al., 1992). Participants were asked how many people they could count on for emotional support and responses were allocated to four categories: no support, 1 person, 2-3 people, 4 or more people.

4.3.3 viii) Cook and Medley Hostility Scale

The Cook and Medley Hostility (Ho) scale (1954) is a measure of hostility derived from the Minnesota Multiphasic Personality Inventory and found to be related to both the severity of coronary artery disease and the development of coronary artery disease (Williams et al., 1980; Barefoot et al., 1983). Barefoot et al. (1989) described three of the derived subscales as predictive of mortality: cynicism, hostile affect, and aggressive responding. The reliability of the scale is satisfactory with an internal consistency being reported by the original authors as 0.86 and this has been further confirmed in other studies (Smith et al., 1985). I used 14 items in the hostility scale with 10 being related to cynicism and 4 related to aggressive responding. It has been suggested that high scores on cynical hostility is associated with a particularly unhealthy psychosocial risk profile for CAD (Smith et al., 1985).

4.3.3 ix) Health Locus of Control

This scale was developed from the original Health Locus of control developed by Wallston et al. (1976) as a unidimensional measure of peoples' beliefs that their health is or is not determined by their behaviour. The scale has subsequently been developed to

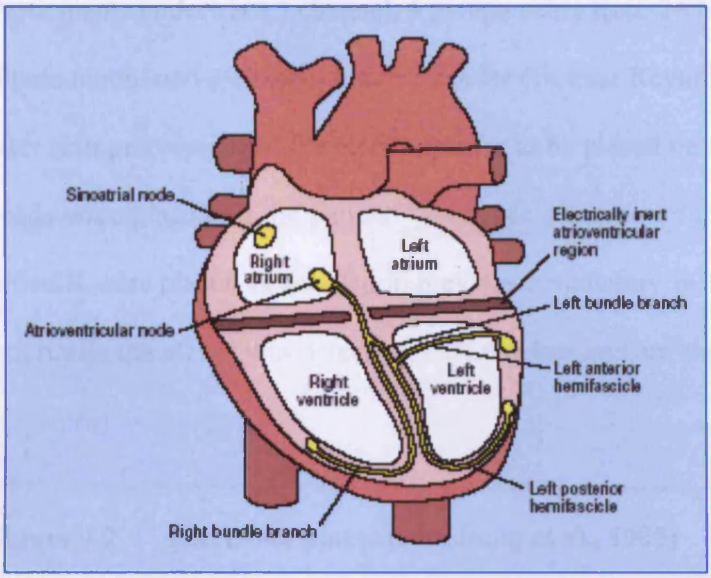
form a multidimensional health locus of control scale (Wallston et al., 1978) to include three 6 item Likert scales. This reflects three dimensions of health locus of control beliefs: internality (IHLC) i.e. a person believes his behaviour influences his health status; powerful others (PHLC) i.e. a person believes his health is influenced by the actions of other people e.g. doctors; and chance (CHLC) externality i.e. the person believes his health status is influenced by the actions of other people or due to fate, luck or chance. These health related behaviours determine a persons health status in part. The scales are internally consistent and valid. Each subscale is correlated approximately 0.6 with its counterpart (Wallston et al., 1978).

4.4 Ambulatory ECG monitoring

4.4.1 Background

I will first explain the basic principles on which the ECG is based on, followed by an explanation of the ECG electrode placement and ECG changes that occur with cardiac ischaemia.

Figure 4.1 Schematic representation of the heart.



Briefly, deoxygenated blood from the body is received by the top chamber- the right atrium. There is a pacemaker here called the SAN (Sino-Atrial Node). This fires across the atria to the Atrio-Ventricular Node (AVN), through the bundles of electrical fibres and then across the right and left ventricles. This wave of electrical excitation across the ventricles or the bottom chambers of the heart causes them to contract simultaneously to pump out oxygenated blood through the aorta to the body once more. The electrical signals correspond to the firing of the atria and the contraction and relaxation of the ventricles i.e. the bottom chambers of the heart. These anatomical, functional and corresponding electrical changes that occur can be represented on the ECG, which is essentially an electrical recording from the heart. The changes corresponding to transient myocardial ischaemia in everyday life setting are illustrated in Figure 4.3.

4.4.2 Electrode placement

Participants underwent 3 channel, 6 patient cable lead, 24 hour holter monitoring. An amplitude modulated 3 channel holter recorder (Delmar Reynolds Life Card CF) was used. After skin preparation of the electrode sites to be placed on the chest, three sets of bipolar leads were placed on the patient. Electrode placement for channels CM2, CM5 and modified II were placed as detailed in previous ambulatory ECG studies (Jiang et al., 1995) to optimise the efficacy in detecting TMI changes and are shown in Figure 4.2.

Figure 4.2 Electrode placement (Jiang et al., 1995)

Monitoring was initiated between 9.00 am and 11.00 am. Postural testing in 5 positions (supine, left lateral, right lateral, sitting and standing) each for 2 minutes was performed after an 8-minute calibration period in order to exclude artefactual ST-segment change.

4.4.3 ECG analysis

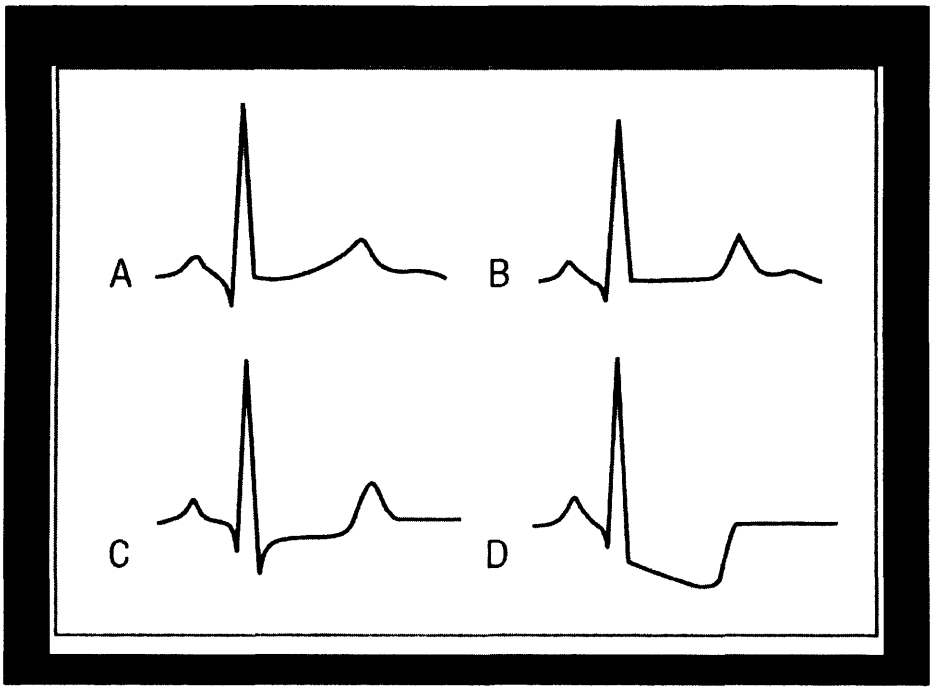
All ECG analyses were carried out by experienced technicians at Hertford Cardiology Services. Calibrated 24 hour tapes were initially analysed visually by an experienced cardiac technician. An ischaemic response is defined as horizontal or downsloping ST depression >1mm or < 1.5mm, upsloping, below the isoelectric baseline, measured at 0.08 seconds after the J point and persisting for at least 40 seconds. Measures of ischaemia were made by two technicians and also verified by a cardiologist blind to patient characteristics, and will be analysed in the SIS study. For each episode, the time of onset, duration and magnitude of ST segment depression, accompanying heart rates at the onset of ST depression and peak heart rate during the episode was recorded. Figure 4.3 illustrates the sequence of ST changes that occur with cardiac ischaemia on an ECG. ST segment analysis is described in chapter 7 in relation to heart rate variability and mood as assessed by the DRM.

Arrythmias on the 24 hour recording were also recorded such as any episodes of a regular, abnormally fast heart beat (tachycardia). A tachycardia refers to a heart rate of greater than 100 beats per minute, caused by rapid firing of electrical impulses. If this is from a focus above the atrio-ventricular node (AVN) in the heart then this is called a supraventricular tachycardia (SVT) because the tachycardia originates above the ventricles of the heart. Episodes of ventricular tachycardia (VT) were also noted, in which there is a tachycardia of three or more beats in a row originating from the ventricle at a rate of more than 100 beats per minute.

As well as this, the number of couplets (two consecutive ventricular beats, preceded and followed by a normal beat), triplets (three consecutive ventricular beats, preceded and followed by a normal beat), and ventricular ectopics were recorded which

is an extra heartbeat originating in the lower chamber of the heart due to abnormal electrical activity.

Figure 4.3 ST changes with ischaemia on an electrocardiograph.



A normal wave form:

The first wave is the P wave – corresponding to the atria firing; followed by the next spike that is the QRS complex-corresponding to the ventricles contracting. The following wave after this is the T wave corresponding to the ventricles relaxing.

***B** flattening of ST segment making T wave more obvious*

***C** horizontal ST segment depression*

The part we are interested in is the ST segment that becomes altered when the heart does not receive an adequate supply of oxygenated blood, due to narrowed coronary arteries.

***D** downsloping ST segment depression*

4.5 Heart Rate Variability analysis

In this study, heart rate variability (HRV) analysis was assessed both in the frequency and time domains.

4.5.1 Method of analysis

HRV analysis was carried out using the HRV tools package designed for Del Mar Reynolds holter monitors. The 24 hour RR sequences were entered into the analysis program and were screened for data quality. The following exclusions were applied, as recommended by the manufacturers:

- Any aberrant beats (ventricular and atrial ectopics).
- Any RR intervals < 300ms or > 3000ms.
- Any RR intervals < 80% or > 120% of the previous RR.
- Any intervals > three times the standard deviation of the preceding period.

Frequency and time domain measures were computed for every 30 minutes of the 24 hour period, and also for day and night period. The timing of day and night was set on an individual case basis, depending on the hours specified in the DRM diary.

4.5.2 HRV indices

The HRV frequency analysis computed values for the following variables:

- Total power in ms^2.

- Very low frequency (VLF) power between the limits 0.003 Hz and 0.04 Hz in ms^2.
- Low frequency (LF) power in the range 0.04 Hz to 0.15 Hz in ms^2.
- High frequency (HF) power in the range 0.15 Hz to 0.4 Hz ms^2.

In addition, the normalised LF and HF power were calculated using the following formulae:

Low frequency normalised (LFn) = (LF*100)/(total – VLF – Ultra low frequency)

High frequency normalised (HFn) = (HF*100)/(total – VLF – Ultra low frequency)

Normalisation minimises the effect of changes in total power on the values of LF and HF.

The time domain analysis generated the following values:

- RR interval in ms.
- The square root of the mean square difference between successive RR intervals (RMSSD) in ms.
- The number of differences between successive RR intervals > 50ms, expressed as a proportion (pNN50).

The indices used for analysis were interbeat interval (IBI or RR interval in ms), normalised high frequency power (HFn) and normalised low frequency power (LFn) in Chapter 5, which presents the overall pattern of HRV results and in relation to time, age, CAD medication and mood. The same indices are used for analysis in Chapter 7, which presents results of HRV patterns in patients with an abnormal ECG and in relation to the ischaemic periods identified on abnormal ECG's. In addition, a further index was

analysed; normalised very low frequency power (VLFn), as this yielded interesting results. The sample rate was 4.0 Hz and detrending was carried out using linear subtraction (which removes the best bit straight line). Interpolation of missing values was carried out using the cubic spine approach (Task Force, 1996).

Each analysis was checked by hand to ensure that the data was satisfactory using the waterfall plot view of the spectrum. This is illustrated in Figure 4.4, which shows the frequency spectrum for one individual from 12:00 h on day one until 12:00 h on day two. The height of the bar at each frequency indicates the power of the spectrum in that wave band. A high frequency peak between 0.2 and 0.3 Hz can be seen during the very early hours of the morning, indicating greater HF power during sleep. I also checked the overlaid spectra for day and night time. An example is shown in Figure 4.5, where the greater power in the high frequency band during the night is apparent.

Heart rate and HRV data were available for 85 patients. Two participants had monitors in which the battery ran low and one individual had the electrodes pulled off and which they then replaced themselves wrongly, invalidating the ECG recordings obtained, and so was not included in the analysis. One other patient was excluded from the analyses since data recorded was unsatisfactory in the quality of the recording, leaving 84 patients in the analysis. Because of the varying start and finish times of the assessments, the analysis of hour means would have resulted in a substantial amount of missing data. Therefore, HRV was divided into four 4 longer phases, as with the DRM: day 1 morning (start of monitoring – 13:00h), day 1 afternoon (13:00 – 18:00h), day 1 evening (18:00 – 23:00h), and day 2 morning (7:30 – end of monitoring). Day and night averages were also analysed.

Figure 4.4 Waterfall spectrum plot

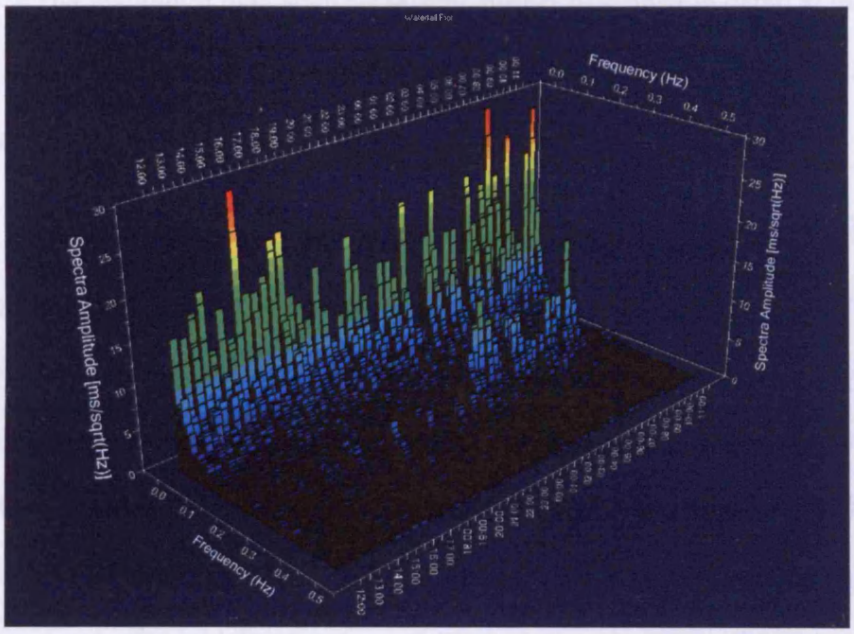
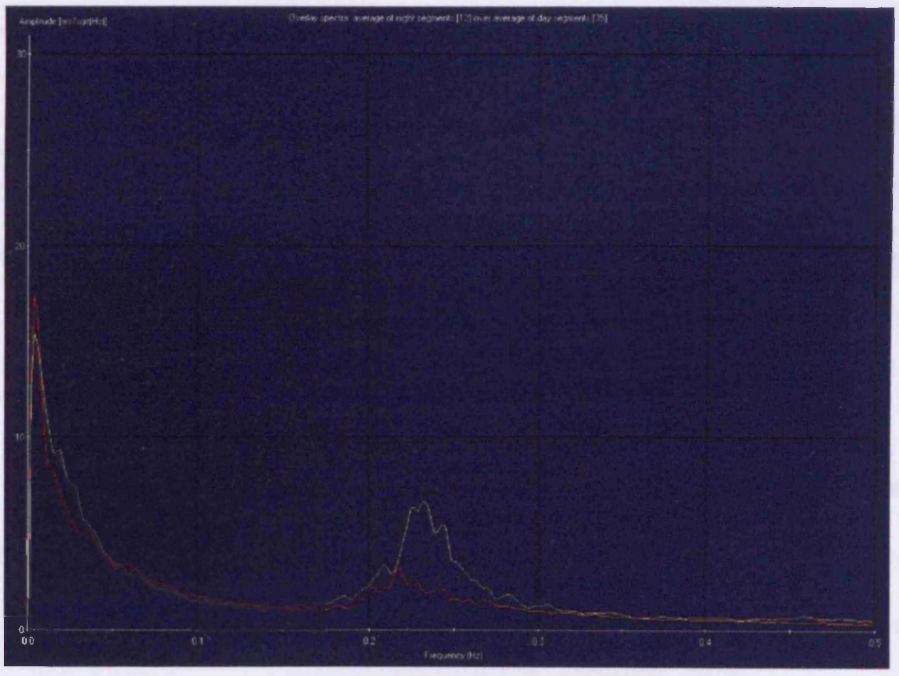


Figure 4.5 Overlay spectra: average of night segments over average of day segments



4.6 Data analysis for transient ischaemia

The method of data analysis will be further described in detail at the beginning of each of the results chapters (chapters 5-8) but a broad overview in general is given in this section.

The analysis of the ambulatory monitoring period involved identifying episodes of symptomatic and asymptomatic ischaemia, and assessing concomitant mood and cortisol profile. Associations with negative moods was based on the case-crossover method, comparing time segments prior to the episode of ischaemia starting with the "control" periods of a) the comparable time segments the hour before and b) the time segments the hour after the ischaemic episode. A similar approach will be used to analyse heart rate and heart rate variability indices, both in the time and frequency domains.

The overall ambulatory records were analysed using analysis of variance and co variance, stratifying by individual in order to control for within-person confounding, and random effects regression models as appropriate.

The patients showing ischaemic changes on ECG were compared with the remainder using χ^2 tests for categorical variables and t-tests for continuous socio-demographic, clinical and psychosocial variables. The groups were also compared on the heart rate, DRM mood variables and cortisol measures using analysis of variance and covariance.

Investigation of the mood and cardiovascular responses surrounding each ischaemic episode was carried out by identifying the minute of onset and offset of each episode. Five minute segments of DRM mood and heart rate variability measures were

then computed for the onset segment, the three 5 minute segments preceding onset, the end segment, and the two 5 minute segments following the end of the episode (seven segments in total). An example of this is given in the results chapter 7. The data over the episode period was compared with control periods.

For DRM mood, we used the corresponding time points for the hour before and the hour after the ischaemic episode. These two control periods were then averaged to generate an aggregate control mood profile to compare with the ischaemic period. In the analyses of heart rate and heart rate variability, only the control period 1 was assessed. The reason is that many ischaemic episodes took place towards the end of the 24 hour monitoring period, so there were too many cases with data missing from control period 2 for it to be included in the analysis.

The analyses of acute mood changes and heart rate variability responses were also carried out as follows. First, a repeated measures analysis of variance was carried out for the 7 *segments* of the ischaemic / arrhythmic period. This showed whether there were systematic changes in mood or HRV in the minutes before and after each ischaemic episode of ST depression / VT. Second, repeated measures analysis was performed with *period* (ischaemia or control) and *segment* (the 7 within-period segments) as within-subject factors. Finally, analysis of covariance was carried out to compare specific segments, with gender and use of beta blockers as covariates.

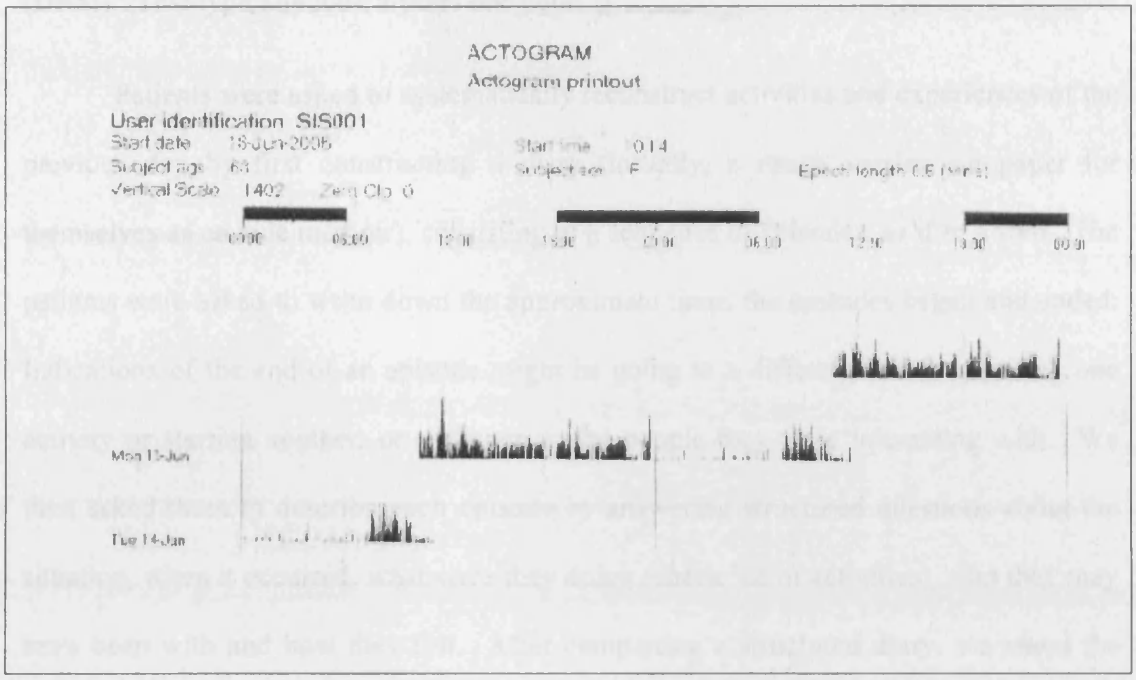
Data relating to the question as to whether mood state before the onset of the ischaemic episode predicted the magnitude of autonomic response during the episode was also analysed. Since mood was relatively stable in the 15 minutes before episode onset, the three 5 minute segments were averaged to generate a single value for each mood. These mood ratings were then correlated with the changes in HRV indices between 15 minute pre-episode, and the 5 minute segment in which the episode started.

4.7 Physical activity monitoring

Energy expenditure was measured using a wrist-worn actiwatch accelerometer, which assessed activity in one dimension (Actiwatch, Cambridge Neurotechnology, Cambridge, UK). This device (distributed in the USA by Mini Mitter) is a piezoelectric motion sensor. Data were analysed using proprietary software to define the following parameters: wake time in the morning, sleep latency (interval between going to bed and falling asleep), and sleep efficiency (proportion of the time in bed spent sleeping). The Actiwatch has been validated against polysomnography in both healthy populations and insomnia samples (Lichstein et al., 2006) and is used extensively in population and clinical studies (Lauderdale et al., 2006).

Subjects were asked to input unprompted ratings of pain whenever they experienced angina and recorded stress levels after any perceived stressful events during the day into the Actiwatch. This was scored on a scale of range 0-10 with 1 being mildly stressed and 10 being much stressed. Figure 4.6 below illustrates a typical actogram report from one of the participants (anonymised for data protection). Here it can be seen from the length and density of black lines corresponding to physical movement sensed by the Actiwatch put on that the participant had the watch placed on approximately at 11.30 am and went to sleep approximately midnight and awoke at about 7.00 am the following day. The actogram produced not only verifies patients' reported awakening times relevant to measuring awakening cortisol responses and compliance regarding salivettes collection but also gives data about the sleep quality which is also thought to affect the HPA axis.

Figure 4.6 Actogram



Data relating the actogram findings with cortisol profile over the 24 hours and further work analysing actogram data with sleep quality and CAD, medication status and ECG changes is being planned in the near future and have thus not been presented in the thesis.

4.8 Physical and mental activity assessment in daily life: DRM

On day 1, before the monitoring period, participants completed a short half hour interview answering socio-demographic, clinical and psychosocial questions. The interview was completed face to face, and answers were recorded directly onto computer SPSS software. After the 24 hour ECG monitoring period, on day 2, a longer semi-

structured interview was carried out to complete the Day Reconstruction Method (DRM). This typically took around one hour.

Patients were asked to systematically reconstruct activities and experiences of the previous day by first constructing a diary (initially, a rough version on paper for themselves as an aide memoir), consisting of a sequence of episodes, as if in a film. The patients were asked to write down the approximate times the episodes began and ended. Indications of the end of an episode might be going to a different location, ending one activity or starting another, or a change in the people they were interacting with. We then asked them to describe each episode by answering structured questions about the situation, when it occurred, what were they doing (check list of activities), who they may have been with and how they felt. After completing a structured diary, we asked the participants to rate the feelings experienced (happy, tired, frustrated etc.) during each episode, on an affect scale ranging from 0 to 4. A rating of 0 meant one did not experience that feeling at all. A rating of 4 meant that this feeling was a very important part of the experience. Participants were asked to choose the number between 0 and 4 that best described how they felt for each of the episodes listed in the 24 hours of monitoring.

The DRM is a relatively recent method involving a retrospective report on an emotional state with a procedure designed to facilitate accurate recall. To date, the method appears to be successful reproducing a complex pattern of diurnal variation in tiredness which has previously been obtained in an ESM study (Kahneman et al., 2003) but there is little in the literature on validity as few studies have used the DRM since it was first described (Kahneman et al., 2004). There are no within-subject comparisons performed with respect to using this new method compared to momentary assessment. From the personal experience of carrying out the SIS study, the majority of participants

found it to be an acceptable, easy-to-follow method but a minority did find it time consuming, laborious, with difficulty recalling episodes accurately unless prompted by the accompanying spouse or required guidance from the interviewer.

4.9 Day Reconstruction Method analysis

4.9.1 Scoring the DRM

The DRM provides a continuous sequence of activities with associated affect ratings. So, for every minute of the waking day, information is available about what activity every patient was engaged in and what affects were being experienced. However, the episodes vary widely in number, timing and duration. This is illustrated in Table 4.1, which details episodes between 12:00h and 15:00h for three patients. It can be seen that two patients reported four episodes during this period, and one patient reported five. However, the length of episodes varies between individuals, as do the activities and affect ratings associated with these activities.

In order to relate affect derived from the DRM to biological measures, it is necessary to derive measures for each period of the day, rather than each activity. The following scoring system was therefore used. The recording was divided into 5 minute segments, timed chronologically from midnight on the first monitoring day (e.g. segment 128 = 10:40 – 10:45h). For each segment, the corresponding DRM episode was identified for every individual. Taking the example in Table 4.1, between 14:15 and 14:20h, patient 1 was in episode 3 of the afternoon (socialising), patient 2 was in episode 3 (travel), and patient 3 was in episode 4 (working). The ratings for each affect were then attached to every time segment, irrespective of ongoing activity. Almost all the

DRM episodes were timed to the nearest 5 minutes (e.g. beginning at 12:20h or 12:25h, but not at 12:23h). The result is a rating on each affect dimension for every 5 minute of the recording period.

Table 4.1 Illustrative DRM results

Activities of three patients between 12:00h and 15:00h

	12:00				13:00				14:00				15:00
P1	Eating	Travelling					Socialising					Housework	
P2	Working						Socialising			Travel		Working	
P3	Preparing food	Watching TV						Dressing		Working		Socialising	

Five minute segments were selected to allow affect surrounding individual biological measures to be analysed precisely. For example, if transient myocardial ischaemia occurred at 14:43, the emotions during the 5 minute segment 14:40-14:45 could be analysed and compared with the segments preceding (14:30-14:35; 14:35-

14:40) and following (14:45-14:50, 14:50-14:55) the episode. However, the 5 minute segments were also averaged into hour means of all the waking time of the 24 hour monitoring period.

4.9.2 Derivation of morning, afternoon and evening affect measures

The DRM was begun at the beginning of day 1. However, patients woke up at different times on both days, went to bed at different times, and continued the DRM until their second interviews at different times of day 2. Table 4.2 summarises the number of patients contributing to hourly affect means for days 1 and 2. DRM data were unfortunately lost altogether from one individual because of a computer failure. Of the remaining 87, one individual did not continue the DRM beyond 16:00h because of an accidental fall in the evening meant that the participant was transferred to hospital.

As can be seen from Table 4.2, 84 patients provided DRM results for most of the hours of day 1, but with some variations. For example, two patients provided no data between 14:00 and 15:00h on day 1, since they were taking afternoon naps throughout that time. On day 2, there was no hour block during which all participants provided DRM data.

In order to maximise the number of patients in the main analysis, the recording period was therefore divided into 4 longer phases: day 1 morning (wake up – 13:00h), day 1 afternoon (13:00 – 18:00h), day 1 evening (18:00 – bedtime), and day 2 morning (wake up 13:00h). 84 patients provided data for all phases. The mean for each affect was also calculated for the entire study period.

Table 4.2 Availability of hourly DRM data

Hours – day 1	N	Hours – day 2	N
4:00 – 7:00	44	4:00 – 7:00	52
7:00 – 8:00	77	7:00 – 8:00	82
8:00 – 9:00	85	8:00 – 9:00	85
9:00 – 10:00	85	9:00 – 10:00	85
11:00 – 12:00	84	11:00 – 12:00	42
12:00 – 13:00	84	12:00 – 13:00	24
13:00 – 14:00	87		
14:00 – 15:00	87		
15:00 – 16:00	85		

Hours – day 1	N	Hours – day 2	N
17:00 – 18:00	87		
18:00 – 19:00	84		
19:00 – 20:00	84		
20:00 – 21:00	84		
21:00 – 22:00	84		
22:00 – 23:00	81		
23:00 – 24:00	40		

The DRM provides ratings of 8 affective states: happiness, warmth, anger, depression, worry/anxiety, frustration/annoyance, impatience, and tiredness. Several of these negative affective states are inter-correlated. In order to reduce the amount of data presentation and avoid the problem of duplication, for this analysis I have focused on 4 states: happiness, depression, tiredness, and combined negative affect (average of anger, depression, frustration and worry). Additionally, when looking at more detail in mood

changes surrounding acute ischaemic episodes in chapter 7, I have focused on additional mood states e.g. combined affect (a composite score of the difference between overall negative affect and positive affect) that may surround the ischaemic episodes.

4.10 Salivary cortisol measurement

Cortisol was assessed from saliva collected with the salivette sampling device (Sarstedt, Rommelsdorf, Germany). This non-invasive technique can be used at home and interferes only minimally with normal daily routines. Cortisol in saliva reliably reflects free (unbound) fraction of cortisol in plasma (Kirschbaum & Hellhammer, 1989).

Awakening was either spontaneous or by alarm clock. Subjects were asked to refrain from drinking caffeinated beverages and smoking before saliva sampling. Furthermore, they were instructed not to brush their teeth before the end of sampling time in the morning, not to eat and drink in the 10 minutes before sampling, and to rinse their mouth with water before sampling.

Nine saliva samples were collected over the 24 hour monitoring period. On the first day that participants arrived, the first sample was taken at 09:00 on arrival. Subsequent samples were then taken at 11:00, 14:00, and 19:00 and before bedtime. On the following day, samples were taken on waking, 15 minutes after wakening and 30 minutes after wakening and then the final ninth sample was taken on arrival for interview at 09:00 (about 2 hours after waking). Some patients were scheduled to start the study at around 11:00 instead of 09:00. The first sample for these individuals was taken at 11:30, the second sample taken at 14:00, then 19:00 and before bed time. On the following day, samples were taken on waking, 15 minutes after wakening, 30 minutes after wakening

and another sample at home at 09:00. The final ninth sample was taken on arrival for interview about 11:00. Samples were collected using cotton dental rolls held in the mouth until saturated, and then stored in salivettes that were collected from participants at the end of the ECG monitoring period. Tubes were returned personally to the investigator on day 2. These were then stored in a freezer at -20°C until analysis, centrifuged at 2400rpm for 5 minutes, and analysed using a high sensitivity chemiluminscence assay at the Technical University, Dresden (Germany).

Separate analyses were carried out of cortisol over the day (measured on day 1) and the cortisol awakening response (CAR) measured on day 2. Cortisol over the day was analysed using repeated measures analysis of variance with clinical group (CAD/non-CAD) and depression group (BDI $\geq$ 10 / < 10) as between-subject factors, and the 5 samples over the day and evening as within-subject factors. Further details of the analysis of the cortisol secretory profile is described in chapter 6.

4.11 Data Storage

All data collected was treated as confidential. Interview data, consent forms, questionnaires and follow up data were kept in a locked filing cabinet with restricted access. Data was anonymised and entered onto a computerised database which was password protected.

4.12 Other statistical analyses

Data was collected using a sample of 88 participants. The data were analysed using the Statistical Package for Social Sciences (SPSS). Different approaches to analysis were considered and these are described further in the result chapters 5-8.

4.13 Clinical follow up

Clinical follow up was carried out on all participants at 6 months after the initial study was carried out. Psychosocial measures were repeated using telephone interview (see appendix 5) and postal questionnaires (see appendix 6), which measured in addition to the previous psychosocial measurement at baseline, social network and support measures, hostility and health locus of control measures as described earlier in section 4.2.

4.13.1 Telephone interview follow up measures

The telephone interview was based on a similar interview format used in an earlier study (Ziegelstein et al., 2000) that assessed 10 adherence behaviours relevant for cardiac patients who had suffered an ACS. Participants were assessed for progression of CAD in terms of recurrence of cardiac symptoms or new cardiac events requiring hospital admission.

Patients were also asked about any other new illnesses diagnosed as well as whether or not they had attended a cardiac rehabilitation programme (if appropriate) and

how many sessions of the total number they had attended. They were also asked whether or not they had implemented advice given to them by medical staff including increasing their level of exercise, maintaining a healthy weight, managing their stress levels appropriately, maintaining their alcohol intake within recommended limits, following a healthy diet and giving up smoking (if applicable). Patients were also asked what medication they were prescribed and whether they were compliant.

An adherence index was developed, similar to the one use by Ziegelstein et al. (2000), to assess 5 adherence behaviours relevant to patients who have had an ACS: (1) taking medications as prescribed, (2) eating a healthy diet, (3) maintaining a healthy weight, (4) exercising regularly, (5) managing / reducing stress levels. Scores ranged from 0 (partial or non-adherence) to 1 (adherent). Patients could therefore score a minimum of 0 to a maximum of 5.

Although this study is not powered to assess prospective associations of psychosocial risk factors and clinical outcomes, analysis of the follow up data will give some indication as to whether a larger scale study would be worthwhile.

Chapter 5: SIS study Results – The relationship between heart rate variability, depression and other moods in patients with suspected coronary artery disease

5.1 Introduction

The aim of these analyses is to describe the associations between heart rate variability and cortisol and depressed mood as assessed with the BDI, and a broader range of mood states monitored using the DRM. These analyses are relevant to the hypothesis outlined in chapter 3.

The results in this chapter will be divided into three broad sections. Firstly, I shall discuss the characteristics of the total sample according to demographic, clinical and psychosocial factors. I will then discuss the differences within the total sample according to gender and depression level. Those participants that scored >10 on the BDI on the pre interview questionnaire pack are classified as having moderate to high level of depressive symptoms.

In the second section, I shall describe the findings from the Day Reconstruction Method diary (DRM) detailing the affect of the participants over the 24 hour period of monitoring on a moment to moment basis, except of course over the night time period when participants were asleep. I shall discuss the overall patterns over the day and evening for all 88 participants for the four different affects - happiness, negative affect, depressed mood and tiredness – in relation to gender and depression level.

In the final section, I shall discuss the results of the HRV analyses. I shall describe the overall pattern of results for each of the HRV indices, and then discuss associations with time of day, medication, gender, and CAD status. Finally, I will discuss the associations of depression and positive affect with HRV.

5.2 Basic characteristics of participant sample

5.2.1 Total sample-demographic and medical characteristics

The total number of participants was 88 (See Table 5.1). Overall, age of participants ranged from 37 years to 82 years with a mean age of 61.6 ± 9.5 years. 68.2% were male, 71.6 % of the sample was white and 60.2% were married. Approximately, 53.4% of the sample had secondary education or higher and 48.3% of the participants had a below average annual household income (< £20,000 per year). Approximately, one third of the sample lived alone (31.4%). Unsurprisingly, 85.8 % were either current or ex smokers.

Table 5.1 Basic demographic and psychosocial characteristics of patient sample (N=88)

		Frequency N	Valid Percentage %
Gender:	Male	60	*68.2*
	Female	28	*31.8*
Marital Status:	Married	53	*60.2*
	Single/other	35	*39.8*
Ethnicity:	Non White	25	*28.4*
	White	63	*71.6*
Age completed education: >16 years		51	*58.6*
Educational Attainment (Secondary and above)		47	*53.4*
Employment (Full time only)		21	*23.9*
Household income (<£20,000)		42	*48.3*
Living alone		27	*31.4*
Smoker current		21	*24.1*

	Frequency N	Valid Percentage %
Smoker past	50	*61.7*
Alcohol current	66	*75.0*
History affective disorder	25	*29.1*
Depression level high (BDI ≥ 10)	37	*43.0*
Anxiety level high (HADS ≥ 8)	34	*38.6*
Emotional Support (two or more)	58	*66.7*
Practical Support (two or more)	50	*56.8*
Physical activity (≥7 days per week)	34	*38.6*
Sexually active current	43	*48.9*

Regarding psychological factors, approximately one third had a history of an affective disorder in the past (29.1%) and correspondingly almost half (43.0%) scored over 10 on the BDI questionnaire indicating a high level of depressive symptoms. 38.6% of the sample scored over 8 on the HADS scale indicating a high level of 'anxiety with a mean score of 6.5 ± 3.7. The mean optimism score was 14.4 ± 3.9. The maximum score

is 24 and generally, the greater the score the greater the optimism (Scheier & Carver, 1985). In this particular sample, the score was just above average. The patients in this study are particularly impaired in vitality (52.4 ± 21.5), have limitations due to physical problems, (50.3 ± 41.3) and scored poorly on general health perceptions (59.9 ± 18.6). By contrast, social and physical functioning is relatively good with SF36 scores of 78.2 ± 20.9 and 68.7 ± 23.1 respectively. With respect to quality of life in terms of the mean physical health, mental health and physical function, SF36 scores were high. Generally, participants were not impaired due to emotional problems or pain, scoring highly on limitations due to emotional problems (61.7 ± 41.1), and on limitations due to pain (73.1 ± 18.3). Thus, it appears that overall, the total sample is quite impaired in their overall quality of life in a variety of dimensions. These scores are summarised in Table 5.2.

Table 5.2 Overall results for SF36, anxiety and optimism for total sample (N=88)

	Frequency N	**Mean (SD)**
BDI depression score	86	*10.2 (7.1)*
HAD anxiety score	88	*6.5 (3.7)*
Optimism score	87	*14.4 (3.9)*
Physical health status score	88	*62.5 (20.8)*
Mental health status score	87	*65.0 (20.8)*
SF36 Physical function score	88	*68.7 (23.1)*
SF36 Vitality	87	*52.4 (21.5)*
SF36 Social functioning	83	*78.2 (20.9)*
SF36 Limitations due to physical problems	87	*50.3 (41.3)*
SF36 Limitations due to emotional problems	87	*61.7 (41.1)*

	Frequency N	Mean (SD)
SF36 Pain scale	84	*73.1 (18.3)*
SF36 General health perception	87	*59.9 (18.6)*
SF36 Mental health perception	87	*68.0 (18.7)*

Clinical factors are summarised in Table 5.3, where it can be seen that a substantial proportion had hypertension and hypercholesterolemia and a family history of relatives diagnosed with CAD before the age of 65 years. Interestingly, only 16.5% of the sample was diabetic. It is known that diabetic patients commonly present with silent myocardial infarction (Stevens et al., 2001) and do not experience the typical symptoms of chest pain. As the patients recruited were on a waiting list for an angiogram following a positive treadmill or myocardial perfusion scan test, this may account for the lower than expected percentage seen for this established cardiac risk factor.

A substantial majority (61.5%) had an above normal body mass index (normal range 18-25). Despite this, 38.6% of the sample reported doing some form of physical exercise on every day of the week.

Clinical diagnoses were not carried out until after the study was complete, but 63.6% were classified as being CAD positive (the participant had a positive angiogram result showing disease in coronary vessels or a positive myocardial perfusion scan along with cardiac symptoms and/or a history of cardiac disease). 36.4% were classified as being CAD negative i.e. either a normal angiogram result or inconclusive results of other cardiac investigations.

40.8% of the total sample went on to have some cardiac interventional procedure, either percutaneous coronary intervention (PCI) which involved either angioplasty or stent insertion or cardiac bypass surgery (CABG). The remaining patients were either reassured after a normal angiogram, or given medical therapy for their symptoms by a cardiologist. Data concerning management following angiography were only available for 80 patients, since the remainder declined the procedure because they became symptom free and no longer wished to have an angiogram. These patients were classed as CAD negative if they had no previous CAD history as well as being symptom free.

Table 5.3 Basic clinical characteristics of patient sample (N=88)

	Frequency N	**Valid Percentage %**
Body Mass Index (BMI) kg/m^2 >25	56	*61.5*
Frequency chest pain (everyday /more than once a day)	25	*29.5*
Exercise ECG test positive	72	*91.1*
Myocardial perfusion scan positive	11	*91.7*
3 vessels diseased angiographically	13	*28.3*
Cardiac Risk Factors		
Diabetes	14	*16.5*
Hypertension	47	*53.4*
Hypercholesterolemia	66	*76.7*
Personal history of cardiac events	16	*18.2*
Family history of cardiac events	57	*67.1*

	Frequency N	Valid Percentage %
Medication		
Aspirin	77	*88.5*
Beta blocker	59	*67.0*
Nitrate	37	*43.0*
ACE Inhibitor	28	*35.0*
Statin	72	*81.8*
Clinical Outcome		
CAD Positive (+ angiogram)	56	*63.6*
CAD Negative	32	*36.4*
Conclusion of Angiogram:		
-Reassure	12	*15.8*
-Medical Therapy	26	*34.2*
-Cardiac By Pass Surgery	10	*13.2*
-PCI γ	32	*42.1*

PCI γ Percutaneous coronary intervention at the time of angiogram or was recommended for a future date.

5.2.2 Gender

Men and women were compared using t-tests for continuous variables and χ^2 tests for categorical variables. These results are presented in Table 5.4. The average age of the men and women was comparable with no significant differences between them, as was the proportion of white people, educational level and employment. A higher proportion of women living alone (46.4%) compared with the men (24.1%) was found (χ^2 = 4.4, p = 0.037). 46.4% of women were married compared with 66.7% of men, although the difference was not significant (χ^2 = 3.3, p = 0.071). This may relate to the

observation that 66.7% of women had a household income of less than £20,000 a year compared to men (40.0%), which was found to be statistically significantly different (χ^2 = 5.3, p = 0.04).

Table 5.4 Demographic factors related to gender

	Men (n=60)	**Women** (n=28)	**Differences** (p)
Age	61.52 ± 10.3	61.75 ± 7.8	0.92
Marital Status	66.7 %	46.4 %	0.1
Ethnicity (white)	68.3 %	78.6 %	0.45
Age of finishing full time education (above 16 years)	59.3 %	57.1 %	1.0
Educational attainment (Secondary and above)	55.0 %	50.0 %	1.0
In employment	40.0 %	32.1 %	0.64
Household income (less than £20,000 p.a)	40.0 %	66.7 % *	0.04*
Living alone	24.1 %	46.4 % *	0.04*

Values are mean ± SD or %. * Significant gender difference, $p < 0.05$.

There were no statistically significant differences between the two groups according to chest pain symptomatology, i.e. presence or absence of chest pain, frequency of chest pain (number of times of chest pain per week) or positive cardiac investigations prior to the angiogram. This is shown in Table 5.5. The two genders were again comparable with regards to BMI, diabetes, hypertension, hypercholesterolemia and personal or family history. The only difference was that fewer women were ex smokers

(41.7%) compared with men (70.2%). (χ^2 = 5.8, p = 0.024). This may be a reflection of the demographic trends of smoking in the past, when there were gender issues of social and cultural norms of a particular era.

Interestingly, fewer women had positive CAD (46.4%) than men (71.7%) after the actual angiogram was carried out. This is consistent with literature relating cardiac symptoms to actual clinical disease in men and women (Bugiardini et al., 2005).

Regarding medication, the only differences to emerge for cardiac drugs relating to gender were related to statin usage. Only 67.9% of the women were taking statins compared with 88.3% of the men (χ^2 = 5.4, p = 0.035). There was a gender difference in beta blocker usage that approached statistical significance. 53.6% women were taking beta blockers, compared with 73.3% of the men (χ^2 = 3.4, p = 0.066).

Table 5.5 Clinical factors related to gender

	Men (n=60)	**Women (n=28)**	**Differences (p)**
Body Mass Index (BMI) (kg/m²)	25.9 ± 4.8	27.5 ± 4.8	0.13
Frequency chest pain (everyday /more than once a day)	28.1 %	32.2 %	0.2
Exercise ECG test positive	92.5 %	88.5 %	0.43
Myocardial perfusion scan positive	85.7 %	100.0 %	1.0
3 vessels diseased angiographically	31.6%	12.5%	0.5
Cardiac Risk Factors			
Diabetes (NIDDM/IDDM)	16.7%	16.0%	1.0
Hypertension	50.0 %	60.7 %	0.37

	Men (n=60)	Women (n=28)	Differences (p)
Hypercholesterolaemia	74.6 %	81.5 %	0.6
Personal history CAD	21.7 %	10.7 %	0.25
Family history CAD	66.1 %	69.2 %	0.81
Medication			
Aspirin	91.5 %	82.1 %	0.28
Beta Blocker	73.3 %	53.6 %	0.09!
Nitrate	46.6 %	35.7 %	0.36
ACE Inhibitor	39.6 %	25.9 %	0.32
Statin	88.3 %	67.9 %	0.03*
Clinical Outcome			
CAD			
Positive(+ angiogram)	71.7%	46.4%	0.03*

*Significant gender difference, $p < 0.05$. ! Approaching significance.

More differences between the sexes emerged in the analysis of psychological and behavioural factors that are presented in Table 5.6. The difference in emotional support approached significance ($\chi^2 = 4.7$, $p = 0.08$) with a higher proportion of women (82.1%) reporting that they had two or more supports than men (59.3%). This difference was not seen in levels of practical support received.

A significantly greater number of women (41.1%) had a history of an affective disorder compared with 20.3% of men ($\chi^2 = 6.9$, $p = 0.01$). Significant differences were

also found in the HADS anxiety scale, with scores averaging 8.0 ± 3.7 in women compared with 5.9 ± 3.6 in men ($t = -2.6$, $p = 0.01$). When scores were categorised with a threshold of 8 and above, 64.3% women had high levels of anxiety compared with 26.7% of the men ($\chi^2 = 11.4$, $p = 0.001$). However, there were no statistically significant gender differences in severity of depressive symptoms with almost identical average BDI score, and 50.0% women and 39.7% men scoring above 10. In addition, there were no significant gender differences in relation to SF36 quality of life measures, optimism, and vital exhaustion.

Regarding lifestyle differences, the average units of alcohol consumed by women per week was lower, being 5.0 ± 8.8 compared to men whose average unit intake was 13.7 ± 15.7 ($F = 6.7$, $p = 0.012$). Women were also more sedentary and did significantly less exercise than men averaging 3.48 ± 3.0 times per week compared with men at 5.0 ± 2.5 times per week ($F = 6.7$, $p = 0.01$).

Table 5.6 Psychological and behavioural factors related to gender

	Men (n=60)	Women (n=28)	Differences (p)
Psychological and QL Factors			
Emotional support (two or more)	59.3%	82.1%	0.01*
Practical support (two or more)	55.0%	60.7%	0.69
History of affective disorder	20.3%	41.1%	0.01*
Depression level high (BDI ≥ 10)	39.7%	50.0%	0.5
Anxiety level high (HAD≥ 8)	26.7 %	64.3 %	0.001*
BDI Depression score	10.0 ± 7.66	10.6 ± 6.0	0.7
Anxiety (HADS) score	5.9 ± 3.6	8.0 ± 3.7	0.01*
Optimism score (LOT 0-24)	14.5 ± 3.8	14.1 ± 4.2	0.6
SF36 Combined Physical health status score	64.1 ± 21.0	59.1 ± 20.3	0.3
SF36 Combined Mental health status score	67.4 ± 21.3	60.1 ± 19.2	0.1
Physical function score	71.7 ± 21.4	62.2 ± 25.6	0.07
Vitality	54.8 ± 22.3	47.3 ± 19.2	0.13
Social functioning	80.4 ± 20.9	73.1 ± 20.2	0.14
Limitations due to physical problems	53.0 ± 42.1	44.6 ± 39.9	0.4
SF36 Pain scale	74.8 ± 18.3	69.5 ± 17.9	0.2
SF36 General health perception	59.7 ± 18.5	60.3 ± 19.3	0.9

	Men (n=60)	Women (n=28)	Differences (p)
SF36 Mental health perception	70.2 ± 18.8	63.3 ± 17.9	0.13
Behavioural Factors			
Smoking current	25.4 %	21.4 %	0.8
Smoking past	70.2 %	41.7 %	0.02*
Alcohol consumption	80.0 %	64.3 %	1.0
Alcohol units per week	13.7 ± 15.7	5.0 ± 8.83	0.01*
Physical exercise frequency (number of times per week)	5.0 ± 2.5	3.48 ± 3.0	0.02*
Physical exercise duration (minutes)	51.75 ± 59.7	61.96 ± 88.6	0.53

Values are mean ± SD or %. * Significant gender difference, $p < 0.05$. I/NIDDM = Insulin /Non Insulin Dependent Diabetes Mellitus

5.2.3 Differences related to BDI scores

Two individuals did not complete the BDI. The remaining 86 patients were divided into those with scores greater than or equal to10 (n = 37) and less than 10 (n = 49). There were no differences between those scoring high and low on the BDI with regards to age, sex, marital status, ethnicity, educational level, income or whether they lived alone or not. The only significant difference in the demographic variables seen was regards to employment. Unsurprisingly, a lower percentage of the sample that scored high on depression was in full time employment (24.3%) compared with those who scored under 10 (44.9%) ($\chi^2 = 3.87$, $p = 0.04$). These differences are summarised in Table 5.7.

Table 5.7 Demographic factors related to depression level

	Depression level low (BDI score <10)	Depression level high (BDI score 10+)	Differences (p)
Age	61.7 ± 10.4	61.9 ± 8.3	0.92
Gender Male Female	62.2%	57.1%	0.5
Marital Status	57.1 %	62.2 %	0.66
Ethnicity (white)	75.5 %	67.6 %	0.5
Age of finishing full time education (above 16 years)	60.4 %	56.8 %	1.0
Educational attainment (Secondary and above)	51.0 %	55.8 %	0.67
In employment	44.9 %	24.3 % *	0.04*
Household income (less than £20,000 per year)	40.8 %	58.3 %	0.13
Living alone	31.3%	33.3 %	1.0

* Significant depression level difference, $p < 0.05$.

There were few differences between the depressed and non-depressed groups in relation to clinical factors, as presented in Table 5.8. A similar number of people were CAD positive in both of the groups. The only statistical significance found between the two groups was aspirin medication. Those scoring high on the BDI were less likely to be taking aspirin (χ^2 =6.1, p = 0.018). This may be due to depressed patients being less likely to adhere to medication (Gehi et al., 2005).

Table 5.8 Clinical factors related to depression level

	Depression level low (BDI score < 10)	**Depression level high (BDI score 10+)**	**Differences (p)**
Body Mass Index (BMI) (kg/m²)	26.3 ± 5.4	26.3 ± 4.1	0.98
Frequency chest pain (everyday /more than once a day)	28.6 %	29.4 %	0.9
Exercise ECG test positive	91.1%	90.9%	0.9
Myocardial perfusion scan positive	100.0%	100.0%	
3 vessels diseased angiographically	33.3 %	25.0 %	0.82
Cardiac Risk Factors			
Diabetes (NIDDM/IDDM)	14.9%	16.7 %	1.0
Hypertension	53.1%	54.1 %	1.0
Hypercholesterolaemia	77.1 %	77.8 %	1.0
Personal history CAD	20.4 %	16.2 %	0.78
Family history CAD	70.2 %	63.9 %	0.8

	Depression level low (BDI score < 10)	Depression level high (BDI score 10+)	Differences (p)
Medication			
Aspirin	95.8 %	78.4 %	0.02*
Beta Blocker	69.4 %	62.2 %	1.0
Nitrate	50.0 %	36.1 %	0.3
ACE Inhibitor	31.8 %	38.2 %	1.0
Statin	81.6 %	81.1 %	1.0
Clinical Outcome			
CAD Positive (+ angiogram)	61.2 %	64.9 %	0.8

Significant depression level difference, $p < 0.05$.

Finally, interestingly, there were no statistically significant differences between the two groups with respect to smoking but there was a difference with respect to alcohol consumption (χ^2 =4.0, p = 0.04). In contrast to what is expected from the literature in that depressed patients adopt unhealthier lifestyles, a significantly higher proportion of the non-depressed group reported to consume alcohol than the depressed group i.e. 83.7% patients in the non-depressed group versus 64.0% in the depressed group. Unsurprisingly, 45.9% of those scoring high on the BDI also had a history of an affective disorder which contrasts to 17.0% of those scoring under 10 (χ^2 =8.23, p = 0.004). However, similar levels of emotional support was reported by the two groups, (depressed and non-depressed). This is summarised in Table 5.9. Consistent with what would be expected, patients who had the higher level of depression scored significantly lower on

all the SF36 quality of life measures, optimism scores, and vital exhaustion. However, those who were more depressed scored greater on the pain scale with differences approaching statistical significance (p = 0.06).

Table 5.9 Psychological and behavioural factors related to depression level

	Depression level low (BDI score under 10)	**Depression level high (BDI score 10+)**	**Differences (p)**
Psychological Factors			
Emotional support (two or more)	66.7 %	64.9 %	0.62
Practical support (two or more)	63.3 %	48.6 %	0.32
History of affective disorder	17.0 %	45.9 %	0.004*
Anxiety level high (HAD≥ 8)	22.4%	59.5%	0.001*
BDI Depression score	5.6 ± 2.5	16.2 ± 6.8	<0.01*
Anxiety (HADS) score	5.2 ± 3.1	8.4 ± 3.8	<0.01*
Optimism score(LOT 0-24)	15.3 ±4.0	13.4 ± 3.7	0.03*
SF36 Combined Physical health status score	70.6 ± 16.1	51.5 ± 21.8	<0.01*
SF36 Combined Mental health status score	74.3 ± 17.2	52.8 ± 19.4	<0.01*
SF36 Physical function score	75.5 ± 16.5	60.1 ± 27.8	0.002*
SF36 Vitality	59.1 ±19.4	43.5 ± 20.8	0.001*
SF36 Social functioning	87.2 ±14.6	67.8 ± 22.8	<0.01*
SF36 Limitations due to physical problems	64.1 ± 39.2	31.8 ± 38.0	<0.01*
SF36 Limitations due to emotional problems	77.1 ± 35.2	40.5 ± 40.2	0.01*
SF36 Pain scale	75.9 ± 16.6	68.3 ± 19.4	0.06
SF36 General health perception	67.6 ± 14.7	49.3 ± 18.6	<0.01*

	Depression level low (BDI score under 10)	Depression level high (BDI score 10+)	Differences (p)
SF36 Mental health perception	74.8 ± 15.6	59.2 ± 19.3	<0.01*
Behavioural Factors			
Smoker current	22.9 %	27.0 %	1.0
Smoker past	34.8 %	45.5 %	1.0
Alcohol consumption	83.7%	64.9%	0.04*
Alcohol units per week	11.98 ± 13.3	9.9 ± 16.35	0.5
Physical exercise frequency (number of times per week)	4.9 ± 2.6	4.2 ± 2.89	0.24
Physical exercise duration (minutes)	64.7 ± 83.1	44.7 ± 46.8	0.19

Values are mean ± SD or %. * Significant depression level difference, $p < 0.05$.

5.2.4 Differences related to CAD status

The patient sample was divided on the basis of subsequently diagnosed CAD. Those with and without definite CAD were compared using t-tests for continuous variables and χ^2 tests for the categorical variables. The purpose of the analysis was to address the question of whether patients with genuine CAD can be distinguished from others on the basis of socio-demographic, clinical, or psychological factors.

Socio-demographically, the CAD group were significantly older ($F = 6.2$, $p = 0.015$) and were more likely to be men (76.8%) than women (23.2%) ($\chi^2 = 5.3$, $p = 0.02$). The increased prevalence in CAD among men is consistent with previous findings (Carroll et al., 2003). There were no other differences between the definite CAD group and no significant CAD group with regards to marital status, ethnicity, educational level, income or whether they lived alone or not. This is summarised in Table 5.10.

Table 5.10 Demographic factors related to CAD

		No significant CAD (n=32)	Significant CAD (n= 56)	Differences (p)
Age (Years ± SD)		53.3 ± 9.73	63.5 ± 9.0	0.03*
Gender	Male	67 (53.1%)	43 (76.8%)	0.02*
	Female	15 (46.9%)	13 (23.2%)	
Marital Status:	Married	22 (68.8%)	31 (55.4%)	0.26
	Single/other	10 (31.3%)	25 (44.6%)	
Ethnicity:	Non White	8 (25%)	17 (30.4%)	0.63
	White	24 (75%)	39 (69.6%)	
Age completed education: >16 years		17 (54.8%)	34 (60.7%)	0.65
Educational Attainment (Secondary and above)		16 (50.0%)	31 (55.4%)	0.66
Employment (Full time only)		13 (40.6%)	20 (35.7%)	0.7
Household income (<£20,000)		15 (48.4%)	27 (48.2%)	1.0
Living alone		8 (26.7%)	19 (33.9%)	0.63

* Significant CAD difference, $p < 0.05$.

There were also few differences between the CAD and the non-CAD group when examining clinical factors, other than the expected finding that the CAD group was more likely to have had a history of CAD ($\chi^2 = 4.8$, $p = 0.02$). In relation to medication, the

only difference was that the CAD group were more likely to have been prescribed ACE inhibitors (χ^2 = 13.2, p = 0.0). However, there were no differences in presence or frequency of angina, positive cardiac investigations or cardiac risk factors. This is shown in Table 5.11.

Table 5.11 Clinical factors related to CAD

	No significant CAD (n=32)	**Significant CAD (n= 56)**	**Differences (p)**
Body Mass Index (BMI) (kg/m^2)	27.6 ± 4.4	25.6 ± 5.0	0.06
Frequency chest pain (everyday /more than once a day)	25 (78.1%)	52 (92.9%)	0.09
Exercise ECG test positive	24 (85.7%)	48 (94.1%)	0.09
Myocardial perfusion scan positive	6 (100%)	5 (83.3%)	1.0
3 vessels diseased angiographically	0	14 (28.3%)	0.01*
Cardiac Risk Factors			
Diabetes (NIDDM/IDDM)	4 (13.3%)	10 (18.2%)	0.8
Hypertension	17 (53.1%)	30 (53.6%)	1.0
Hypercholesterolaemia	25 (78.1%)	41 (75.9%)	1.0
Personal history CAD	2 (6.3%)	14 (25.0%)	0.04
Family history CAD	21 (67.7%)	36 (66.7%)	1.0
Smoker current	7 (21.9%)	14 (25.5%)	0.8
Smoker past	15 (51.7%)	35 (67.3%)	0.23

	No significant CAD (n=32)	Significant CAD (n= 56)	Differences (p)
Medication			
Aspirin	27 (84.4%)	50 (90.9%)	0.5
Beta blocker	18 (56.3%)	41 (73.2%)	0.2
Nitrate	10 (31.3%)	27 (50.0%)	0.12
ACE Inhibitor	3 (10%)	25 (50.0%)	0.01*
Statin	25 (78.1%)	47 (83.9%)	0.6

*Significant CAD difference, $p < 0.05$.

As can be seen from Table 5.12 there were no significant differences in anxiety, depression or any of the quality of life measures. This is inconsistent with findings from previous literature on psychosocial factors relating to CAD as was discussed in chapter 1.1. However, it should be pointed out that the sample in this study was small, so differences might not be expected.

Table 5.12 Psychological and behavioural factors related to CAD

	No significant CAD (n=32)	Significant CAD (n= 56)	Differences (p)
Psychological Factors			
Emotional support (two or more)	21 (67.7%)	37 (66.1%)	1.0
Practical support (two or more)	16 (50.0%)	34 (60.7%)	0.4
History of affective disorder	11 (34.4%)	14 (25.9%)	0.5
Depression level high (BDI ≥ 10)	13 (40.6%)	24 (44.4%)	0.8

	No significant CAD (n=32)	Significant CAD (n= 56)	Differences (p)
	12 (37.5%)	22 (39.3%)	1.0
Anxiety level high (HAD≥ 8)			
BDI Depression score	10.3 ± 8.0	10.2 ± 6.6	0.96
Anxiety (HADS) score	7.0 ± 4.2	6.3 ± 3.5	0.39
Optimism score (LOT 0-24)	13.7 ± 3.6	14.8 ± 4.1	0.2
Physical health status score	65.5 ± 21.0	60.8 ± 20.7	0.3
Mental health status score	67.1 ± 18.5	63.8 ± 22.1	0.5
Physical function score	72.3 ± 18.5	66.6 ± 23.5	0.3
Vitality	55.6 ± 20.9	50.5 ± 21.8	0.3
Social functioning	83.0 ± 15.2	75.3 ± 23.3	0.1
Limitations due to physical problems	54.8 ± 41.0	47.7 ± 41.6	0.45
Limitations due to emotional problems	60.2 ± 38.9	62.5 ± 42.7	0.8
SF36 Pain scale	76.5 ± 15.5	71.0 ± 19.5	0.18
SF36 General health perception	60.0 ± 20.3	59.9 ± 17.8	0.99
SF36 Mental health perception	70.5 ± 15.5	66.5 ± 20.3	0.34
Behavioural Factors			
Smoker current	7 (21.9%)	14 (25.5%)	0.8
Smoker past	15 (51.7%)	35 (67.3%)	0.2
Alcohol consumption	24 (75%)	42 (75%)	1.0
Alcohol units per week	8.9 ± 12.5	12.2 ± 15.5	0.3
Physical exercise frequency (number of times per week)	4.1 ± 3.0	4.7 ± 2.6	0.3
Physical exercise duration (minutes)	49.5 ± 79.1	58.1 ± 64.4	0.6

5.2.5 Differences related to beta blocker medication

When the same psychological and quality of life factors were assessed in relation to beta blocker medication, the only differences to arise were in the mean anxiety score. Those participants on beta blocker medication were significantly less anxious ($t = -1.7$, $p = 0.099$) with a mean anxiety score of 7.5 ± 3.7 compared to a mean score of 6.1 ± 3.7. In contrast, beta blocker medication made no difference to depression scores. Beta blocker medication blocks the sympathetic overdrive in stress provoking situations, reducing the heart rate and has an established use in medicine for treatment of panic attacks (Heiser & Defrancisco, 1976) and so it is unsurprising that it may alleviate the anxiety levels of participants taking the medication and hence make a significant difference to the anxiety scores of the patient sample. Of note, the beta blocker medication did not affect the patients' quality of life (see Table 5.13).

Table 5.13 Overall results for SF36, anxiety and optimism in relation to beta blocker medication for total sample (N=88)

	Beta blocker medication	Frequency N	Mean (SD)	Differences (p)
BDI depression score	Yes	57	9.9 (7.4)	0.6
	No	29	10.8 (6.6)	
HAD anxiety score	Yes	59	6.1 (3.7)	0.01*
	No	29	7.5 (3.7)	
Optimism score	Yes	58	14.4 (4.3)	0.99
	No	29	14.4(3.1)	
Physical health status score	Yes	59	65.2 (20.8)	0.08
	No	29	57.0 (20.1)	
Mental health status score	Yes	58	67.0 (20.5)	0.2
	No	29	61.0 (21.1)	

	Beta blocker medication	Frequency N	Mean (SD)	Differences (p)
Physical function score	Yes	59	70.5 (22.5)	0.3
	No	29	65.0 (24.4)	
Vitality	Yes	58	53.1 (22.3)	0.7
	No	29	51.0 (20.1)	
Social functioning	Yes	55	80.7 (20.5)	0.1
	No	28	73.4 (21.1)	
Limitations due to physical problems	Yes	58	53.9 (41.0)	0.25
	No	29	43.1 (41.7)	
Limitations due to emotional problems	Yes	58	65.5 (40.9)	0.2
	No	29	54.0 (41.2)	
SF36 Pain scale	Yes	56	75.8 (18.2)	0.05!
	No	28	67.5 (17.4)	
SF36 General health perception	Yes	58	62.6 (18.8)	0.06
	No	29	54.5 (17.4)	
SF36 Mental health perception	Yes	58	68.7 (18.5)	0.63
	No	29	66.6 (19.3)	

* Significant medication difference, $p < 0.05$. ! Approaching significance

Of note, there were no significant differences between those participants on beta blockers, and those who were not, in relation to age, gender, and any of the clinical variables. (see Table 5.14).

Table 5.14 Characteristics of patients on beta blocker medication and patients not on beta blocker medication.

	Beta blocker medication (n= 59)	No beta blocker medication (n= 29)	Differences (p)
Age (years)	61.95 yrs ±9.1 SD	60.9 yrs±10.5 SD	0.62
Body mass index (BMI) $kg/m^2 > 25$	26.3 ± 5.3 SD	26.6 ± 3.95 SD	0.78
Frequency chest pain (everyday /more than once a day)	51.1 %	11.5 %	0.3
Exercise ECG test positive	94.2 %	85.2 %	0.4
Myocardial perfusion scan positive	80.0 %	100.00 %	0.4
Risk Factors for CAD			
Diabetes (NIDDM/IDDM)	16.9 %	15.4 %	0.6
Hypertension	50.8 %	58.6 %	0.55
Hypercholesterolaemia	77.2 %	75.9 %	0.32
Personal history CAD	22.0 %	10.3 %	0.2
Family history CAD	33.3 %	32.1 %	0.56

5.3 Affect over the study period assessed using the Day Reconstruction Method

5.3.1 Overall Patterns

Figures 5.1 and 5.2 show the pattern of DRM ratings of the following mood variables : happiness, combined negative affect, depression and tiredness over the study period. These variables were chosen, as we wanted to analyse the emotions over the day that occur commonly and frequently in the period analysed and have relation to CAD development and triggering of ACS (Sirois & Burg, 2003; Tofler & Muller, 2006). In addition, the moods chosen were similar to those studied in mood adjective check lists such as the PANAS (Clark et al., 1989). One hour means are plotted to give an idea of the changes over time, although the formal statistical analysis involved four aggregated periods (see section 4.8.2). The figures begin at 7:00 - 8:00 am on day 1, continuing throughout that day, then restarting when patients woke up on day 2 and finishing at 10:00 - 11:00 am on day 2.

Ratings of happiness from the total sample of participants showed an average of around 3 (on the 0-6 scale) in the morning on waking, rising about midday with a further rise to more than 4 in the evening before falling slightly when retiring to bed (see Figure 5.1). Participants rated their lowest happiness on first waking the following day. There is a mid morning rise, a mid afternoon rise and a mid evening peak. Broadly speaking, participants are generally scoring greater in happiness affect than they are in negative affect.

In contrast, looking at negative affect, there are fewer changes over the day with an average rating of below 1 first thing in the morning and remaining fairly constant rating throughout the day with a very minimal increase in negative affect rating at

approximately mid afternoon. The negative affect rating the following day was similar to that experienced on the morning of day 1.

Figure 5.1 Happiness and negative affect

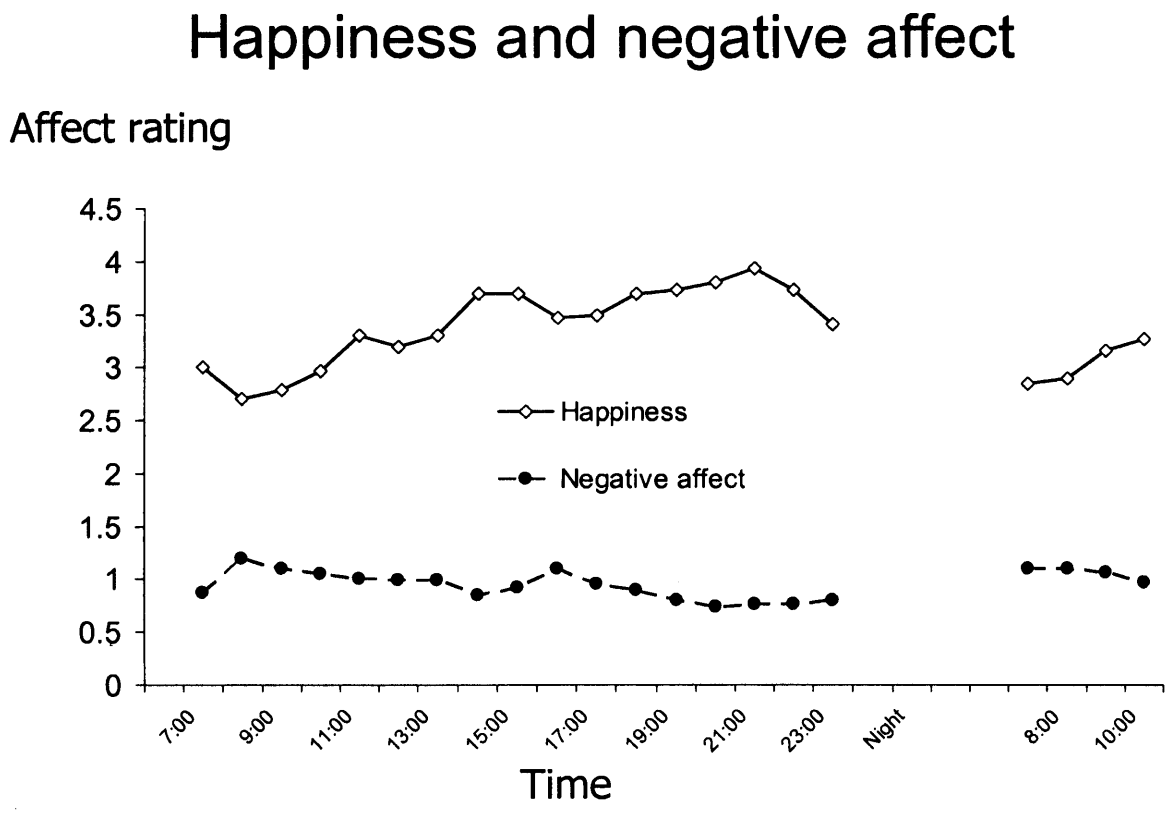
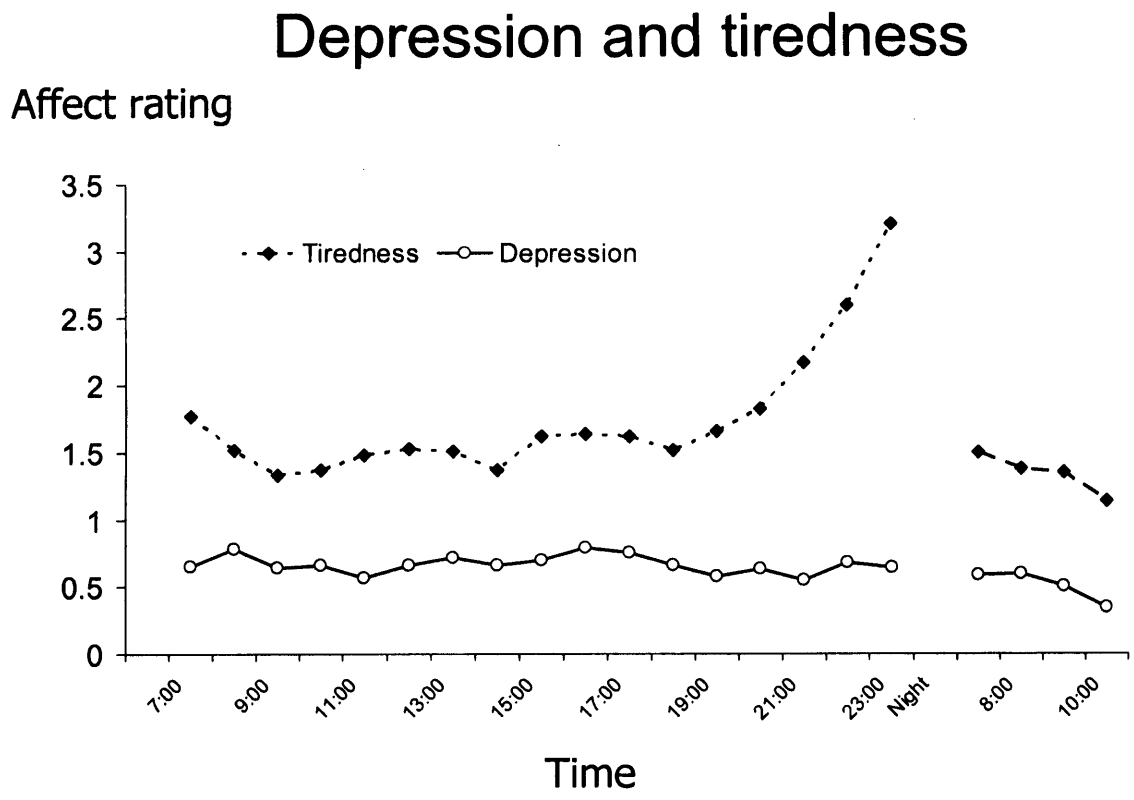


Figure 5.2 shows the general pattern of depressed mood and tiredness over the study period. We can see significant differences in tiredness over the course of the day with a rating of almost 2 on waking and then a steady increase as would be expected from 19.00 till bedtime. The lowest tiredness rating was seen on waking the following day. In contrast, DRM ratings for depression were fairly constant, varying between 0.5 and 1.0 with no particular peaks and troughs through the period of monitoring. (See Figure 5.2)

Figure 5.2 Depression and tiredness



5.3.2 Ratings of affect over time of day with relation to gender

Table 5.15 summarises the ratings of affect over time according to gender, with the DRM ratings divided into four phases over the day. Repeated measures analysis of variance showed a main effect of time for happiness ($F = 13.6$, $p < 0.001$), with higher ratings in the afternoon and evening compared with the mornings, with no differences between men and women. There was a similar result for negative affect, with the significant time effect reflecting the mirror image of happiness ($F = 3.52$, $p = 0.020$), namely lower negative affect in the afternoon and evening compared with the morning. Tiredness also showed a difference over time ($F = 6.06$, $p < 0.001$) with tiredness reaching maximal levels in the evening period as expected. There was also a main effect of gender ($F = 4.53$, $p = 0.036$), since overall, women reported greater tiredness than

men. The analysis of depression again showed significant differences over time, ($F = 3.89$, $p = 0.015$). In this case, the effect was due to lower levels of depressed mood on the morning of day 2, since the other three values did not differ. However, there were no significant effects seen between the sexes.

Table 5.15 Mean affect ratings over time of day with relation to gender

	Morning (SD)	*Afternoon* (SD)	*Evening* (SD)	*Morning2* (SD)
Happiness				
Male	**3.08 (1.3)**	**3.5(1.4)**	**3.7 (1.5)**	**3.05(1.3)**
Female	2.74 (1.2)	3.5(1.4)	3.8 (1.5)	3.1(1.3)
Negative Affect				
Male	**1.0(0.9)**	**0.95(1.0)**	**0.8 (0.85)**	**1.03 (0.94)**
Female	1.1(0.9)	0.96 (0.97)	0.84 (1.0)	1.1(0.75)
Tiredness				
Male	**1.3(1.8)**	**1.3(1.5)**	**2.0 (1.6)**	**1.1(1.7)**
Female	1.9(2.0)	2.2(1.9)	2.5 (1.6)	2.0(1.8)
Depression				
Male	**0.6(1.1)**	**0.7(1.3)**	**0.5 (0.9)**	**0.5(1.2)**
Female	0.7(1.2)	0.85(1.6)	0.8 (1.3)	0.5(0.9)

Mean Values. (SD) = Standard Deviation.

5.3.3 Ratings of affect over the day in relation to BDI depression level

I compared the affect ratings from the DRM in patients with high and low BDI scores using repeated measures analysis of variance with BDI group as the between-subject factor, and phase of the day as the within-subject factor. The results are summarised in Figures 5.3 to 5.6. Although it can be seen from Figure 5.3 that

happiness ratings tended to be higher in participants with low BDI scores, this effect was not significant. But there were main effects for BDI depression in the analyses of negative affect ($F = 8.64$, $p = 0.004$), tiredness ($F = 13.5$, $p < 0.001$) and depressed mood ($F = 9.89$, $p = 0.002$). As might be expected, depressed individuals had greater negative affect, greater tiredness and more depressed mood over the study period. These effects did not interact with time of day. These data provide some corroboration for the affect ratings made with the DRM.

Figure 5.3

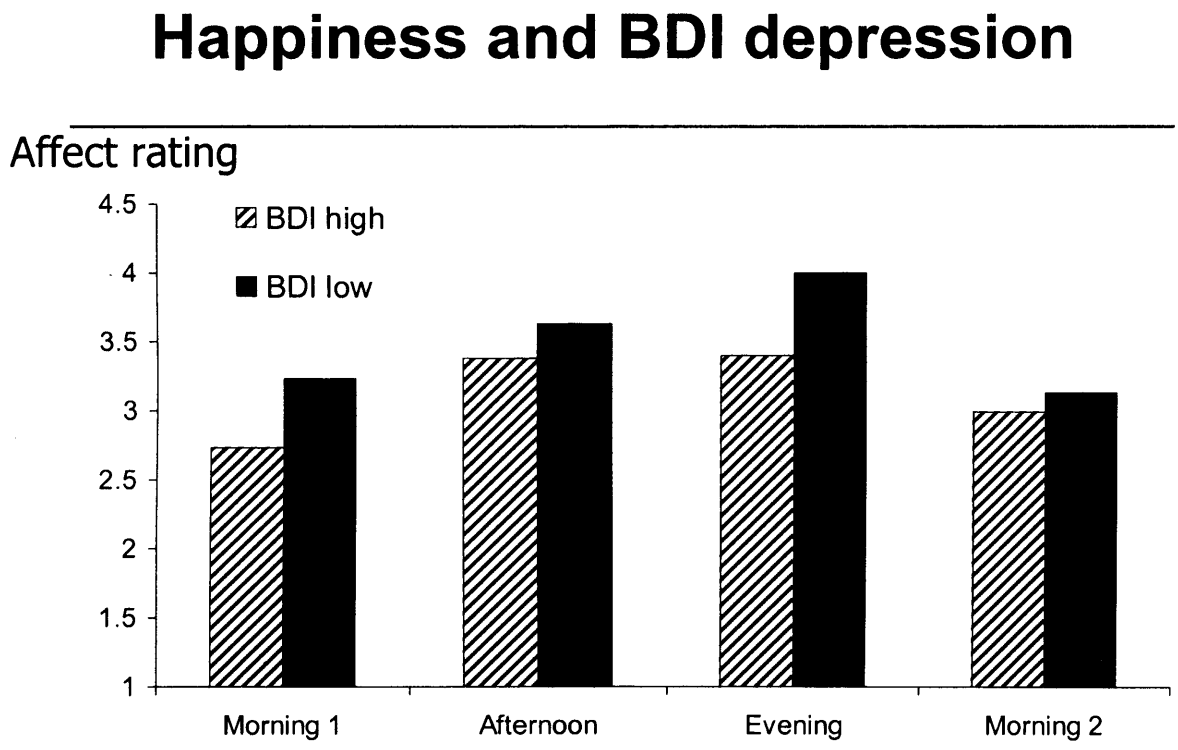


Figure 5.4

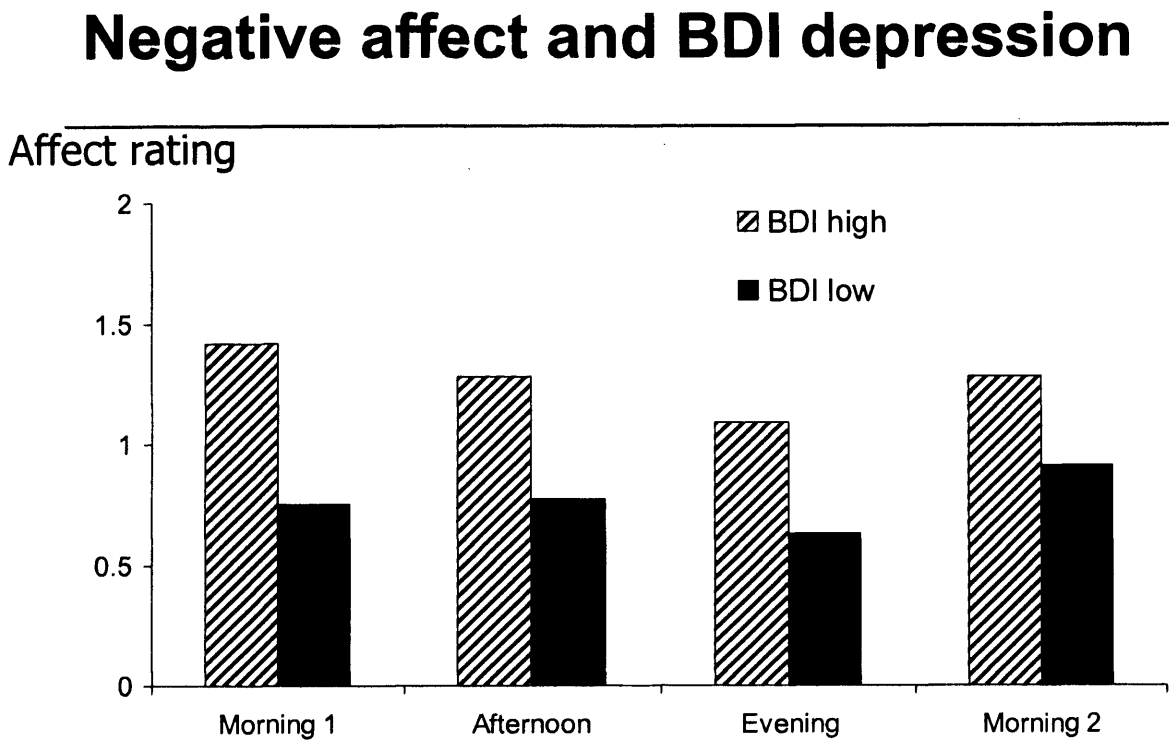

Negative affect and BDI depression
Affect rating
2
1.5
1
0.5
0
BDI high
BDI low
Morning 1
Afternoon
Evening
Morning 2

Figure 5.5

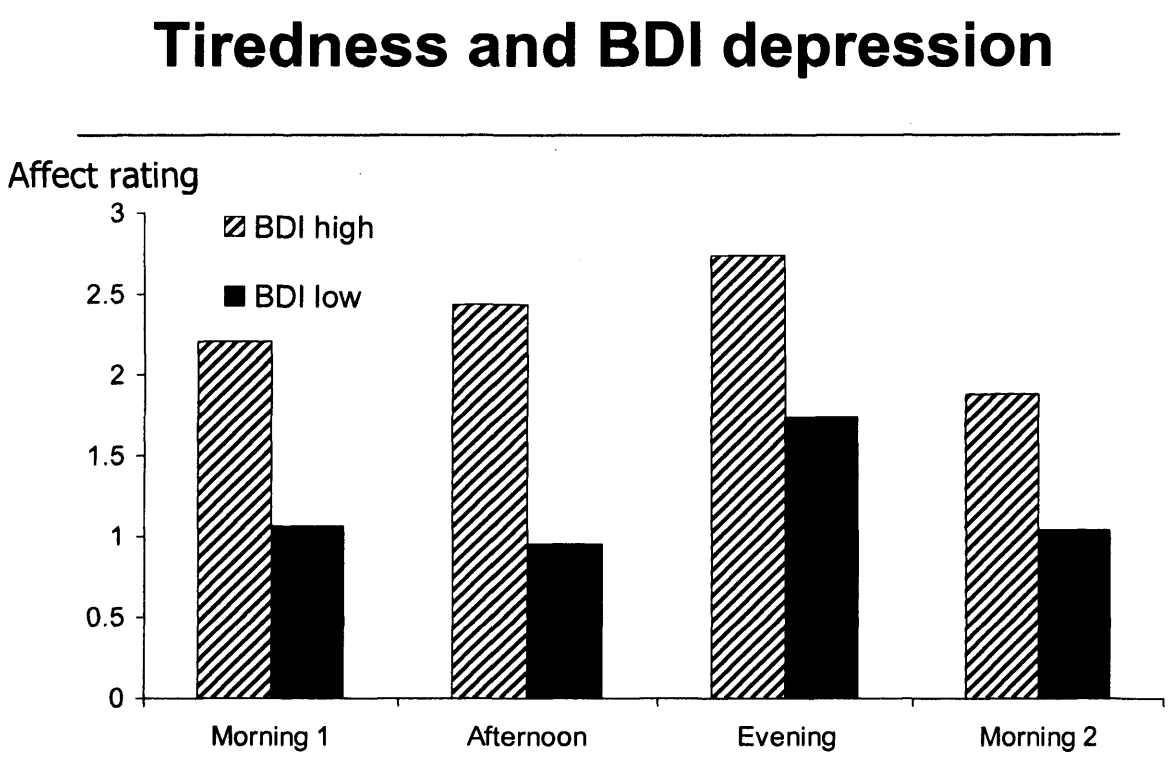
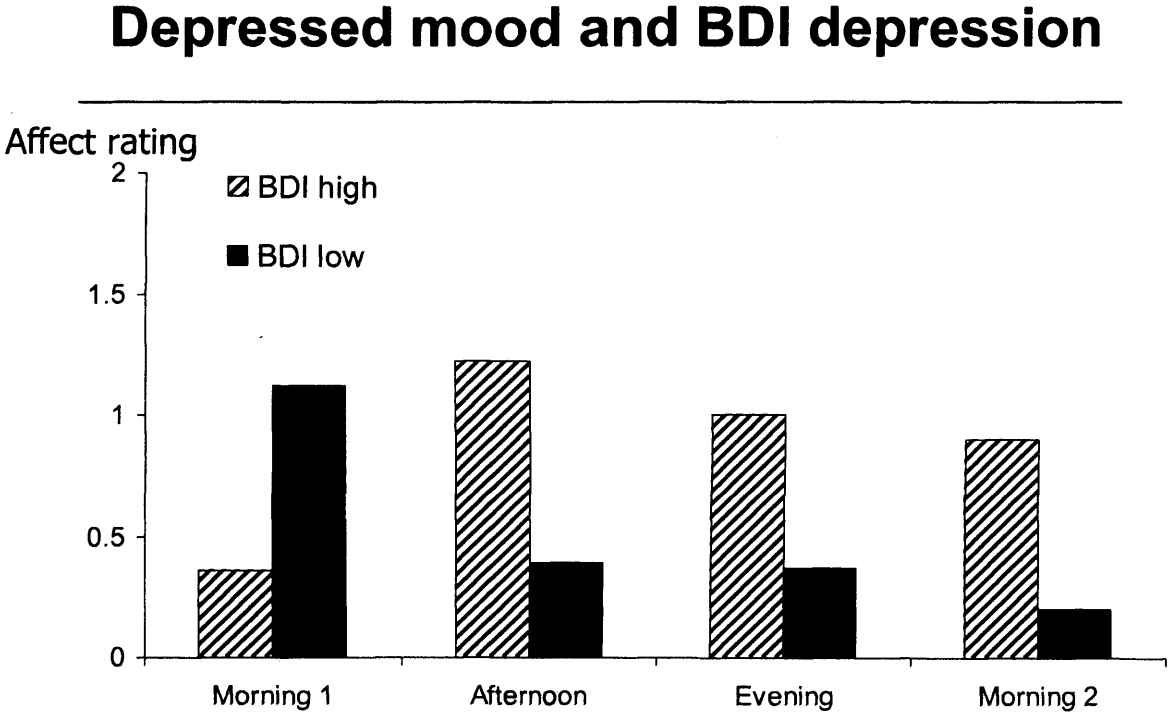


Figure 5.6



5.4 Heart rate variability (HRV)

5.4.1 Method of statistical analysis

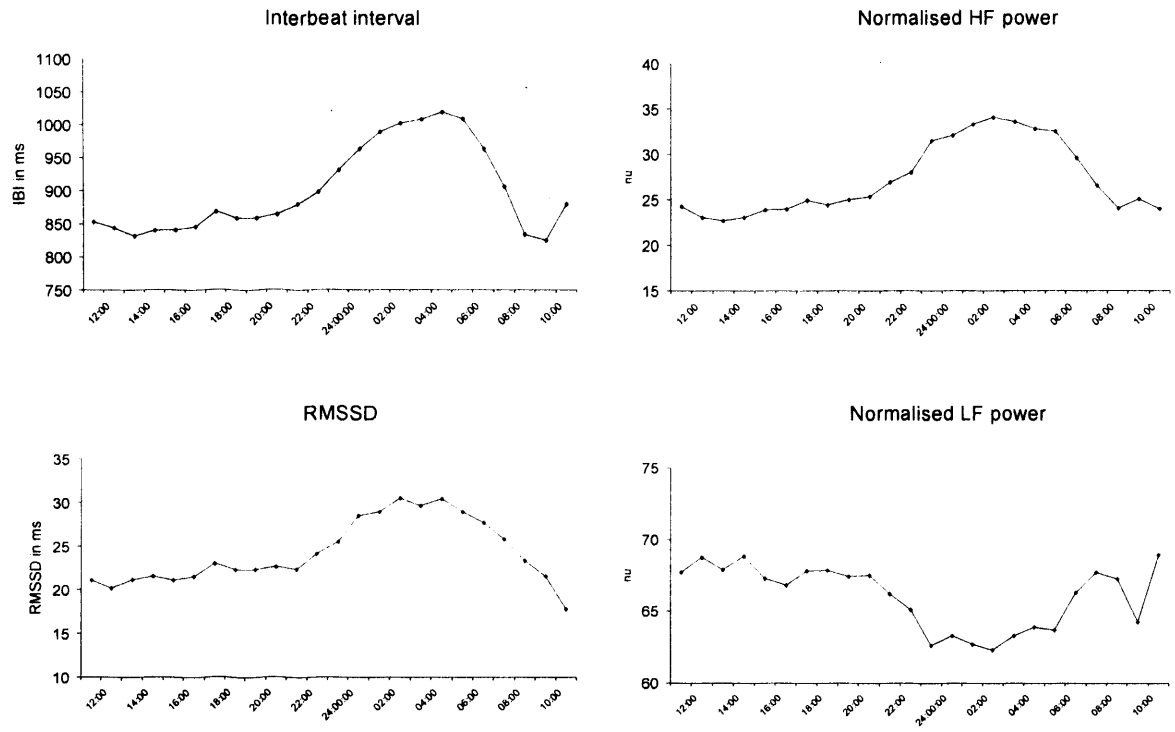
Satisfactory heart rate variability data for all time periods were obtained from a total of 76 patients. One patient failed to complete the BDI, and affect data (DRM) was lost for another individual. Patients included and excluded from the analyses did not differ on socio-demographic, clinical or psychological characteristics. Several measures of heart rate and HRV were obtained, but in the interests of space I have limited the results to the interbeat interval, the root mean square standard deviation (RMSSD) and two frequency domain measures: normalised high frequency (HF n) and normalised low frequency power (LF n). Patterns of IBI, RMSSD, normalised HF and LF power over the day were analysed using repeated measures analysis of variance, with time period (morning 1, afternoon, evening, night, morning 2) as the within-subject factor. The Greenhouse-Geisser correction was applied when sphericity assumptions were violated. The associations between heart rate variability measures and age and BMI were analysed with product-moment correlations, while *t* tests were used to assess relationships with gender, ethnicity, smoking status, CAD status, and medication with beta blockers.

Participants were divided into depressed and non-depressed groups according to whether their BDI scores were $< \text{or} \geq 10$. Depression groups were compared on heart rate variability measures using repeated measures analysis of covariance, with time period as the within-subject factor, and age, gender, CAD status and medication with beta blockers as covariates. A similar method was used to investigate associations with positive and depressed affect over the day, dividing the sample by median split on these variables. Subsequently, analyses were repeated on the subset of patients with definite CAD. Data are presented as means ± (SD).

5.4.2 Overall pattern of HRV indices

Figures 5.7 show the general pattern of HRV results over the 24 hours for all participants. As for the DRM, hour means are presented, although in the case of HRV, these continue throughout the night as well as the day. What can be seen is the lower interbeat interval and increase in HRV at night time in all indices except for the low frequency power index when participants are asleep during which the vagal tone is predominant. This reflects the inhibitory influence of the parasympathetic nervous system on the resting heart rate. The drop in power seen in the normalised low frequency index possibly represents less sympathetic activation of participants when asleep, as this index reflects more of the balance between the sympathetic and parasympathetic branches of the autonomic nervous system. This pattern is consistent with the normal physiological pattern we would expect the participants to show.

Figure 5.7 Overall pattern of heart rate variability over the study period



R-R = 30 minute average R-R intervals.

RMSSD = Root mean square of difference of successive R-R intervals.

HFn = normalised High Frequency (0.15 to 0.40 Hz) in ms^2

LFn = normalised Low frequency ratio (0.04 to 0.15 Hz) in ms^2

5.4.3 Effect of time on HRV indices

The primary analyses of interbeat interval and HRV were carried out with the four time periods specified in section chapter 4.5.2, namely the morning, afternoon, and evening of day 1, the night period, and the morning of day 2. *Post hoc* comparisons were carried out using Tukey's LSD test. The mean values for each of the HRV indices across the five time periods are shown in Table 5.16.

Table 5.16 Effect of time on HRV

	Morn 1 **mean** (SD)	**Noon** **mean** (SD)	**Eve** **mean** (SD)	**Night** **mean** (SD)	**Morn 2** **mean** (SD)
IBI (RR)	844.8 (128.0)	844.0 (130.2)	870.9 (140.7)	1001.8 (158.0)	849.1 (146.0)
RMSSD	20.3 (10.3)	21.7 (9.6)	22.9 (10.8)	29.4 (14.2)	21.6 (9.95)
HF n	23.6 (9.8)	23.4 (9.2)	25.5 (10.1)	32.3 (14.1)	24.2 (8.5)
LF n	68.1 (13.3)	68.55 (12.0)	67.3 (12.8)	63.9 (14.8)	67.4 (11.5)

Mean values with standard deviation in parentheses

There were significant time effects on IBI ($F=81.6$, $p < 0.001$). The IBI interval was significantly longer at night compared to all other four periods ($p < 0.001$). This is to be expected as the heart rate drops when asleep due to the predominance of the parasympathetic system. This was consistent with the pattern seen in Figure 5.7. The IBI in Morning 1 and in the afternoon period was also significantly different to the evening period ($p = 0.01$). The IBI in Morning 2 was additionally significantly different but less so, to the prior evening period ($p = 0.05$). There were significant time effects on RMSSD ($F=21.4$, $p <0.001$). The RMSSD interval was similarly significantly longer at night, compared to all other four periods ($p < 0.001$). This was consistent with the pattern seen in Figure 5.7. The only other significant effects seen were when comparing RMSSD in the morning period of the first day with the evening period ($p = 0.05$).

In the frequency domain, there are again significant time effects on HFn ($F=24.4$, $p <0.01$). Once more, there were significant differences at night compared to all other four periods ($p < 0.001$) i.e. there was greater HFn at night compared to all other times of the day of monitoring and the morning after. As well as this, there were significant differences when comparing the HFn in the first morning period with evening ($p = 0.021$) and again when comparing the HFn in the afternoon with the evening ($p = 0.003$). The differences between periods are greater with HFn than with LFn or any of the time domain measures.

There are also time effects with LFn ($F= 4.6$; $p = 0.08$) but the changes seen when comparing different time periods of the 24 hours are less sensitive. In fact, significant effects are *only* seen at night with each of the other time periods: morning 1 ($p = 0.01$); afternoon ($p = 0.005$); evening ($p = 0.02$); morning 2 ($p = 0.02$). The changes seen at night i.e. less LFn power reflecting less sympathetic activation at night, or

conversely greater parasympathetic influence and is consistent with the pattern expected physiologically.

5.4.4 Effect of beta blocker medication, coronary artery disease status, gender and age on HRV indices

The association of heart rate and HRV with beta blocker use, CAD status (present/absent), gender and age were first analysed using point-biserial correlations for medication, CAD and gender, and product-moment correlations for age. Further detailed analyses of significant effects were carried out using repeated measures analysis of variance and the primary analyses of these are presented here.

Beta blockade had a pronounced effect. As can be seen in Table 5.17, patients medicated with beta blockers had longer IBIs during all periods except the night (t = 2.17 to 4.59, all $p < 0.05$). Medicated patients also had reduced HF power in the night (t = -2.11, p = 0.039) together with greater LF power (t = 2.05, p = 0.044) compared with non medicated patients. The IBI result is plotted in Figure 5.8 (y axis shows IBI in ms; x axis shows the five time periods).

Beta blockers would normally be expected to reduce heart rate and increase heart rate variability, so we expected medicated patients to have longer IBIs, higher HFn and lower LFn. The results for IBI were as expected, while the HRV results were not. Other investigators have noted greater HRV in patients medicated with beta blockers (Carney et al., 1988). However, the data on the effect of beta blockers on HRV in cardiac patients is surprisingly limited (Sandrone et al., 1994). The differences observed here were very modest, despite being statistically significant. However, it is of note that beta

blockade prevents the rise in the LF component observed in the morning hours (Sandrone et al., 1994).

Figure 5.8

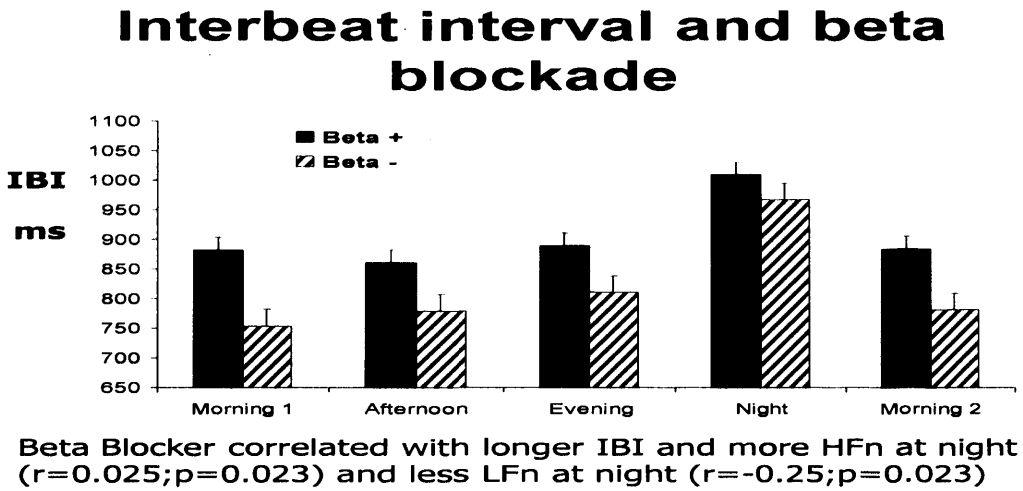


Table 5.17 Effect of beta blockade on IBI, HFn and LFn

	Beta blocker Medication	Morn 1 mean (SD)	Noon mean (SD)	Eve mean (SD)	Night mean (SD)	Morn 2 mean (SD)
IBI	YES	889.6 (117.0)	876.2 (131.3)	900.0 (150.6)	1018.4 (161.0)	882.6 (142.5)
	NO	759.3 (108.3)	788.6 (119.7)	822.1 (114.1)	974.7 (151.6)	786.1 (134.4)

	Beta blocker Medication	Morn 1 mean (SD)	Noon mean (SD)	Eve mean (SD)	Night mean (SD)	Morn 2 mean (SD)
HF n	YES	25.7 (11.0)	24.8 (10.2)	26.8 (11.8)	30.8 (13.9)	25.2 (10.3)
	NO	20.5 (8.4)	21.8 (8.6)	24.3 (8.5)	37.1 (15.4)	23.8 (8.1)
LF n	YES	67.2 (13.7)	67.3 (13.4)	66.2 (14.3)	65.5 (14.6)	66.9 (12.9)
	NO	68.5 (14.5)	69.5 (11.8)	68.1 (12.0)	59.1 (16.2)	66.3 (12.6)

Interbeat interval and RMSSD did not differ in men and women. But there were significant gender by time interactions for HFn and LFn HRV indices ($F = 6.55$ and 3.82 respectively, $p < 0.01$). As can be seen in Table 5.18, men and women did not differ substantially over the day. But in the night, women had greater HFn and less LFn than men did. This indicates that women had greater parasympathetic activity and sympathetic withdrawal in the night.

Table 5.18 Effect of gender on IBI, HFn and LFn

	Gender	Morn 1 mean (SD)	Noon mean (SD)	Eve mean (SD)	Night mean (SD)	Morn 2 mean (SD)
HF n	MALE	23.7 (9.84)	23.9 (10.0)	25.5 (11.2)	29.7 (13.6)	23.7 (9.5)
	FEMALE	24.6 (11.9)	23.7 (9.3)	27.1 (10.5)	39.6 (14.7)	26.9 (9.8)
LF n	MALE	67.2 (13.7)	67.3 (13.4)	66.2 (14.3)	65.5 (14.6)	66.9 (12.9)
	FEMALE	68.5 (14.5)	69.5 (11.8)	68.1 (12.0)	59.1 (16.2)	66.3 (12.6)

This finding is consistent with the previous literature (Liao et al., 1995; Yamasaki et al., 1996).

Age was positively associated with IBI in the afternoon and evening (r = 0.27 and 0.33, $p < 0.01$), and with a longer IBI, greater HF power and reduced LF power during all time periods except the night (r = 0.41 to 0.60, all $p < 0.001$). This is consistent with previous studies (Tsuji et al., 1996) in which age is a major determinant of HRV and in which the impact of a 10 year increment in age was that of a 10 beat/min increment in

heart rate (Tsuji et al., 1996). In addition, with increasing age, the parasympathetic and sympathetic spectral power components decrease (Liao et al., 1995). Negative correlation between LF power and age has also been shown in studies by Tsuji et al. (1996).

There was no association between heart rate variability measures and ethnicity, smoking status, BMI, or the presence of significant CAD.

5.4.5 Association between BDI depression and HRV indices

As noted in Chapter 3.4.2, I hypothesised that patients who were more depressed would show reduced HRV, specifically lower RMSSD, lower HFn and possibly greater LFn. The primary analysis involved repeated measures analysis of variance with BDI $\geq$10 or <10 (i.e. comparing depressed and non-depressed groups) as the between-subject factor and revealed no significant associations between depression and HRV for any of the parameters tested. In each case, the main effect for BDI depression status was not significant nor did depression interact with time of day. In the absence of group effects, we examined the associations further using regression analysis with BDI score rather than depression group as an independent variable, along with age, gender, CAD status and beta blockade. None of the associations in any time period with any variable was significant. There were no significant relationships between HRV and depression level as categorised using the BDI score. These results are summarised in Table 5.19. It is possible that effects will only be present among patients with definite CAD. The analyses were therefore repeated comparing the 20 high BDI and 26 low BDI patients with CAD. Again, none of the differences was significant. A third approach was to use the full scale of the BDI, and correlate BDI scores with IBI and HRV measures for each period of the day and night. Once again, none of these associations was significant.

Table 5.19 Effect of depression level (BDI) on HRV time and frequency domain indices

	Morn 1 mean (SD)	Afternoon mean (SD)	Eve mean (SD)	Night mean (SD)	Morn 2 mean (SD)
RR					
BDI low	862.6 (133.6)	854.8 (134.6)	884.4 (147.7)	1010.2 (157.9)	862.8 (142.8)
BDI high	822.2 (120.5)	834.6 (133.6)	856.0 (137.7)	992.5 (162.2)	833.3 (153.4)
RMSSD					
BDI low	23.2 (16.6)	22.2 (13.1)	23.3 (12.96)	30.2 (16.2)	22.3 (15.0)
BDI high	18.8 (7.4)	22.9 (10.9)	23.6 (12.1)	30.6 (16.7)	22.8 (10.5)
HF n					
BDI low	24.6 (10.6)	24.7 (9.9)	26.8 (11.8)	33.7 (14.5)	25.2 (10.1)
BDI high	23.1 (10.5)	22.63 (9.7)	24.5 (9.5)	31.4 (15.0)	23.9 (9.2)

	Morn 1 mean (SD)	Afternoon mean (SD)	Eve mean (SD)	Night mean (SD)	Morn 2 mean (SD)
LF n					
BDI low	65.9 (14.7)	65.8 (14.1)	65.2 (15.1)	62.9 (15.5)	65.2 (14.3)
BDI high	70.0 (12.7)	71.0 (10.7)	69.3 (64.3)	64.3 (15.5)	68.8 (10.3)

BDI low/high = Beck Depression Inventory score low (<10) high (>10)

5.4.6 HRV and DRM-derived affect measures

The absence of associations between BDI scores and HRV does not mean that cardiac autonomic control is unrelated to psychological state. It is possible that HRV will be associated with the more refined measures of mood derived from the DRM interview. For this analysis, I took the aggregate levels of DRM happiness, depression, and negative affect, and divided the sample on each variable by median split. I then compared HRV indices in high and low groups on happiness, depressed mood and negative affect. Repeated measures of analysis of covariance was carried out with mood group (high/low) as the between-subject variable, and time of day as the within-subject variable, with age, gender, CAD status and beta blocker use as covariates. These variables have been chosen, as there is extensive literature on HRV and the influence of both positive and negative emotions. Bacon et al. (2004) showed that in 135 cardiac patients, negative emotions such as stress and sadness were associated with both high

and low frequency power whereas positive emotions were associated with an increase in low frequency power independent of age, posture and medication.

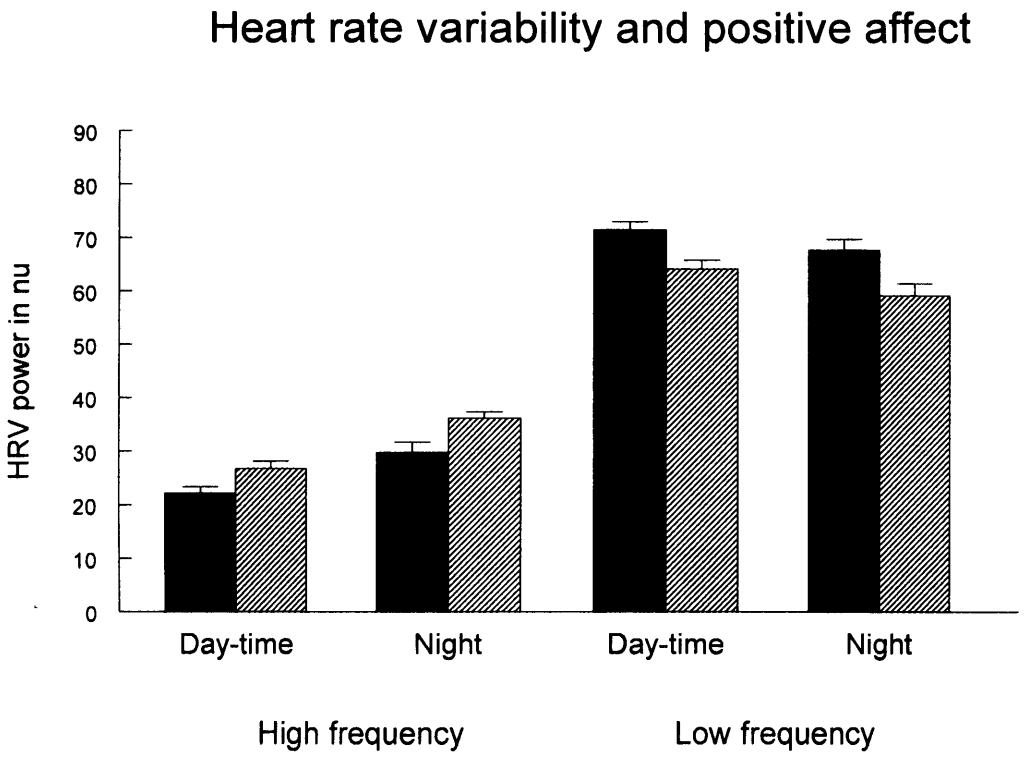
5.4.6.1 HRV and positive affect

Happiness was related to the two frequency domain HRV measures. The results for LFn power are summarised in Figure 5.9, adjusted for covariates. The repeated measures analysis of covariance showed a main effect of happiness ($F= 12.21$; $p <0.001$), together with a happiness group by time interaction effects ($F= 8.42$; $p < 0.001$). Happier people showed lower LF power throughout the study period, with particularly large differences in the mornings. If LF power indexes sympathetic/parasympathetic balance, this result suggests that happier individuals have less cardiac sympathetic activation.

The reverse effects were observed for HFn power, where again the main affect for happiness group ($F=8.06$; $p <0.001$) and the group by time interaction were significant ($F=4.6$; $p = 0.035$). These results indicate that happier people showed significantly increased HF power (i.e increased heart rate variability) at all times of the day after taking into account other factors such as age, gender, CAD and beta blocker use. When BDI scores were included as additional covariates, the effect for positive affect remained significant for HF and LF power ($F = 8.27$ and 16.95 respectively, $p < 0.005$). These results are shown in Figure 5.9, where it is evident that the greater HF and reduced LF power in patients experiencing more positive affect was sustained throughout the study period.

Figure 5.9

Mean normalised HF and LF heart rate variability across day-time and night periods in lower positive affect (solid bars) and higher positive affect (hatched bars) groups (n = 75). Values are adjusted for age, gender, CAD status, medication with beta blockers, BMI, smoking status and habitual physical activity. Error bars are s.e.m.



5.4.6.2 HRV and negative affect

There were no significant associations between DRM depressed mood and HRV. No significant effects involving negative affect were observed in these analyses either. The pattern of results for LFn and HFn is illustrated in Figure 5.10. Depressed affect was not related to heart rate or HRV in the sample as a whole. But when analyses were

limited to the 46 patients with documented CAD, differences did emerge. Specifically, patients reporting greater DRM depressed affect had significantly less HF power ($F = 5.07$, $p = 0.030$), and greater LF power ($F = 4.93$, $p = 0.032$) over the study period, after controlling for age, gender and medication with beta blockers.

Figure 5.10

Mean normalised HF and LF heart rate variability across day-time and night periods in patients with documented CAD (n = 46) who experience higher depressed affect (stippled) and lower depressed affect (hatched bars) assessed with the DRM. Values are adjusted for age, gender, medication with beta blockers, BMI, smoking status and habitual physical activity. Error bars are s.e.m.

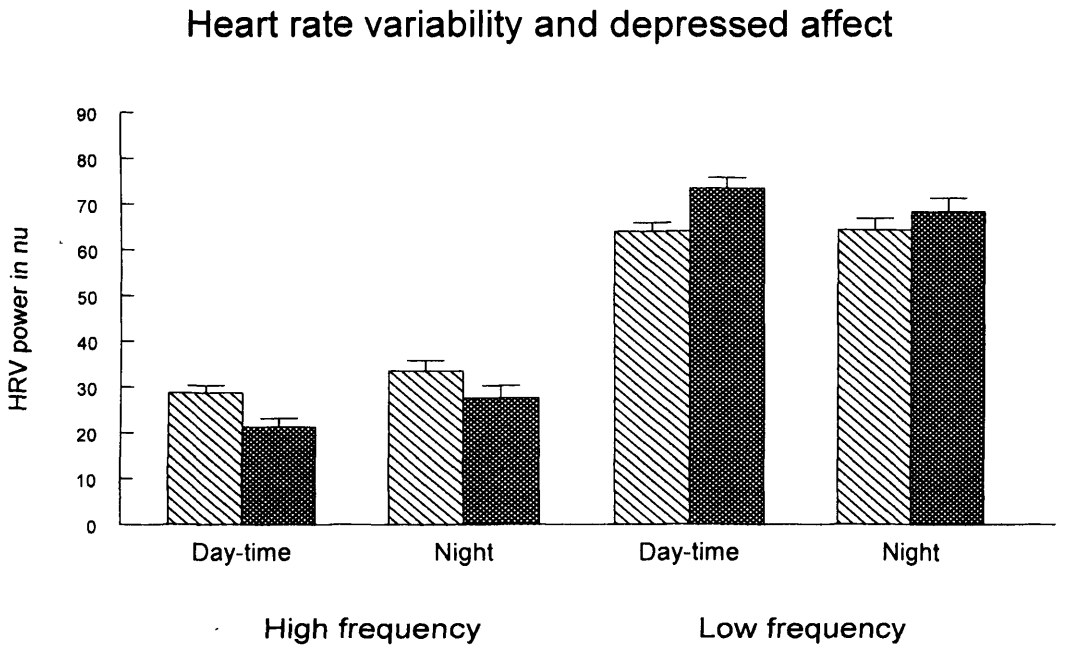
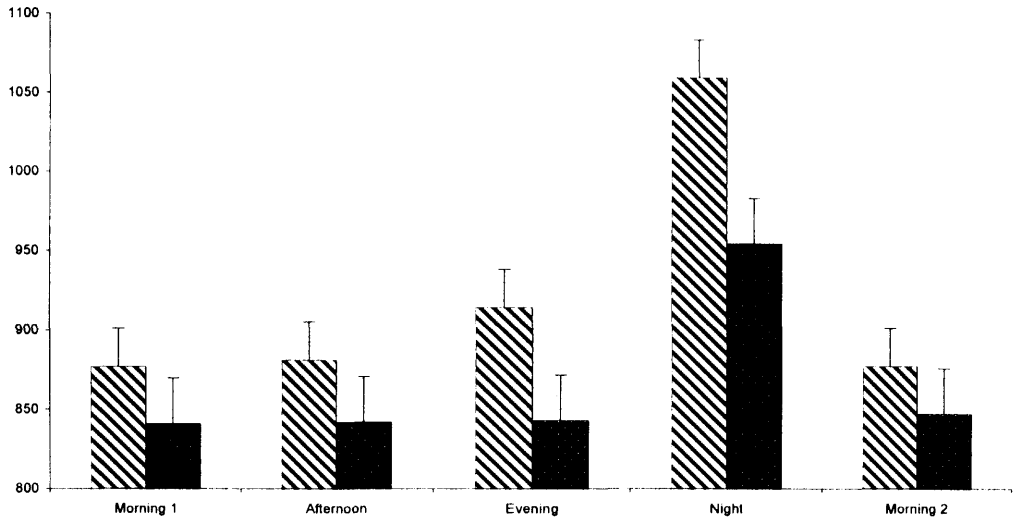


Figure 5.11

Mean interbeat interval across five periods of the day in higher depressed affect (stippled bars) and lower depressed affect (hatched bars) groups of patients with documented CAD (n = 45). Values are adjusted for age, gender, and medication with beta blockers. Error bars are s.e.m.



Additionally, the depressed affect group by time interaction was significant in the analysis of IBI ($F = 3.48$, $p = 0.009$), after adjustment for covariates. The results, shown in Figure 5.11, indicate that IBIs tended to be shorter in the higher depressed affect group, with the difference being most prominent in the night, i.e. a higher heart rate is seen in the depressed group especially so at night. Thus it emerged that HRV was related to positive affect in the complete sample, but to depressed affect only in the patients with documented CAD.

5.5. Discussion

5.5.1 Summary of DRM results

Summarising the overall patterns found, positive affect was shown to be lowest in the morning on first awakening and a mid morning rise, mid afternoon arise was observed with a peak rating in mid evenings. Overall happiness had the higher levels of endorsement and negative affect (NA) had lower levels. The fact that overall people are generally happier than they are sad is consistent with a study by Stone et al. (2006), which used the DRM approach to study diurnal rhythms of emotion on a working day in 909 women. Our study also agrees with Stone et al. (2006), with the findings of PA being greater in the evening rather than the morning and having a diurnal rhythm. This contrasts to previous studies that have shown PA to be highest in the morning (Wood & Magnello, 1992), not in the evening. However, in the study by Wood and Magnello (1992), the authors used only 6 time points in contrast to the more detailed timings used in the DRM.

NA and depression were both shown to be rather constant through out the day and this lack of diurnal rhythms supports the study by Wood et al. (1992) but not some other previous studies (Stone et al., 2006; Monk et al., 1985). Tiredness was shown to increase progressively during the day and at an accelerated rate in the evening, as would be expected, and supports other studies that used the DRM (Stone et al., 2006). Tiredness was also significantly greater in women compared to men. This supports findings of gender differences in tiredness in cardiac patients. In a study by Wiklund et al. (1993) comparing the subjective symptoms and well-being in women and men 12 months post MI, after controlling for differences in age and co-morbidity, women

reported significantly higher frequencies of psychological and psychosomatic complaints, including sleep disturbances.

Comparing the different affects in relation to depression the findings from the DRM correlated well with what would be expected when mood was assessed by the questionnaire (BDI). The negative emotions and not the positive emotion of happiness were significantly greater in the depressed group as assessed by the BDI. This, to some extent, provides support for the methodology of the DRM.

5.5.2 Strengths and limitations of the DRM

The strengths of the DRM are centred round the fact that multiple assessments of affect are used to assess patterns and allow a more fine tuned analysis of fluctuating emotions in the day than can be achieved with standard retrospective questionnaires or with ecological momentary assessment (EMA) techniques. EMA methods provide the most immediate and direct measures of affect in everyday life, but have a high respondent burden. There is also the problem that EMA measures cannot be very frequent (e.g. every 15 minutes), or else they will interrupt ongoing behaviour. This means that significant experiences over the day might be missed if they did not coincide with the timing of EMA. The DRM overcomes this problem by conceiving of the day as a continuous sequence. Because episodes are defined concretely, the recall of incidents and their associated affect should be more precise than is the case with standard retrospective methods The DRM interview takes approximately an hour to complete and feasibly could be done efficiently by large numbers of participants in a communal setting by self-report questionnaires or on the internet. The new method is acceptable to the patients, not time consuming and relatively easy to follow. The patterns of affect

seem sensible and the association between daily activities and emotions provide further support for validity of the assessment method.

The limitations in the DRM method as applied in this study include the fact that although affect was analysed in relation to time of day, gender and BDI, we did not analyse affect in relation to age. Age has been shown to affect emotional experience in daily life, with positive emotions increasing with age after 60 years (Carstensen et al., 2000). Younger people have less PA in the mornings than older patients (Kahneman et al., 2004; Stone et al., 2006). The study sample I tested was too small and biased towards older ages to allow such comparisons to be made. The DRM was only completed over a single day. The study could have been repeated to divide the participants according to whether they were being tested in a working day or a non-working day. Diurnal rhythms may well be associated with activities associated with or caused by working. In order to determine whether stable individual differences in diurnal mood patterns exist, the assessment of multiple days is required.

Overall, the DRM appears to provide a valuable picture of emotional experience in daily life with minimal recall bias and provides a user friendly efficient assessment. But studies that use EMA and DRM methods simultaneously are required definitively to confirm that the pattern and intensity of affects recalled using the DRM provide an accurate representation of moods as they were actually experienced. Unfortunately, it was not possible to include EMA measures in this study. The relationship between various affects and the triggering of ECG changes in patients with suspected CAD is discussed in chapter 7.

5.5.3 Summary of heart rate variability results

The results suggest that reduced HRV may not be related to aggregate measures of depressive symptomatology in patients with suspected CAD, but that the relationship may depend on prevailing levels of affect during the study period. By contrast, positive affect is associated with a favourable profile of HRV both in patients with and without confirmed CAD. These associations may be relevant both to the processes through which depression increases risk in cardiac patients, and the pathways relating positive mental states with CAD prevention.

When characterising the emotions of patients suspected of coronary artery disease, it appears that the BDI, a validated depression questionnaire, did not show a consistent relationship with autonomic function. I found no association between depressive symptoms assessed with the BDI and indices of HRV in this study. The relationship was tested in the complete sample and in the subset of patients with definite CAD, and was investigated both with a categorical division between high and low BDI groups, and using the BDI as a continuous variable. This result may reflect a genuine lack of association between depressive symptoms and HRV in patients with suspected CAD. Although a relationship between reduced HRV and depression has repeatedly been observed in patients following acute coronary syndromes, the literature on stable CAD is mixed and this has been described in the earlier chapter 2.5.2.3 on heart rate variability.

Similar samples of patients with cardiac symptoms and positive non-invasive tests awaiting angiography have been involved in previous studies of HRV (Carney et al., 1988, 1995), although analyses have often been limited to patients with definite coronary stenosis. A number of studies have shown that depressed cardiac patients have reduced HRV (Carney et al., 1995, 2000, 2001).

The proportion of patients with significant stenosis and definite CAD was similar to that of other studies (Dumville et al., 2007). Patients without significant CAD may not be at elevated risk for cardiac problems but nevertheless use increased medical resources (Potts et al., 1993). BDI levels did not differ between CAD and non-CAD patients.

Most studies relating depression with HRV have either measured the ECG's over a short time period (Guinjoan et al., 2004), or else have averaged 24 hour recordings into a single value (Gehi et al., 2005; Krittayaphong et al., 1997, Carney et al., 1988). I decided that it would be interesting to discover whether the diurnal pattern of HRV varied with depression and positive affect. The diurnal HRV was as expected, with increased HF power and reduced LF power in the night compared with the day. The same profile has been observed both in healthy populations and cardiac patients (Yamasaki et al., 1996), and reflects the normal profile of increased parasympathetic and reduced sympathetic activation at night. We found that women had greater HF and lower LF than men, as is typical in the literature (Liao et al., 1995). Negative correlations between LF power and age have also been described before (Yamasaki et al., 1996).

The null result may have been due to other factors. For example, our patients continued with their cardiac medication including beta blockers, and this could have obscured the relationship between HRV and depression. However, the dominant effect of this medication was on heart rate rather than HRV.

The sample size of 75 is relatively small, though comparable with many previous studies of depression and HRV (Krittayaphong et al., 1997, Stein et al., 2000). Around 42% of patients had BDI scores $\geq$ 10, but it is possible that some of the patients who refused to take part were more depressed.

However, a stronger possibility is that the dissociation arose because some patients with elevated BDI scores were not particularly depressed over the HRV monitoring period. We used the DRM to measure affect over the study period to characterise participants' emotional experience of daily life, a different picture emerged relating depressed mood with HRV (section 5.4.6.2). This study throws some light on the explanation for these inconsistencies, in showing that associations between HRV and with depressed mood over the day as measured by the DRM are present.

This new method has been advocated by Kahneman and co-workers (Kahneman et al., 2004) as a useful alternative to ecological momentary assessment. As discussed in Chapter 3.3, on methodological issues relating to the SIS study, the DRM has the advantages that it provides concurrent assessment of subjective experience, activities and social situations, so that experience-weighted analyses can be carried out. Because all waking hours are covered, there is a lower likelihood that emotionally salient events will be missed, in comparison with momentary sampling techniques involving ratings every one to two hours.

Depressed affect from the DRM was positively correlated with BDI rating ($r = 0.65$). However, the association between the two is not very tight, and there was only 42% shared variance. Interestingly, depressed affect was associated more closely with HRV than was the BDI, with higher LF power and lower HF power in the more depressed individuals (Figure 5.10). Additionally, heart rates were faster in patients experiencing more depressed affect, particularly at night (Figure 5.11). It is notable that these effects were only observed in patients with definite CAD, and not in the complete study group. This suggests that moment to moment depression may be associated with impaired autonomic cardiac control in patients with coronary disease.

By contrast, the associations between positive affect and HRV were evident in the complete study group. Individuals who were happier over the day had greater HF and reduced LF power throughout the study period (Figure 5.9). This effect was independent of age, gender, CAD status and medication with beta blockers. It was also independent of BDI scores, suggesting that positive affect has distinct biological correlates that are not simply the product of the absence of negative affective state (Steptoe et al., 2005). These results indicate that patients with suspected CAD who report high positive affect have greater parasympathetic activation and reduced sympathetic/parasympathetic balance compared with less happy individuals. There is growing evidence from laboratory studies on healthy participants that greater positive affect is directly related to health relevant biological processes in terms of reduced neuroendocrine, inflammatory and cardiovascular activity (Steptoe et al., 2005).

5.5.4 Strengths and limitations of study

A strength of this current study is that it suggests that not only in the laboratory but also in naturalistic real life settings, greater positive affect has a direct relationship with reduced sympathetic/ parasympathetic cardiac autonomic control. These results suggest that one biological mechanism that may be relevant is a favourable pattern of autonomic cardiac control. An additional strength of the study is that it had a prospective design, since neither the investigators nor the participants were aware of their diagnosis at the time of investigation.

This study has a number of limitations. The sample size was relatively small, and we did not test a control group of participants with no cardiac complaints and no medication. A substantial minority of eligible patients declined to take part; although travel problems and business were the main reasons given for refusal, it is possible that

more severely depressed individuals were excluded. The majority of participants were white men, and it would have been desirable to recruit a wider range of ethnic minority groups and a larger percentage of women. The DRM is dependent on accurate recall of emotional experiences during the episodes that made up the study period. It was completed during face to face interactions with the researcher, and this could have influenced reported affective responses to some activities. A longer period of ECG recording may have picked up more consistent associations with mood, though the DRM has not been used on periods greater than 24 hours in the past. The BDI may not be the most appropriate instrument for assessing depression in this population. We chose it because of its associations with prognosis in patients with acute coronary syndromes (Nicholson et al., 2006) and because it has been recommended for this population (Davidson et al., 2006), but studies of HRV have used interviews to define clinical depressive disorder (Gehi et al., 2005; Carney et al., 2001). A further limitation is the absence of ejection fraction data, since HRV is known to be reduced in those with poor left ventricular function (Nolan et al., 1998).

In summary, it may well be that it is the absence of positive affect rather than presence of negative affect that is more important, since there was a strong relationship with HRV that was independent of important covariates such as medication. This may have clinical implications for cardiac patients. However, HRV is not the only biological indicator investigated in this study, and different patterns might emerge for other measures such as cortisol profile over the day, cortisol awakening response (CAR) and transient myocardial ischaemia. These findings are presented in chapters 6 and 7.

Chapter 6: The relationship between cortisol, depression and other moods in patients with suspected coronary artery disease

6.1 Introduction

It is described in chapter 1.1.3 and 1.3.3 that depression is prevalent in CAD patients and associated with increased risk of future CAD events and mortality (Burg & Sirois, 2003; Frasure–Smith et al., 1993; Lesperance et al., 2000, 2003). However, little is known about mechanisms linking depression or emotion and subsequent cardiac events. Elevated cortisol levels or an elevated cortisol awakening response (CAR) due to enhanced activity of the hypothalamic-pituitary-axis (HPA) is a possible mechanism with attendant changes in hypertension, hyperlipidaemia, endothelial changes and insulin resistance, which all serve to increase risk of CAD development and prognosis (Girod & Brotman, 2004).

Several studies have been described in chapter 2.7.2, showing associations between cortisol and CAD (Koertge et al., 2002). Prospective associations between cortisol and future fatal, and non fatal cardiac events have also been described in post ACS patients (Bain et al., 1989).

The literature relating cortisol with depression is complex, but impaired suppression of cortisol secretion by dexamethasone is characteristic of a subset of clinically depressed individuals, and elevated basal levels may also be present (Gold et al., 1988; Weber et al., 2000; Wong et al., 2000; Holsboer, 2001). Other studies have suggested that elevated morning cortisol may be a pre-morbid factor for subsequent depression (Goodyer et al., 2000; Harris et al., 2000) and has been associated with a

history of depression (Bhagwagar et al., 2003). An association between cortisol levels over the day and depressed mood assessed with the Beck Depression Inventory (BDI) has also been described (Peeters et al., 2006).

Cortisol shows a diurnal pattern in healthy adults peaking at 20-45 minutes (Cortisol awakening response: CAR) after waking and then steadily decreasing to its lowest levels in the night and early morning. Patients with CAD exhibit a cortisol pattern that is markedly different (Nijm et al., 2007). Patients with depression also show a markedly different cortisol pattern and these have been described earlier in the review in chapter 2.7.1 (Harris et al 2000; Pruessner et al., 2003). As well as depression being associated with elevated levels of cortisol in healthy patients (Young et al., 1994) it has also been shown to be elevated in patients with CAD (Otte et al., 2004). Additionally, in patients with CAD, this potential association between depression and increased cortisol may be attenuated by co morbid medical conditions, e.g. hypertension (Litchfield et al., 1998), medication use e.g. beta blockers (Deininger et al., 2001) and depression severity (Nelson et al., 1997).

Despite the evidence that depression is prevalent in CAD patients and cortisol output is related to depression in both healthy and CAD patients, there is limited evidence directly linking depression with cortisol in CAD patients (Otte et al., 2004). Limitations are that awareness of the disease itself may contribute to disturbed mood and cortisol profiles. A diagnosis of coronary disease is stressful, and patients may respond with neuroendocrine activation and depressed mood, making it difficult to analyse the relationship between cortisol profiles in depressed CAD patients.

In the present study, I therefore investigated patients with chest pain who had been referred to hospital for specialist diagnosis before definitive coronary angiography had been carried out. The majority of patients were diagnosed with CAD, but some were

found not to have occluded arteries. Neither investigators nor patients were aware of actual clinical disease state at the time of cortisol measurement. This allowed us to assess the relationship between depressed mood and cortisol in patients with and without definite CAD who had endured similar clinical experiences in terms of diagnostic testing. Evaluation of the possible role of sleep is potentially possible by analysis of actigraphy readings, since disturbed sleep in depression may influence diurnal cortisol profiles (Madjirova et al., 1995). The cortisol awakening response and cortisol rhythm over the remainder of the day and evening were analysed separately.

Two broad questions were addressed in these analyses.

1. Do patients with CAD who are more depressed have a flatter slope over the day, independent of age, gender, medication, and times of waking and sleeping?

2. Do patients with CAD have a greater cortisol measured on waking and 15 and 30 minutes after waking independent of the relation to depression?

In summary, in this chapter, I shall discuss the results of the cortisol analyses. Firstly, I will compare the overall pattern of results of the cortisol profile between CAD patients who are more depressed with those who are less depressed as measured by the BDI and DRM. Secondly, independent of depression, I shall discuss whether those patients with CAD have a greater cortisol awakening response and how this may contribute to elucidating the biological pathway by which depression can cause CAD.

6.2 Method

Patients

The method of the SIS study including selection criteria of recruitment of patients is described in detail in chapter 4. Here is a brief summary of the method in relation, particularly, to the cortisol sampling method and analysis.

Participants were 88 patients referred to the rapid access chest pain clinic and were regarded as probable CAD cases on the basis of symptomatology plus positive exercise tests or positive myocardial perfusion scans. They participated in the study prior to coronary angiography. All the patients had experienced new onset chest pain, had been referred to the specialist clinic, and had positive risk-stratifying tests. Patients who were and were not subsequently diagnosed as having definite current CAD thus underwent identical clinical procedures, and were all likely to have anticipated a cardiac diagnosis at the time of the study. 144 patients were eligible to take part, of which 56 refused. The main reasons given were travel problems (patients had to come to the laboratory on two consecutive days), or because patients were too busy with work or other commitments. Patients who declined were significantly older (mean 64.9, SD 10.2 years) than those who took part (mean 61.1, SD 9.8 years, $t = 2.16$, $p = 0.032$), but did not differ in gender distribution.

Procedure

Patients were recruited in the hospital outpatient clinics. Subsequently, they attended the research laboratory at University College London individually on the morning of day 1 of the study. Anthropometric measures were taken and participants

were equipped with a 24 hour holter monitor (data described elsewhere) and a wrist actigraph. The cortisol sampling procedure was explained and practiced. Patients returned to the laboratory at the same time on the next day (day 2), at which time an interview about the study period was completed. A questionnaire including the BDI was also administered.

Measures

Depression was assessed with the BDI. Socio-demographic and clinical information was obtained by interview. Weight and height were measured, from which body mass index (BMI) was calculated. Prior history of CAD was obtained from clinical notes. After the patients had completed the study, we collected findings from their subsequent angiography, recording the presence or absence of definite CAD, and the number of significantly diseased coronary arteries.

Cortisol was collected from saliva samples using Salivettes (Sarstedt, Leicester, UK). Measures were taken soon after arriving in the laboratory (between 9:00 and 10:00 am), and patients were instructed to take further samples at 11:00am, 4:00pm, 7:00pm and just before bed. On day 2, they were asked to take samples immediately on waking and at 15 and 30 minutes after waking. Samples were returned to the laboratory later in the morning, and salivas were stored in a freezer at -20°C until analysis which was carried out using a high sensitivity chemiluminscence assay at the Technical University, Dresden (Germany). Inter and intra-assay coefficients of variance (CVs) were <8 %.

Physical activity was measured with a wrist actigraph (Actiwatch, Cambridge Neurotechnology, Cambridge, UK). This device (distributed in the USA by Mini Mitter) is a piezoelectric motion sensor. Data were analysed using proprietary software to define the following parameters: wake time in the morning, sleep latency (interval between going to bed and falling asleep), and sleep efficiency (proportion of the time in bed spent

sleeping). The Actiwatch has been validated against polysomnography in both healthy populations and insomnia samples (Lichstein et al., 2006) and is used extensively in population and clinical studies (e.g. Lauderdale et al., 2006). Patients were also asked whether they had slept well on the night before morning cortisol assessments.

Statistical analysis

Two patients failed to complete the BDI, and two patients had missing cortisol data over the day, so analyses were carried out on 84 individuals. 52 (61.9%) were diagnosed as having CAD on the basis of having one or more vessels with ≥ 50% stenosis on angiography, while 32 (38.1%) did not have CAD. The CAD group had an average 1.95 ± 0.82 significantly stenosed vessels. The CAD and non-CAD groups were compared on socio-demographic, clinical and sleep characteristics using χ^2 for categorical and t-tests for continuous variables. Separate analyses were carried out of cortisol over the day (measured on day 1) and the cortisol awakening response (CAR) measured on day 2. Cortisol over the day was analysed using repeated measures analysis of variance with clinical group (CAD/non-CAD) and depression group (BDI ≥ 10 / < 10) as between-subject factors, and the 5 samples over the day and evening as within-subject factors. The Greenhouse Geisser correction of degrees of freedom was computed when appropriate. Subsequently, analyses of covariance were performed with age, gender and medication with beta blockers as covariates. The slope of cortisol decline was calculated as the reduction in cortisol per hour between the laboratory (10:00 am) and bed time sample.

The CAR is the change in cortisol that occurs over the first over 20-30 minute following waking, (Clow et al., 2004) and was assessed by repeated measures analysis of the waking, 15 and 30 minute saliva samples. The CAR is critically dependent on the

waking cortisol sample being obtained without substantial delay, since postponement can reduce the magnitude of the awakening response (Wright & Steptoe, 2005). Time of waking on day 1 was based on self-report, while time of waking on day 2 (when the CAR was assessed) was defined objectively on the basis of characteristic increases in physical activity assessed using the Actiwatch. Delaying the 'waking' sample by up to 15 minutes following objectively defined waking does not substantially influence the CAR (Kupper et al., 2005; Dockray et al., 2008). Only individuals with delays >15 minutes were therefore excluded from CAR analyses, leaving 72 patients in the analyses.

6.3 Cortisol results

Patients with CAD were significantly older and more likely to be male than those without CAD (Table 6.1). There were no differences in education, marital status, smoking or history of clinical depression. The majority of the participants were prescribed beta blockers, aspirin and statins, with no differences between groups. However, CAD patients were more likely to be prescribed ACE inhibitors. CAD patients were more likely to have a history of CAD (previous ACS, etc), though rates were low. 19% of the total sample had a previous history of coronary heart disease (CHD), and as would be expected, significantly more (26.9%) of the CAD positive group had a previous history of CHD compared to those who had none (6.3%) ($p = 0.02$). Scores on the BDI averaged 10.17, with 42.9% scoring ≥ 10, while 14% had BDI scores ≥ 18. There were no differences between CAD and non-CAD patients group in depression scores. The two groups did not differ in sleep characteristics.

6.3.1 Depression and cortisol over the day

The reported times of cortisol samples over day 1 were 09:48h ± 30.7min, 11:34h ± 43.0min, 16:14h ± 26.1min, 19:18h ± 37.4min and 23:24h ± 68.5min, indicating good adherence to the protocol. Cortisol averaged 6.25 ± 2.5 nmol/l over the day, and the cortisol slope averaged 0.74 ± 0.48 nmol/l/h. Cortisol over the day was not associated with age, smoking status, BMI, medication with statins, aspirin or ACE inhibitors, or with time of waking in the morning. But women had lower cortisol over the day than men (means 5.04 ± 1.79 vs 6.79 ± 2.53 nmol/l, $p = 0.002$), and flatter cortisol slopes (means 0.46 ± 0.30 vs 0.87 ± 0.49 nmol/l/h, $p < 0.001$). Additionally, patients taking beta blockers had higher average cortisol over the day and evening (means 6.67 ± 2.55 vs 5.39 ± 2.06 nmol/l, $p = 0.024$).

There was a significant interaction between CAD status, depression and time in the repeated measures analysis of variance ($p = 0.009$). Depression was related to cortisol output in CAD patients ($p < 0.001$), but not in the non-CAD group ($p = 0.68$). The results for CAD patients are summarised in Figure 6.1. Cortisol early in the day was lower in the depressed than non-depressed CAD patients after adjustment for age, gender, beta blockade, and time of waking in the morning ($p = 0.003$). But the reverse pattern emerged later in the day, with cortisol being higher among depressed CAD patients at bed time ($p = 0.038$), with a near significant effect at 7 pm ($p = 0.060$). The cortisol slope over the day was therefore substantially lower in depressed than non-depressed CAD patients (means 0.51 ± 0.49 vs 0.99 ± 0.46 nmol/l/h, adjusted for age, gender, beta blockade, and time of going to bed, $p < 0.001$). The same pattern of results emerged when the BDI was entered as a continuous variable into a regression on the cortisol slope over the day, and when a more stringent criterion for depression (BDI ≥

15) was applied. Cortisol over the day and evening was unrelated to sleep latency, sleep efficiency, or subjective sleep quality.

6.3.2 Depression and cortisol awakening responses

Participants woke at 06:19h ± 65min on average. Cortisol increased markedly between waking and 30 minutes in the complete sample ($p < 0.001$). Sleep efficiency and sleep latency were unrelated to CAD status or to cortisol over the early morning period. More depressed patients woke earlier in the morning, and early waking was in turn associated with a lower cortisol on waking ($r = 0.26$, $p = 0.029$). However, the CAR was not related to depression, but cortisol levels were greater in CAD than non-CAD groups ($p = 0.04$). As shown in Figure 6.2, cortisol was higher in the CAD than non-CAD groups throughout the waking period after adjustment for gender, beta blockade and waking time. The increase in cortisol between waking and 30 minutes did not differ in CAD and non-CAD groups.

Table 6.1 Characteristics of patients with and without coronary artery disease

	Coronary artery disease (n = 52)	No coronary artery disease (n = 32)	p
Gender: Men	41 (78.8%)	17 (53.1%)	0.017
Women	11 (21.2%)	15 (46.9%)	
Age (years)	63.9 ± 8.8	58.3 ± 9.7	0.008*
Ethnicity (white)	37 (71.2%)	24 (75.0%)	0.80
Educational attainment (High school and above)	30 (57.7%)	16 (50.0%)	0.51
Marital status (married)	29 (55.8%)	22 (68.8%)	0.26
Smoking status			
Current smoker	13 (25.0%)	7 (21.9%)	0.45
Former smoker	23 (44.2%)	12 (37.5%)	
Never smoker	16 (30.8%)	13 (40.6%)	
Body mass index (kg/m^2)	26.0 ± 3.5	27.7 ± 4.4	0.078
Medication			
Beta-blockers	38 (73.1%)	18 (56.3%)	0.15
Statins	44 (84.6%)	25 (78.1%)	0.56
Aspirin	47 (92.2%)	27 (84.4%)	0.30
ACE inhibitors	24 (52.2%)	3 (10.0%)	0.001*
Previous CAD	14 (26.9%)	2 (6.3%)	0.022*
History of depression	8 (15.4%)	9 (28.1%)	0.17

	Coronary artery disease (n = 52)	No coronary artery disease (n = 32)	p
BDI (mean)	10.12 ± 6.7	10.25 ± 8.0	0.94
BDI ≥ 10	23 (44.2%)	13 (40.6%)	0.82
Sleep latency (min)	12 ± 14	20 ± 26	0.073
Sleep efficiency (%)	78.9 ± 16.9	79.1 ± 17.0	0.96
Wake up time (hours: min)	6:14 ± 64	6:03 ± 63	0.43
Sleep quality (good)	31 (59.6%)	23 (74.2%)	0.24

N (%) and Mean ± standard deviation *Significant CAD difference, $p < 0.05$.

Figure 6.1 Mean salivary cortisol across the five sample points of the day and evening in CAD patients with BDI scores ≥10 (solid lines), and <10 (dashed lines), adjusted for age, gender, beta blockade and reported time of waking and going to bed. Error bars are standard errors of the mean (s.e.m.).

Figure 6.1 Cortisol in depressed and non-depressed CAD patients

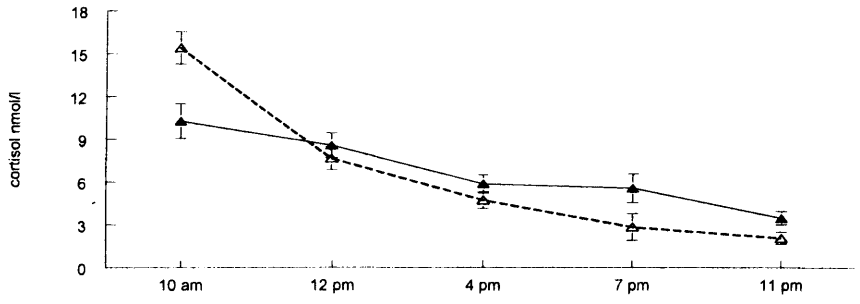
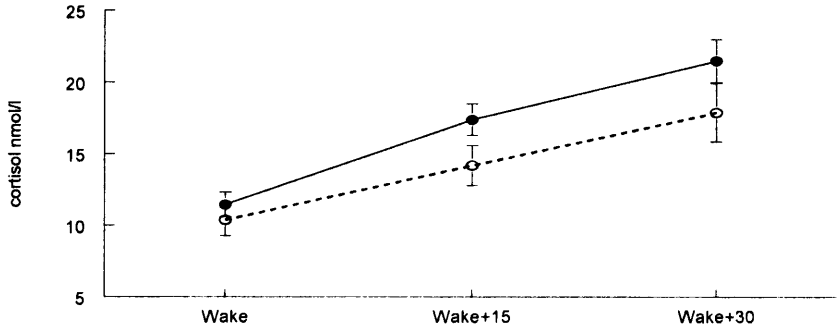


Figure 6.2 Mean salivary cortisol on waking (wake), 15 minutes (wake+15) and 30 minutes (wake+30) after waking in CAD patients (solid line) and non-CAD patients (dashed lines), adjusted for age, gender, beta-blockade and objective time of waking. Error bars are s.e.m.

Figure 6.2 CAR in CAD and non-CAD patients



6.4 Discussion

This study evaluated cortisol output over the day in patients with suspected CAD in relation to depressive symptoms measured with the BDI. The results indicate that the cortisol slope over the day was flatter in depressed patients with CAD, but was not related to depression in patients without CAD. This effect was due to the combination of lower cortisol early in the day and higher cortisol in the evening in the more depressed CAD patients, and was independent of age, gender, medication, and times of waking and sleeping. Additionally, cortisol early in the day, measured on waking and 15 and 30

minutes after waking, was greater in CAD than non-CAD patients, but did not relate to depression.

Depression was assessed as a subclinical mood variable rather than a clinical category in this investigation. The reason is that subclinical depressive symptoms are associated with the development of CAD and with prognosis following acute cardiac events (Nicholson et al., 2006). Moderately elevated BDI scores ($\geq$ 10, the same criterion as used in this study) have been shown to predict cardiac mortality and non-fatal recurrence in patients following ACS (Lesperance et al., 2002; Spijkerman et al., 2006). The association with the flatter cortisol rhythm over the day in CAD patients is therefore potentially significant clinically.

Previous studies of cortisol and depression in patients with documented CAD have been mixed. Otte et al. (2004) showed a positive relationship between depression assessed both by diagnostic interview and questionnaire and 24-hour urinary cortisol in the Heart and Soul Study. This was independent of age, gender, BMI, smoking, co-morbid illness, medication and cardiac function. 24-hour measures do not allow the profile of cortisol output over the day to be analysed. Whitehead et al. (2007) measured salivary cortisol over the day and evening in patients hospitalised for ACS and found no association with depression. By contrast, a positive correlation between morning cortisol and depression was recorded in a study of 285 patients assessed 3-6 months after ACS (Von Kanel et al., 2007). The absence of an association in patients without CAD is consistent with Taylor et al's (2006) findings in depressed individuals with elevated cardiovascular risk factors but without coronary disease.

Flatter cortisol rhythms over the day can only be defined using repeated sampling, and are difficult to assess using blood sample in an everyday life settings. Flatter cortisol slopes have previously been associated with greater tension and anger

over the day (Adam et al., 2006), posttraumatic stress disorder (Aardal-Eriksson et al., 2001), and poor marital relationships quality in both younger and older adults (Barnett et al., 2005). Matthews et al. (2006) recently demonstrated that flatter cortisol profiles were associated with coronary artery calcification (an indicator of sub-clinical CAD) in apparently healthy middle-aged adults. One feature of flatter rhythms is that cortisol levels are elevated in the evening, even though values are low compared with earlier in the day. This pattern was apparent in the present study, with higher cortisol among depressed than non-depressed CAD patients. An elevation of cortisol in the evening has been demonstrated in a number of studies of clinically depressed patients (Plotsky et al., 1998).

Cortisol early in the day and the CAR were analysed separately from cortisol over the remainder of the day and evening. The CAR is a distinctive component of the diurnal cortisol profile and correlations between the CAR and other indicators of cortisol over the day are low (Schmidt-Reinwald et al., 1999).

In the present study, we found no differences in the magnitude of the CAR (the rise from waiting to 30 minutes) in relation to depression, or between CAD and non-CAD patients. However, the overall level of cortisol output was elevated in CAD patients (Figure 6.2). This indicates that raised cortisol levels in the early morning period are associated with definite coronary disease in patients with cardiac symptoms. This study was cross-sectional, so the causal significance of this pattern can not be determined. Nevertheless, the findings are consistent with the study of 238 women following ACS, in which early morning cortisol was elevated in only those with significant ($\geq$ 50%) coronary stenosis (Koertge et al., 2002). Davey Smith et al (2005) showed that cortisol/testosterone ratios predicted the incidence of CAD over a 16.5 year follow-up of middle-aged men in Wales, but that effects were mediated by insulin

resistance. In a large case-control study, patients prescribed oral glucocorticoids were found to be at an increased risk of CAD and heart failure (Souverein et al., 2004).

6.5 Strengths and limitations

A particular strength of this study is that patients were investigated prior to a definitive diagnosis of current CAD. Thus, the CAD and non-CAD groups were both in the same clinical situation, and knowledge of illness could not influence either depression ratings or cortisol. The study therefore included a comparison group of patients without CAD, unlike most studies of depression and cortisol in relation to cardiovascular disease (Otte et al., 2004, Whitehead et al., 2007). The delineation between the two groups was based on whether they had current CAD of a sufficient severity to cause chest pain. Some patients may have had a previous history of CHD but a normal coronary angiogram, and would not then be placed in the CAD positive group. It should also be noted that the non-CAD group not only had chest pain, but also positive exercise and/or myocardial perfusion scans. These participants were therefore distinct from the group of patients who present with chest pain of non-cardiac origin but no other positive objective test results, among whom psychiatric problems are relatively common (Bass & Mayou, 2002). We do not know whether mild atheroma or other factors such as gastro-oesophageal disease or chest wall syndromes accounted for the positive objective test results (Fruergaard et al., 1996), since it was not feasible to follow the non-CAD group further to establish a definitive diagnosis of the causes of their chest pain. It is probable, however, that these factors would serve to reduce the differences between CAD and non-CAD groups, so the presence of distinctive cortisol patterns is even more striking. It should also be noted that the levels of depressed mood were comparable with

those found in other investigations of patients with CAD (Otte et al., 2004; Vaccarino et al., 2007).

The study also has a number of limitations. The sample size was relatively small, and patients could not be assessed in the absence of medication. Cortisol was recorded over a single day, and repeated measures are likely to generate findings that are more robust. Compliance with the sampling times was assessed by self-report and it was not possible to assess the reliability of these reports objectively.

Chapter 7: Transient myocardial ischaemia and ventricular tachycardia

7.1 Introduction

The ECG records were analysed by Hertford Medical for episodes of ST segment depression and ventricular tachycardia (VT). ST depression was defined as horizontal or downsloping ST depression > 1mm or 1.5 mm upsloping below the isoelectric baseline, measured at 0.08 seconds after J point and persisting for at least 60 seconds. VT was defined as three or more beats in a row on an ECG that originated from the ventricle at a rate of more than 100 beats per minute.

Nine patients experienced one or more episodes of ST depression and five experienced VT (one had both ST depression and VT). The characteristics of these episodes are summarised in Tables 7.1 and 7.2.

Table 7.1 Details of ST segment depression episodes

ID	Sex	Age	CAD?	Episode onset	Duration (mins)	Patient self-report of chest pain	Observations
008	M	68	Yes	20:08, day 1	17	Yes	
						9:00 day.2	
				08:24, day 2	6		
				08:57, day 2	8		
030	M	55	No	5:00, day 2	23	No	No DRM before episode onset (asleep)
034	M	56	No	06:03, day 2	3	Yes	Asleep during episode, no DRM
						17:00 day 1	
						21:00 day 1	
						09:00 day 2	
035	F	72	Yes	13:27, day 2	1	Yes	DRM data lost
						11:30 day 1	
				08:22, day 2	2	15:45 day1	
						19:30 day 1	
				08:30, day 2	3		
049	M	80	Yes	20:04, day 1	1	No	
				08:54, day 2	15		
				09:33, day 2	3		

ID	Sex	Age	CAD?	Episode onset	Duration (mins)	Patient self-report of chest pain	Observations
066	F	61	No	08:49, day 2	2	Yes	
						14:15 day 1	
				09:13, day 2	24	15:30 day 1	
						16:00 day 1	
						19:30 day 1	
						21:30 day 1	
						05:30 day 2	
						06:30 day 2	
						07:00 day 2	
						08:00 day 2	
072	F	70	Yes	15:16, day 1	7	Yes	ECG data lost
						13:15 day 2	
				10:36, day 2	17		
080	F	52	Yes	15:33, day 1	3	No	
				19:52, day 1	7		
				07:41, day 2	3		
084	F	63	No	08:46, day 2	6	No	

Table 7.2 Details of ventricular tachycardia episodes

ID	Sex	Age	CAD?	Episode onset	Duration (secs)	Patient self-report of chest pain	Observations
027	M	74	No	19.53, day 1	2	No	
				20:52, day 1	2		
028	M	58	No	16:55, day 1	2	No	
059	M	55	No	08:45, day 2	11	Yes 13:15 day 1 13:05 day 2	
072	F	72	Yes	01:10, day 2	2	Yes 13:15 day 2	Asleep during episode (no DRM)
081	M	64	Yes	06:44, day 2	2	No	Asleep during episode (no DRM)

It can be seen that three patients had a single episode of ST depression, two patients had two episodes, and the remaining four patients had three episodes. These episodes lasted from 1-17 minutes, and occurred at a range of times of day and night, with a high proportion on the morning of day 2 (13/19 episodes). The VT episodes were all short, with the exception of one that lasted 22 minutes. Interestingly, although 7 patients reported one or more episode of chest pain over the study period, only one of these (patient 008, episode 3) coincided with ST depression or VT. This indicates that

the episodes of cardiac abnormality in this study were predominantly silent, without chest pain.

Three broad questions were addressed in these analyses:

1. Do patients who experience ST depression and / or VT differ from the remainder in terms of socio-demographic characteristics, clinical factors, psychosocial variables, DRM mood, heart rate variability or cortisol profiles? These issues were addressed by between-subject comparisons of ST depression / VT patients and the remainder.

2. Are there characteristic changes in heart rate, heart rate variability or DRM mood around the ST depression / VT episodes in patients who experience these cardiac problems? This question was investigated by studying the profiles of cardiac and mood changes around the time of each episode, in comparison with control periods in the 13 ST depression / VT patients.

3. Are there associations between mood and cardiac responses at the time of ST depression / VT episodes? These issues were studied by correlating mood, heart rate and heart rate variability responses around the time of each episode.

7.2 Methods

The 13 ST depression / VT patients were compared with the remainder using χ^2 tests for categorical variables and t-tests for continuous socio-demographic, clinical and psychosocial variables. The groups were also compared on the heart rate, DRM mood variables and cortisol measures detailed earlier, using analysis of variance and covariance. Analyses comparing the combined ST depression / VT group were followed by analyses of the ST depression group only.

Investigation of the mood and cardiovascular responses surrounding each ST depression / VT episode was carried out, by identifying the minute of onset and offset of each episode. Five minute segments of DRM mood and heart rate variability measures were then computed for the onset segment, the three 5 minute segments preceding onset, the end segment, and the two 5 minute segments following the end of the episode. An example is shown in Table 7.3 of the first ST depression episode for patient 008, which started at 20:08 on day 1, and continued until 20:25.

Table 7.3 Timing of acute ST depression / VT episodes

Pre 3 -15	Pre 2 -10	Pre 1 -5	Start	End	Post 1 +5	Post 2 +10
19:53 – 19:58	19:58 – 20:03	20:03 – 20:08	20:08 – 20:13	20:25-20:30	20:30 – 20:35	20:35 – 20:40

This procedure made it possible to identify acute changes leading up to and following each episode. When the episode was > 5 min, the 'end' segment followed directly on from the 'start' segment.

It is possible that mood and / or heart rate variability could be altered throughout this 40-45 min period. The data over the period of the episode was therefore compared with control periods. For DRM mood, we used the corresponding time points for the hour before and the hour after the ST depression / VT episode. So for the episode starting at 20:08, the periods centred on 19:08 and 21:08 were analysed, as detailed in Table 7.4.

Table 7.4 Timing of control periods for acute ST depression / VT episodes

Control period 1							
Pre 3 -15	Pre 2 -10	Pre 1 -5	Start	End	Post 1 +5	Post 2 +10	
18:53 – 18:58	18:58 – 19:03	19:03 – 19:08	19:08 – 19:13	19:25-19:30	19:30 – 19:35	19:35 – 19:40	
Control period 2							
Pre 3 -15	Pre 2 -10	Pre 1 -5	Start	End	Post 1 +5	Post 2 +10	
20:53 – 20:58	20:58 – 21:03	21:03 – 21:08	21:08 – 21:13	21:25-21:30	21:30 – 21:35	21:35 – 21:40	

These two control periods were then averaged to generate an aggregate control mood profile to compare with the ST depression / VT period. In the analyses of heart rate and heart rate variability, only the control period 1 was assessed. The reason for this is because many ST depression / VT episodes took place towards the end of the 24 hour monitoring period, so there were too many cases from control period 2 which were missing data and therefore could not be analysed.

7.3 Comparison of ST depression / VT patients and the remaining participants in relation to general characteristics, mood, HRV measures and cortisol profile

7.3.1 Comparison of ST depression / VT patients and the remaining participants with relation to socio-demographic, clinical, psychological and quality of life characteristics of participants with ECG changes and the remainder

Comparing the socio-demographic variables between the participants who had ECG abnormalities of ST depression and VT, and those who had no changes, revealed no significant differences between the two groups in relation to gender, age, ethnicity, education or marital status (see Table 7.5). Additionally, there were no significant differences between the two groups in terms of clinical risk factors of hypertension, diabetes or smoking status. When comparing the groups on medication, the main significant effect was the differences in beta blocker use ($p = 0.03$). A greater percentage of the participants (72.0%) who had normal ECG's were on beta blocker medication than those who displayed an abnormal ECG response (38.5%). Given that beta blocker medication is anti-arrhythmic, increases parasympathetic drive, and reduces heart rate, this is an unsurprising result.

Another significant difference between the two groups ($p = 0.02$) was related to sleep quality. Of those who had an abnormal ECG, only 33.3% had good sleep quality, compared to 68.9% participants who had a normal ECG. On the physiological side, the differences in cortisol are quite striking and these have been described in section 7.3.4.

Results from the SF36 suggest that participants with ECG abnormalities have significantly greater impairment to certain aspects of their quality of life. Participants with ECG abnormalities had significantly lower SF36 scores in the following dimensions: limitations due to emotional problems, mental health and pain. Participants with ECG changes scored 65.3 ± 40.1 on limitations due to emotional problems versus 29.2 ± 37.5 in the remainder ($p = 0.02$). The group with ECG abnormalities also scored worse on the limitations due to mental health score (66.4 ± 20.7 versus 50.4 ± 19.3 in the

normal ECG group, p = 0.03). Additionally, the group with ECG abnormalities scored significantly worse on the pain scale (60.6 ± 17.0 versus 74.4 ± 18.1 in the normal group; p = 0.03). Accordingly, in addition to poor mental health and quality of life, a trend was noted towards greater limitation in social functioning amongst the group with ECG changes approaching significance (79.0 ± 20.4 in the ECG changes group versus 64.8 ± 24.5 in the remainder, p = 0.07). SF36 results are summarised in Table 7.6.

Table 7.5 Characteristics of patients with ST depression or VT on ECG

		Normal ECG (n = 75)	**ST depression and VT on ECG (n= 13)**	**Differences (p)**
Gender	Men	52 (69.3%)	8 (61.5%)	0.75
	Women	23 (30.7%)	5 (38.5%)	
Age (years)		61.2 ±9.7	64.3 ± 9.4	0.36
Ethnicity	White	55 (73.3%)	8 (61.5%)	0.51
	Other	20 (26.7%)	5 (38.5%)	
Educational qualifications	Primary	36 (48.0%)	5 (38.5%)	0.56
	Secondary/above	39 (52.0%)	8 (61.5%)	
Marital status	Married	45 (60.0%)	8 (61.5%)	1.0
	Not married	30 (40.0%)	5 (38.5%)	
Smoking status	Current	20 (26.7%)	1 (7.7%)	0.30
	Ex / non-smoker	55 (73.3%)	12 (92.3%)	
Diabetes	Yes	11 (14.9%)	3 (27.3%)	0.38
	No	63 (85.1%)	8 (72.7%)	
Hypertension	Yes	41 (54.7%)	6 (46.2%)	0.76
	No	34 (45.3%)	7 (53.8)	
Beta Blocker medication	Yes	54 (72.0%)	5 (38.5%)	0.03*
	No	21 (28.0%)	8 (61.5%)	

		Normal ECG (n = 75)	ST depression and VT on ECG (n= 13)	Differences (p)
Statin medication	Yes	63 (84.0%)	9 (69.2%)	0.24
	No	12 (16.0%)	4 (30.8%)	
Aspirin medication	Yes	65 (87.8%)	12 (92.3%)	1.0
	No	9 (12.2%)	1 (7.7%)	
Baseline HAD anxiety score		6.41±3.8	8.0±3.7	0.24
Baseline BDI depression score		10.1±7.5	11.1±5.6	0.73
Moderate/severe depression (BDI score>10)	Yes BDI >10	31 (42.5%)	6 (46.2%)	0.56
	No BDI <10	42 (57.5%)	5 (53.8%)	
CAD	Positive	50 (66.7%)	6 (46.2%)	0.21
	Negative	25 (33.3%)	7 (53.8%)	
Sleep quality	Good	51 (68.9%)	4 (33.3%)	0.02*
	Poor	23 (31.1%)	8 (66.7%)	

* Significant difference, $p < 0.05$.

Table 7.6 Mental health and SF36 in patients with ST depression or VT on ECG

	Normal ECG (n = 75)	ST depression and VT on ECG (n= 13)	Differences (p)
BDI depression score	10.2±7.5	11.1±5.65	0.73
HAD anxiety score	6.4±3.8	8.0±3.7	0.24
Physical health status score	63.3±21.1	54.6±20.5	0.24
Mental health status score	66.4±20.7	50.4±19.3	0.03*
Physical function score	68.6±23.6	61.0±19.4	0.36

	Normal ECG (n = 75)	ST depression and VT on ECG (n= 13)	Differences (p)
Vitality	52.2±22.1	48.9±20.3	0.67
Social functioning	79.0±20.4	64.8±24.5	0.07!
Limitations due to physical problems	52.7±41.0	34.4±44.2	0.24
Limitations due to emotional problems	65.3±40.1	29.2±37.5	0.02*
SF36 Pain scale	74.4±18.1	60.6±17.0	0.03*
SF36 General health perception	60.3±18.9	57.6±21.1	0.7
SF36 Mental health perception	68.9±18.6	57.3±19.4	0.08!

*Significant difference, $p < 0.05$. !Approaching significance.

7.3.2 Comparison of ST depression / VT patients and the remaining participants with relation to DRM mood

In addition to the DRM moods of happiness, negative affect, depression and tiredness that were included in chapter 5, I will also include, in this chapter, data on two additional moods; anger and worry. This is because I am particularly interested in discovering whether these specific moods can also be found in those participants who show ECG changes during the day. There is substantial literature relating hostility to atherosclerosis development (Barefoot et al., 1983). Anger has been shown to be a trigger of myocardial ischaemia (Steptoe et al., 2006; Culic et al., 2005). Worry, or anxiety, has also been shown to predict cardiac morbidity and mortality in susceptible patients (Kubzansky et al., 1998).

In this chapter, I present mean values of affect ratings over the day, rather than over the broader categorisation of five time periods, as described in chapter 5. This is because in chapter 5 I looked at the general pattern of mood in relation to HRV, whereas in this chapter I use a more fine grained analysis of mood in relation to the ECG recording of the patient.

Table 7.7 compares mean values for the DRM affect measures in the two groups. In particular, it allows analysis of the mood at the specific time points surrounding the ischaemic periods. Although Table 7.7 suggests increased negative affect and depression scores in participants with ECG changes compared to the remainder, there were no statistically significant differences in affect ratings between the two groups.

Table 7.7 Mean affect ratings across all episodes in day in relation to changes on ECG

Affect rating across all episodes	N	Mean	SD	p differences
Happiness				
No ECG changes	75	3.25	1.0	0.67
ST or VT	12	3.1	1.2	
Negative affect				
No ECG change	75	0.87	0.77	0.36
ST or VT	12	1.1	0.77	
Angry				
No ECG change	75	0.36	0.58	0.68
ST or VT	12	0.29	0.57	
Depression				
No ECG change	75	0.62	1.1	0.6
ST or VT	12	0.8	1.2	
Worry				
No ECG change	75	1.1	1.3	0.4
ST or VT	12	1.5	1.1	
Tiredness				
No ECG change	75	1.7	1.6	0.95
ST or VT	13	1.7	1.1	

7.3.3 Comparison of ST depression / VT patients and the remaining participants with relation to heart rate and other HRV indices

Table 7.8 summarises heart rate and HRV levels over five periods of the day (morning 1, afternoon, evening, night, and morning 2) in the two groups. There were no significant differences in any of the HRV indices between participants who experienced ST depression and/or VT, and the remainder, at any time of day.

The results in section 7.3 indicate that patients who experience ST depression and/or VT could not be distinguished from the remainder of participants in terms of mood or HRV over the study period. This suggests that if there are differences, they are more likely to be detected in finer grained analyses of the periods surrounding each episode of ischaemia or arrhythmia.

Table 7.8 HRV time and frequency domain indices with relation to changes on ECG.

	Morn1 mean (SD)	Noon mean (SD)	Eve mean (SD)	Night mean (SD)	Morn2 mean (SD)
IBI (RR)					
No ECG changes	851.4 (128.4)	858.2 (132.1)	878.1 (142.9)	1003.2 (158.8)	858.3 (142.5)
Both ST or VT	825.2 (136.1)	804.9 (124.5)	861.3 (118.1)	1005.6 (120.6)	826.4 (140.0)
HF n					
No ECG change	24.1 (10.5)	23.9 (9.9)	26.0 (11.7)	31.7 (14.3)	24.5 (9.8)
Both ST or VT	23.56 (10.7)	25.5 (9.2)	28.4 (9.1)	39.4 (16.7)	27.4 (9.0)
LF n					
No ECG change	67.8 (14.4)	67.6 (13.6)	66.5 (14.6)	64.7 (15.1)	66.6 (14.0)
Both ST or VT	66.7 (11.4)	64.4 (12.7)	65.3 (12.9)	55.6 (17.1)	62.1 (12.6)
vLF n (log)					
No ECG change	7.2 (0.73)	7.1 (0.7)	7.1 (0.7)	7.4 (0.69)	7.3 (0.65)
Both ST or VT	7.3 (0.82)	7.1 (0.69)	7.0 (0.8)	7.4 (0.69)	7.2 (0.65)

NN = 5 minute average N-N intervals. (R-R intervals)

HF n = Normalised High Frequency (0.15 to 0.40 Hz) in ms^2

LF = Normalised Low Frequency (0.04 to 0.15 Hz) in ms^2

vLF.n.log = Log of normalised very low frequency (0.03 to 0.15 Hz) in ms^2

(SD) = Standard deviation of mean value of HRV indices.

7.3.4 Comparison of ST depression / VT patients and the remaining participants with relation to cortisol profile

Separate analyses were carried out on cortisol sampled over the day and the cortisol awakening response (CAR). As expected, cortisol levels were high early in the morning, and declined over the day. Patients experiencing ST depression / VT were compared with the remainder. In repeated measures of analysis of cortisol over the day and evening, there was a main effect of group ($F = 5.74$, $p = 0.019$). Cortisol levels were significantly lower in participants showing ST/VT changes than those with no such changes on the ECG (See Figure 7.1).

Figure 7.1

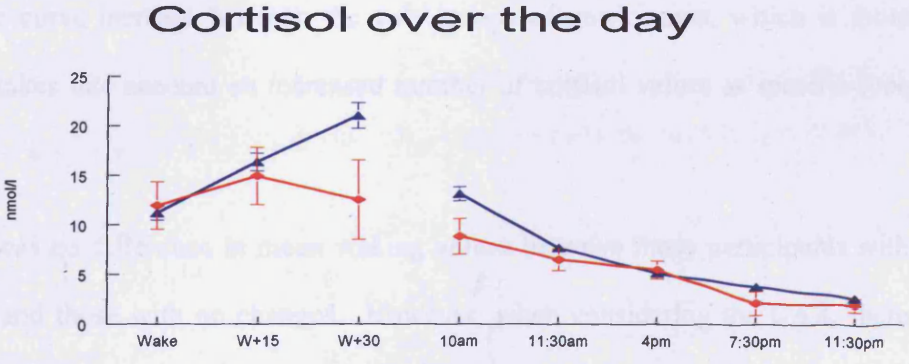


Figure 7.1 Mean salivary cortisol on waking (wake), 15 minutes (wake+15) and 30 minutes (wake+30) after waking in patients showing ST/VT changes (red solid line) and patients showing no changes on ECG (solid blue line), unadjusted for age, gender, beta blockade and objective time of waking. Error bars are s.e.m.

However, after adjustment for beta blocker medication, gender and bed time this difference was no longer quite significant ($F = 3.7$, $p = 0.058$). When analysing cortisol over the day with participants who had ST depression only, a similar pattern was found with a main effect of group ($F = 7.02$, $p = 0.01$). But once again, after adjustment for the same covariates, this difference was no longer significant ($F = 3.75$, $p = 0.056$).

With regard to cortisol slope, there were no significant associations found in relation to participants showing either ST/VT changes on ECG ($F = 0.12$, $p = 0.73$) or ST depression only on ECG ($F = 1.61$, $p = 0.21$), and those with no ECG changes after adjustment for the same covariates.

However, the most interesting result is the CAR effect, which is significant after controlling for covariates, both using CAR area under the curve increase and the increase between waking and 30 minutes.

The difference in CAR between the participants showing ST depression on ECG and those with no changes on ECG were analysed in two ways. One way is to analyse the difference between the 30 minute cortisol mean values after waking and the initial cortisol mean value on waking. The second way is to analyse the difference between the area under the curve increase between the two groups of participants, which is more accurate as it takes into account an increased number of cortisol values at specific time points.

There was no difference in mean waking values between those participants with ECG changes and those with no changes. However, when considering the CAR, there was a significant difference between the groups after adjustment for covariates, including beta blocker medication, gender, and wake time. Patients with ECG changes had significantly lower CAR's, whether analysed using changes between waking and 30

minutes ($F = 4.09$, $p = 0.047$), or analysed by area under curve increase (AUC) ($F = 3.996$, $p = 0.05$).

7.4 The acute changes in mood and HRV within the participants showing ECG abnormalities

This section presents the data on the acute responses within the ECG abnormality group. The analyses of the acute mood change surrounding the ischaemic episode is first described, followed by the analyses of the acute heart rate and HRV changes surrounding ischaemic episodes.

The analyses of acute mood changes (section 7.4.1) and heart rate variability responses (section 7.4.2) were carried out as follows. First, a repeated measures analysis of variance was carried out for the 7 *segments* of the ischaemic / arrhythmic period. This showed whether there were systematic changes in mood or HRV, in the minutes before and after each episode of ST depression / VT. Second, repeated measures analysis was performed with *period* (ischaemia or control) and *segment* (the 7 within-period segments) as within-subject factors. Finally, analysis of covariance was carried out to compare specific segments, with gender and use of beta blockers as covariates.

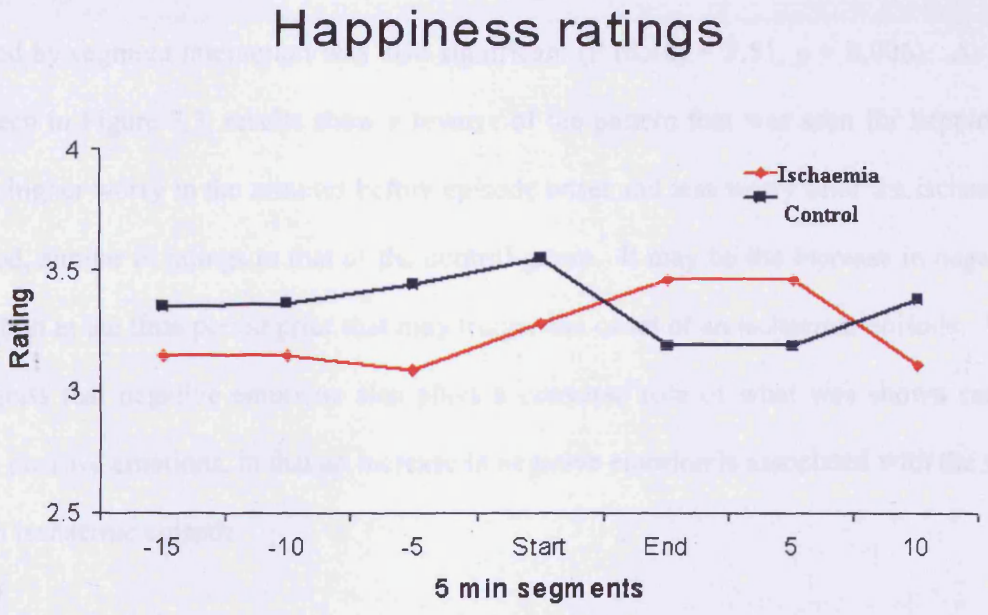
The DRM analyses were carried out with 9 of the 13 patients (6 ST depressions / 3 VT). For three patients, episodes of cardiac abnormalities on the ECG occurred when the individual was asleep, and one DRM dataset was lost.

7.4.1 Mood changes preceding and following ST depression / VT episodes

In the analyses of acute mood changes, significant results were found in relation to moods of happiness and worry, and ischaemic/arrhythmic episodes of the participants.

Happiness: There was near significant cubic effect in analysis of the ischaemic period, ($F(1,8) = 4.57$, $p = 0.065$), together with a significant cubic period by segment interaction, ($F(1,8) = 6.24$, $p = 0.037$) (see Figure.7.2).

Figure 7.2

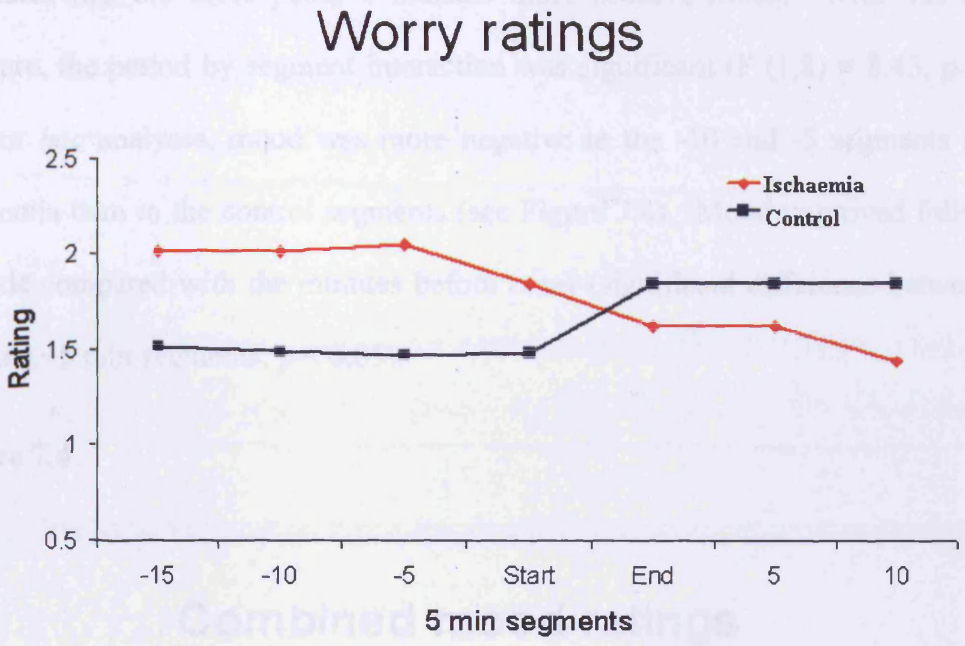


As can be seen in Figure 7.2, positive affect was relatively low in the 15 minutes before onset of the ischaemic or arrhythmic episode, and rose after the episode started. In *post hoc* tests, there were significant differences (after adjusting for gender and beta blocker use) between ischaemia and control periods for segment -15, segment -10, segment -5, and the episode start segment (all $p < 0.05$). However, there were no differences *after* the episode starts. These results suggest that happiness is lower in the

15 minutes before onset of ST depression / VT episodes. This association between emotion and the cardiovascular response suggests a possible pathway linking emotion with triggering of cardiac events. It may be that the absence or a drop in positive affect (or conversely a greater negative affect) could be significant in triggering an acute ischaemic episode. However, it is feasible that the ischaemic episode itself may trigger a less positive affect or negative affect in the individual, particularly if accompanied by chest pain.

Worry: A main effect of segment in the analysis of the ischaemic period ($F(6,48) = 2.54$, $p = 0.032$) was seen. In the analysis, including the ischaemic and control periods, the period by segment interaction was also significant ($F(6,48) = 3.51$, $p = 0.006$). As can be seen in Figure 7.3, results show a reverse of the pattern that was seen for happiness, with higher worry in the minutes before episode onset and less worry after the ischaemic period, similar in ratings to that of the control group. It may be the increase in negative emotion in the time period prior that may trigger the onset of an ischaemic episode. This suggests that negative emotions also plays a converse role of what was shown earlier with positive emotions, in that an increase in negative emotion is associated with the start of an ischaemic episode.

Figure 7.3

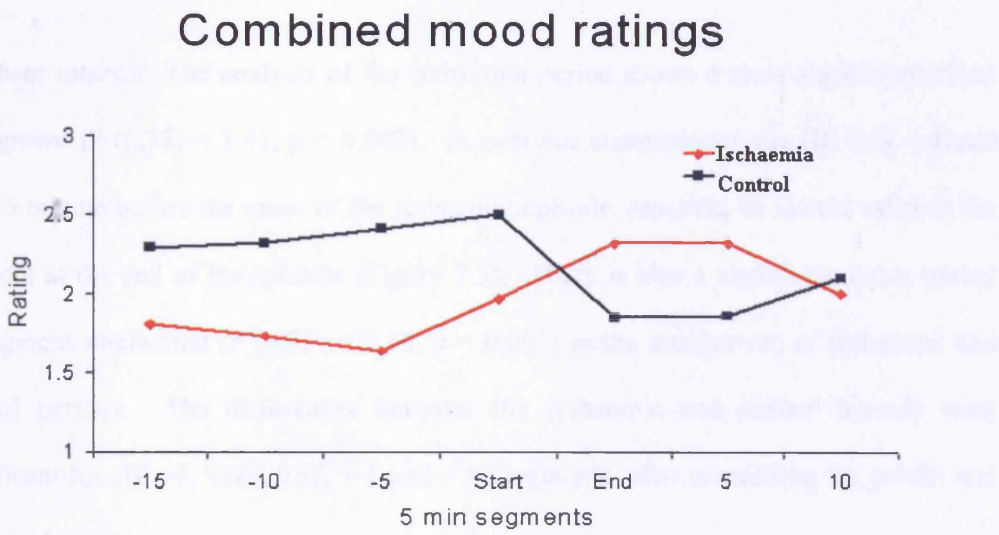


Angry and depressed moods: Analysis revealed that there were no significant effects, although period by segment interaction approaching significance for depression (F (1,8) = 4.82, p = 0.059) was found, with greater depressed mood in the minutes before episode onset. The near significant association supports the limited literature, in that depressed mood can act as an acute trigger in ACS (Steptoe et al., 2006).

Tiredness: There were no significant changes or differences in ratings of tiredness in the period immediately surrounding episodes of ST depression / VT. There was neither a significant main effect of segment in the analysis of the ischaemic period, nor a significant period by segment interaction in the analysis, including the ischaemic and control periods.

Combined mood: A combined mood measure was generated by adding together ratings of anger, depression, worry and tiredness and subtracting them from happiness. Measures that are more positive indicate more positive mood. With this combined measure, the period by segment interaction was significant ($F(1,8) = 8.43$, $p = 0.020$). In *post hoc* analyses, mood was more negative in the -10 and -5 segments preceding ischaemia than in the control segments (see Figure 7.4). Mood improved following the episode compared with the minutes before onset (significant difference between -5 and end and +5 min segments, $p < 0.05$).

Figure 7.4



What is striking is the consistency seen in the magnitude of change in the various emotions prior to an ischaemic episode and after the ischaemic episode, compared to the control segments within each individual, and the converse patterns that has been seen for the positive emotion of happiness and negative emotion of worry.

7.4.2 Heart rate and HRV changes preceding and following ST depression / VT episodes

Repeated measures analysis of variance was carried out for the 7 *segments* of the ischaemic/arrhythmic period, in order to discover whether there were systematic changes in the HRV indices (i.e. IBI, HFn, LFn, and VLF power) in the minutes before and after each episode of ST depression / VT. As for mood, repeated measures analysis was performed with *period* (ischaemia or control) and *segment* (the 7 within-period segments) as within-subject factors, followed by analysis of covariance which was carried out to compare specific segments, with gender and use of beta blockers as covariates.

Interbeat interval: The analysis of the ischaemia period shows a main significant effect of segment ($F(6,72) = 5.41$, $p = 0.002$). In *post hoc* comparisons, the IBI was reduced from 5 minute before the onset of the ischaemic episode, reaching its lowest value in the segment at the end of the episode (Figure 7.5). There is also a significant cubic period by segment interaction ($F(6,72) = 3.58$, $p = 0.005$) in the comparison of ischaemic and control periods. The differences between the ischaemic and control periods were significant for -10, -5, Start, End, + 5 and + 10 segments, after controlling for gender and beta blocker use.

In summary, Figure 7.5 demonstrates how the heart rate speeds up prior to the ischaemic episode and then reduces in rate afterwards, promptly returning almost to baseline levels. What is striking is that the increased heart rate does not occur over the 10-15 minutes before the episode (when mood was different), but much more acutely. This makes it unlikely that the elevated heart rate is involved in triggering of the episodes of ST depression / VT, unless this is a very short-term effect. Rather, it may be

a compensatory mechanism of increased vagal tone produced after or with the ischaemic episode and hence a lowering of the heart rate, in order to limit the extent of the ischaemic episode occurring.

LFn power: The analysis of the ischaemia period shows a main significant effect of segment ($F(6,72) = 3.25$, $p = 0.017$) and a cubic period by segment interaction ($F(1,12) = 10.39$, $p = 0.007$) in the comparison of ischaemic and control periods. In *post hoc* analysis controlling for gender and beta blocker use, the only difference was in the start segment, where LFn abruptly decreases (Figure 7.6).

Figure 7.5

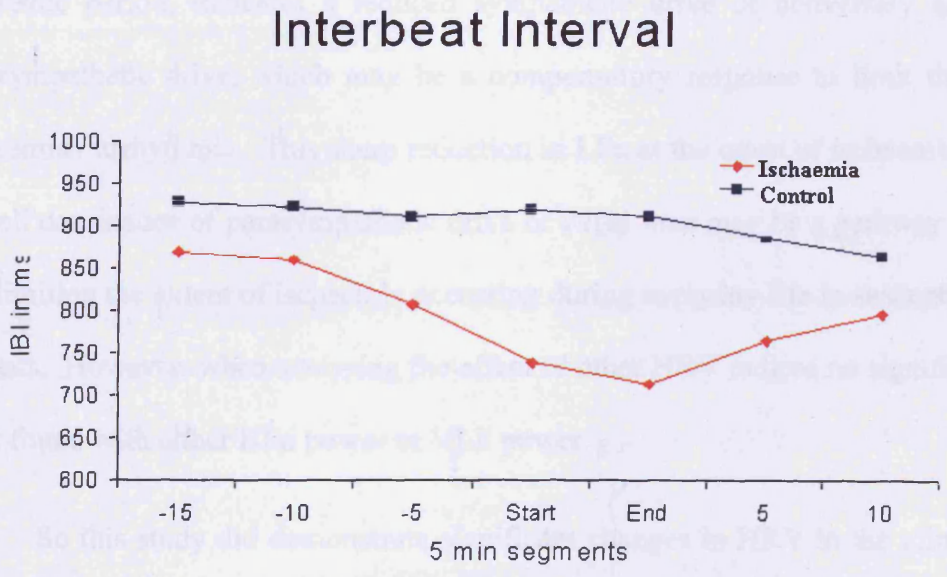
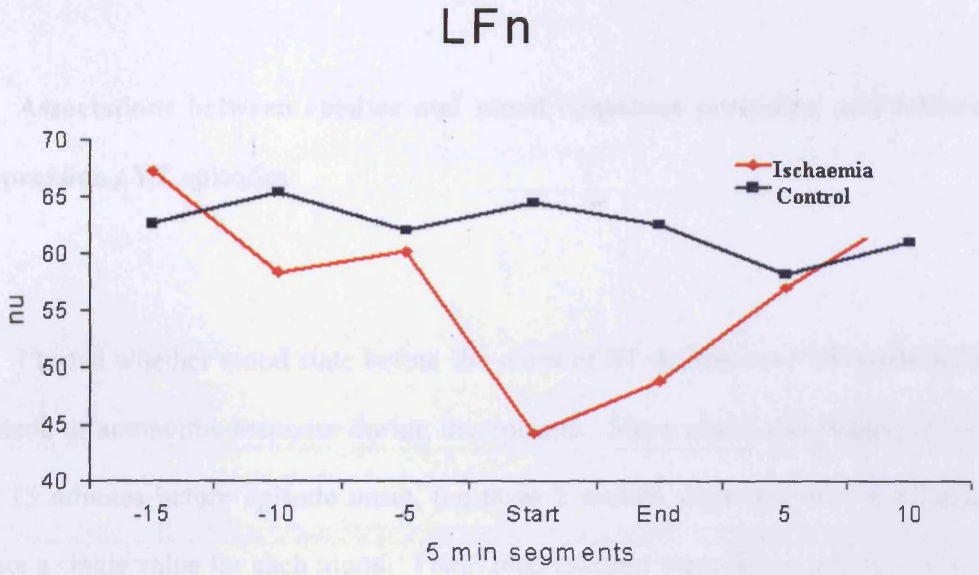


Figure 7.6



The sharp reduction of LFn power seen in Figure 7.6 here only at the start of the ischaemic period, indicates a reduced sympathetic drive or conversely an increased parasympathetic drive, which may be a compensatory response to limit the extent of ischaemia / arrhythmia. This sharp reduction in LFn at the onset of ischaemia and hence overall dominance of parasympathetic drive or vagal tone may be a pathway in adapting and limiting the extent of ischaemia occurring during everyday life in susceptible cardiac patients. However, when analysing the effect of other HRV indices no significant effects were found with either HFn power or VLF power.

So this study did demonstrate significant changes in HRV in the minutes before onset of ST depression / VT, despite the small number of patients contributing to these effects. Results were the same when analysis was limited to ST depression cases alone. These findings are not consistent with some other literature on HRV and the relationship

with transient myocardial ischaemia as discussed in chapter 2.5. These results and their implications will be further discussed in section 7.6 and Chapter 11.

7.5 Associations between cardiac and mood responses preceding and following ST depression / VT episodes

I tested whether mood state before the onset of ST depression / VT predicted the magnitude of autonomic response during the episode. Since mood was relatively stable in the 15 minutes before episode onset, the three 5 minute segments were averaged to generate a single value for each mood. These mood ratings were then correlated with the change in IBI and change in LFn power between 15 minutes pre-episode, and the 5 minute segment in which the episode started.

The results of these correlations are shown in Table 7.9. The data indicate strong associations between mood and cardiac responses to the onset of ST depression / VT. Individuals with more positive combined moods showed smaller IBI reductions and decreases in LFn power (i.e. less sympathetic drive) than those with less positive moods. These effects were due to a combination of greater happiness and less depression and worry in the more positive individuals. The negative relationship between combined mood and IBI response remained significant after adjusting for gender, use of beta blockers, and IBI 15 minutes before the episode ($r = 0.89$ $p = 0.007$). The associations with worry and depressed mood also remained significant ($p < 0.05$). This indicates that the association was not due to beta blocker users having moods that are more positive and smaller IBI responses, or patients in a more positive mood having slower heart rates and smaller responses.

Table 7.9 Correlations between mood and cardiac responses during ST depression / VT episodes

	IBI difference -15 min to episode onset ***R***	**LF n power difference** -15 min to episode onset ***R***
Total mood	0.94***	0.73*
Happiness	0.84**	0.66*
Worry	-0.83**	-0.33
Anger	-0.72*	-0.60
Depression	-0.78*	-0.76*

* $P < 0.05$; ** $P < 0.01$; *** $P < 0.001$

The relationship between combined mood and IBI response is illustrated in Figure 7.7. It can be seen that patients with more positive mood in the 15 minutes before ST depression /VT episodes had smaller reductions in IBI when the episode started. A similar pattern was present for happiness in the 15 minutes before episode onset, as illustrated in Figure 7.8. Patients who were happier during this period showed smaller IBI responses.

Figure 7.7

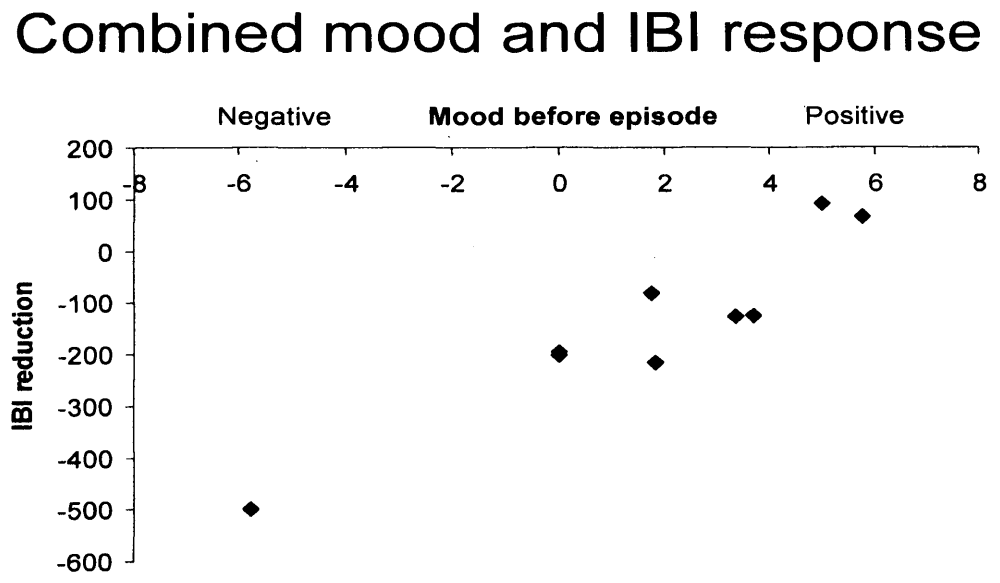
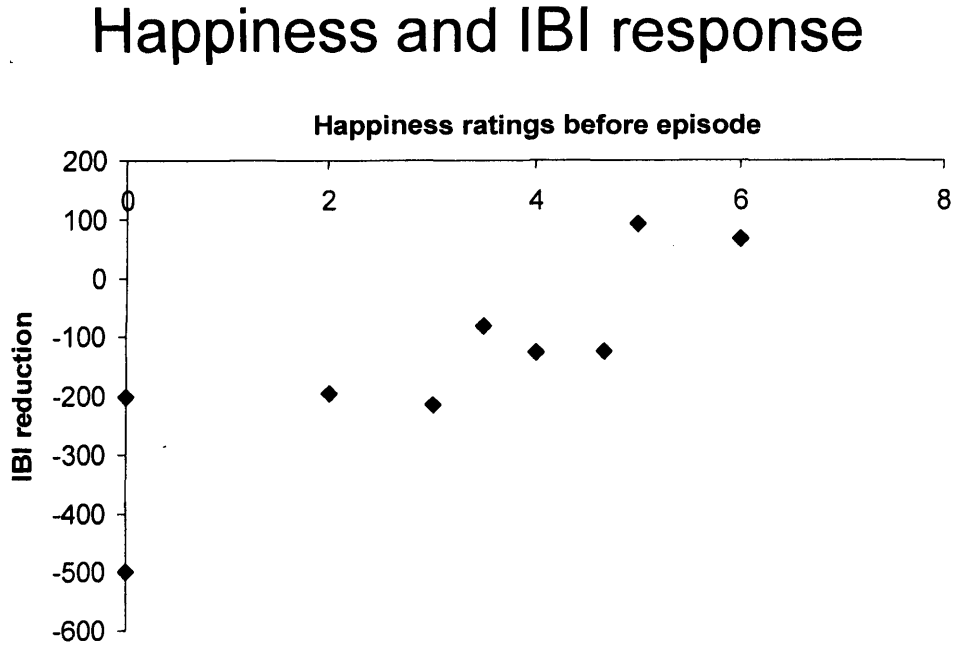


Figure 7.8



7.6 Discussion

7.6.1 General

There were no significant differences between the group with ECG changes compared to the remainder with respect to socio-demographic and clinical variables. The two exceptions were for those on beta blocker medication and those who had good sleep quality. The patients were significantly more likely to be on beta blocker medication in the group with no ST or VT ECG changes. This finding from the SIS study is to be expected, as beta blocker medication blocks sympathetic drive and thus reducing the heart rate and depresses the myocardium. As a result, physicians often prescribe this medication to CAD patients to reduce the frequency of ischaemic episodes by altering the myocardial demand for oxygenated blood (Chierchia et al., 1990).

The second finding was of better sleep quality in the group with no ischaemic or arrhythmic ECG changes. Poor sleep quality has been associated with adverse cardiac prognosis, and the association is not explained by depression or standard coronary risk factors (Leineweber et al., 2003). However, it remains to be further elucidated whether it is the ischaemic changes that causes poor sleep quality or that poor sleep promotes cardiac ischaemia.

Regarding quality of life, overall the patients in the ST / VT group were significantly impaired with regards to mental health status, emotional health, and pain. Poorer mental health and increased limitations due to emotional problems associated with the group with ECG changes of ST depression / VT, supports the body of evidence relating mental stress and negative emotions to cardiovascular parameters (Sirois & Burg, 2003; Rozanski et al., 1999, 2006).

7.6.2 DRM

Analysis of affect by the DRM in relation to the group with ECG changes, revealed that there were no significant differences between the two groups with respect to the different affects of happiness, anger, worry, and tiredness. There was a trend seen with results approaching statistical significance, in that the group with ST and / or VT changes had an increase in negative affect ($p = 0.36$) and depressed mood ($p = 0.4$). Whilst the trend seen supports, to an extent, findings from previous ambulatory studies in which negative emotions have been associated with ischaemia, e.g. anger; (Gabbay et al., 1996; Ironson et al., 1992); tension, sadness (Gullette et al., 1997) and stress (Barry et al., 1988; Krantz et al., 1996), I did not detect any significant differences between the two groups regarding different types of negative affect or positive affect. It could be that the sample size was too small or the number of actual ECG ischaemic changes detected were too few for analysis in conjunction with affect. A substantial majority were on cardiac medication, which may attenuate any ischaemic event. Previous ambulatory studies assessed mood by periodic diary ratings in the monitoring period, not by the more continuous assessment which the DRM provides.

Specific emotions like worry have been associated with an increased risk of CAD (Kubzansky et al., 1997; Kawachi et al., 1995). However, changes or lack of changes of negative emotions associated with the ischaemic episodes seen in this study are not supported by findings in other studies. For example, Lampert et al. (2002) systematically evaluated whether emotional or physical stressors can trigger spontaneous ventricular arrhythmias. In this work, patients with implantable cardioverter-defibrillators (ICDs) were given diaries to record levels of defined mood states and physical activity, during 2 periods preceding spontaneously occurring ICD shocks (0 to 15 minutes and 15 minutes to 2 hours) and during control periods 1 week later. In

contrast to findings from this study, anger was independently associated with the pre shock period whereas worry was not associated. A limitation in our study is that during the 24 hour period of monitoring, there may be insufficient frequency or level of arousal in the various affects like anger or depressed mood to show strong effects.

There were significant results for happiness, a positive emotion. The affect rating just before the onset of the ischaamic episode is low but becomes higher just after the ischaemic episode starts. This is consistent with findings from the derived index, combined mood, in which a lower positive mood is seen just before the onset of the ischaemic episode and a higher positive mood just after the ischaemic episode started. These acute changes in mood occur within minutes, correlating with the transient myocardial ischaemic episode, again suggesting that the DRM provides a better tool in the assessment of affect on a moment to moment basis, in relation to cardiovascular reactivity. There has been little in the literature to date relating the momentary effects of positive emotions to favourable biological states. It may be that the rise in positive mood correlating with the ischaemic episode just after it has started, may act as a protective factor in limiting the extent of ischaemia.

7.6.3 HRV

There were no significant differences between the group with ECG changes and the remainder in any of the HRV indices. But analysis of the specific indices just prior to the onset of ischaemic episode, and just after, revealed significant differences in relation to the interbeat interval and LFn. An increased heart rate just prior to the ischaemic episode is seen followed by a reduction in heart rate afterwards, returning to the baseline in minutes. In addition, a sharp reduction in LFn power (reduction in sympathetic drive) is seen prior to the ischaemic episode with a more gradual return to

the baseline. The HR is an index of myocardial oxygen supply. LFn represent the sympathetic / parasympathetic balance of the autonomic nervous system. The SIS study analysis of the HRV in relation to the acute ECG changes, revealed a reduced parasympathetic and an increased sympathetic drive, just after the ischaemic episode has started. An initial increase in HR prior to the episode and then a prompt decrease in HR is observed, just after the start of the ischaemic episode. This autonomic dysregulation can lower the threshold for myocardial ischemia and VT in patients with CAD and supports findings from the previous literature (Carney et al., 2002, Podrid et al., 1990). Many studies have found a higher heart rate at rest is a risk factor for sudden cardiac death in the general population, increases the risk of progression to atherosclerosis (Palatini et al., 1999) ventricular arrhythmia (Podrid et al., 1990) and ischaemia (Palatini et al., 1997).

It is possible that both the HR increase at the start of the episode and the reduction in LFn serve as a compensatory reflex mechanism to increase vagal tone in order to act as a 'brake' on the cardiovascular system in prevention of the ischaemic episode extending further into a full blown myocardial infarct.

7.6.4 The associations between DRM mood and HRV

The associations of increased positive (combined mood) with a reduction in IBI interval and a reduced LFn at the start of the episode followed by a rise, is consistent with the notion that positive emotion was associated with an increased HRV and supports other studies in the literature. McCraty et al. (1995) shows that positive emotional state is associated with an increase in medium frequency power in healthy participants. Bacon et al. (2004) showed that higher levels of positive emotions to be associated with an increase in low frequency power independent of age, posture and

medication in CAD patients. However, previous studies have shown that mental stress reduced vagal control of the heart as evidenced by reduced HF in CAD patients (Grossman et al., 1996; Kop et al., 2001) and higher levels of negative emotions like anger, stress and sadness have been associated with decreases in high and low frequency power (Bacon et al., 2004). Depression has been shown, in particular, to relate to reduced levels of HF power (Carney et al., 2001) and other studies have shown that those with anxiety and depression are associated with 24 hour reduction in HF power (Gorman et al., 2000). Thayer et al. (1996) found worry to be associated with shorter IBI's and lower high frequency power. In summary, there is an extensive literature on the associations of negative emotions with reduced HRV but less so on positive emotions and HRV. This may be because of reduced frequency of such positive emotions in CAD patients or that previous studies are unable to detect momentary cardiac changes with momentary changes in affect.

The advantage of our study is that the HRV changes surrounding with the acute ischaemic episode can be analysed in conjunction with the moment to moment affect, allowing a more accurate assessment of emotions relation to transient autonomic tone.

7.6.5 Cortisol

The results suggest that patients with ST depression and / or VT on the ECG showed significantly lower levels of mean cortisol values and a significantly lower CAR compared to the group with normal ECG's. There were no significant associations with cortisol slope.

The cortisol awakening response (CAR) is a reliable biological marker for assessing adrenocortical activity (Pruessner et al., 1997). In healthy adults, salivary free

cortisol concentrations increase by between 50 and 60% in the first 30 minutes immediately post-awakening (approximate average increase of 9 nmol/l, range 4-15 nmol/l). However, there are no agreed norms for the absolute concentrations, of free cortisol in saliva, either immediately post-awakening (range of 4.7-18.5 nmol/l) or 30 minutes post-awakening (range of 8.6-21.9 nmol/l). Reasons for these discrepancies include confounding factors such as gender, age, awakening time, light and participant adherence (Clow et al., 2004). The CAR is under a distinct regulatory influence, different from the rest of the diurnal cortisol secretory cycle and studies have demonstrated an association between the CAR and psychosocial variables. Some studies have shown a larger CAR in depressed people (Pruessner et al., 2003) and low positive affect (Steptoe et al., 2005). On the other hand, smaller CAR's have been seen in those with chronic fatigue syndrome (Roberts et al., 2004) and it remains unclear whether good health is consistently associated with larger or smaller awakening responses.

The SIS study results found a reduced CAR in those patients who exhibited ischaemic ECG changes. The these ischaemic changes may be speculated as an ECG marker of chronic cardiac stress or a type of fatigue similar to the findings by Roberts et al. (2004). The reduced CAR associated with the ECG changes in cardiac patients supports a potential pathway as to how TMI may be induced in everyday life in response to mood. The findings from the SIS study of lower mean cortisol values throughout the 24 hours contradict findings from studies that have shown positive associations between higher mean values of cortisol values and increased CAD risk (Bain et al., 1989; Troxler et al., 1977, Von Kanel et al., 2007). The fact that mean cortisol levels were lower in the group with ECG abnormalities may be related to other factors unmeasured such as IL-6, a pro inflammatory circulating cytokine as in the study by Fantidis et al. (2002), as a mediator to cause CAD in the long term in the group with ischaemic or arrhythmic changes on ECG.

From both this chapter and the previous chapter, the SIS study found HRV to be related to ischaemic episodes and mood, whilst the cortisol slope was flatter in the depressed CAD patients as well as showing an exaggerated CAR in the total CAD patients group, independent of depression. Also, a reduced CAR was seen in the group exhibiting ECG changes. This association between changes in both HRV and cortisol profile in relation to ischaemia and changes in affect is supported by previous stress findings indicating HRV and cortisol differences such as in the study by Taylor et al. (2006). However, Ansgar et al. (2007) investigated temporal variation in HRV, cortisol and mood across the day and focused on differences between depressed and non-depressed individuals at risk of CAD (increased number of cardiac risk factors). Participants recruited completed PANAS questionnaires at baseline and during laboratory stress tests as well as completing mood questionnaires at prompted times. They underwent ECG ambulatory monitoring, wearing an accelerometer to account for physical activity and provide cortisol samples. In contrast to the SIS study, the interesting finding in this study is firstly, the lack of HRV and cortisol differences between the depressed and the non-depressed at risk patients in daily life. Secondly, high levels of negative emotions are related to HRV in the non-depressed and not the depressed individuals, and there was no indication of hypercortisolaemia in the depressed sample as in previous studies (Maes et al., 1994; Keller et al., 2006; Stewart et al., 2005). The evidence is mixed with findings from the SIS study supporting some studies but not others.

7.7 Summary

To answer the questions posed at the beginning of the chapter, patients who experience ST/VT do differ from those with normal ECG's but only slightly. There are characteristic changes in the DRM affect, HR and HRV surrounding the ischaemic episodes and there are definite associations between mood and cardiac responses.

Overall, patients who experienced ST depression or VT on ECG slightly differed from those with normal ECG's with respect to beta blocker medication and sleep quality only . Otherwise, the two groups did not differ with respect to socio-demographic factors or clinical factors. There were differences between the two groups on the quality of life, particularly relating to mental health and emotional issues. An altered cortisol profile was seen in the group with ECG changes in that they had a significantly lower CAR and lower mean cortisol values throughout the period of monitoring but this was not the case for the other biological markers assessed. In general, there were no significant differences between the two groups as a whole in relation to affect as assessed by the DRM or HRV.

However, when the actual ST or VT episodes were examined in more detail, particularly in the time period before the onset and after the episode started, there were characteristic changes seen in DRM affect, HR and HRV with significant differences emerging with respect to these particular biological markers and the ischaemic episode.

With regards to affect, as measured by the DRM, both happiness and worry were significantly associated with the ischaemic episodes and was a converse picture of each other. There were no significant differences seen with other negative emotions such as depression, anger and tiredness. This contradicts the extensive literature on negative

emotions and its' associations with CAD, particularly depression (Strike & Steptoe, 2002).

Of the HRV indices, HR and LFn both changed significantly with the ischaemic episode, consistent with an increased parasympathetic drive, increased vagal tone and reduced sympathetic drive just after the ischaemic episodes starts.

Finally, positive associations between increased combined (more positive) mood and cardiac responses (reduced IBI and LFn) surrounding the episode were seen and could represent a compensatory mechanism to limit ischaemia and provide a possible explanatory link as to how mood and emotion may influence CAD development.

Chapter 8: 6 month SIS data analyses

8.1 Introduction

The SIS study examined psychosocial factors influencing cardiac or neuroendocrine changes acutely in relation to mood in daily life. All patients recruited were those who had experienced symptoms, had undergone cardiac investigations, and were awaiting a definitive diagnosis to confirm CAD by angiography. At 6 months, the majority had undergone the hospital procedure and were either reassured, advised medical management, or underwent a surgical procedure; namely percutaneous coronary intervention (PCI) or coronary artery by pass graft (CABG).

There is an extensive literature to suggest that both emotional factors like depression and anxiety may influence prognosis with CAD in cardiac patients (Strik et al., 2003; Wiklund et al., 1989; Brown et al., 1999). Additionally, a variety of clinical factors including methods of management or severity of disease e.g. heart failure, angina are also related to CAD prognosis (Heller et al., 1997). In patients who have experienced an actual MI, it is noted that a high degree of emotional distress may occur in the hospital setting (Cay et al., 1972) and in the few months following diagnosis (Wiklund et al., 1984). This may have an impact on the patients' quality of life (QOL) at a later stage in terms of mental and physical health adaptation. Indeed, quality of life in patients following an MI is predicted by a variety of emotional (anxiety, depression) and clinical factors at hospitalisation (congestive heart failure) with adverse outcomes (Frasure-Smith et al., 1991; Heller et al., 1997).

In the SIS study follow up at 6 months, patients had not recently experienced an MI but had newly been given a diagnosis of CAD disease or not. The diagnosis of cardiac disease may affect the patients psychologically. Patient's perceptions of cardiac disease and their beliefs are known to influence psychological and clinical outcomes (Petrie et al., 1996; 2002). However, to date, much of the literature on psychosocial factors and prognosis of CAD focuses on patients' who have actually suffered an acute MI with accompanying aggressive management in hospital, not at an earlier stage of disease, as in the SIS follow up. Disease in the coronary arteries for some participants had probably been identified at an early enough stage that they were able to help avoid an acute MI. Armed with this knowledge at 6 months after the initial study, patients may have had the potential to reduce the risk of cardiac events by modifying known cardiac risk factors and take measures to reduce emotional stresses and strains and hence significantly improve quality of life. On the other hand, knowledge of heart disease may provoke anxiety, depression and worry which could influence emotional and physical adaptation in the long term. Psychosocial factors influencing the psychological and physical outcomes and QOL of such a group of patients at an early stage of CAD development has been little addressed so far.

The main issues that will be investigated in this chapter are the following:

1. Does psychological distress (anxiety/depression) and health-related quality of life improve over the 6 months following investigation and hospital management? Do these changes vary with diagnosis (definite CAD or not) and with method of management (PCI, reassurance only, or medical management)?

2. What factors assessed at time 1 (including HRV, cortisol and mood measures) predict clinical outcomes (readmission, recurrence of symptoms), psychological distress, and QOL at 6 months?

8.2 Method

Clinical follow up was carried out on all participants at 6 months, after the initial study was carried out. 88 participants of the SIS study were all individually contacted by telephone and a brief 15 minute structured clinical interview was carried out between the investigator and participant. This enquired about general health, cardiac symptom recurrence, re-admission to hospital, changes in health behaviour (with respect to diet, exercise, weight, stress, smoking and alcohol consumption) and medication adherence. The interview was recorded on paper records and the anonymised data were then inputted into an SPSS file for further analysis.

In addition to the telephone interview, a questionnaire consisting of a compilation of standard psychometric instruments designed to assess different aspects of emotional experience and well-being, together with measures of health behaviours was sent to the participant to post back in a self-addressed envelope.

Similar to the baseline questionnaire used, the measures used in the 6 month questionnaire were:

i) Illness Attributions Questionnaire

ii) Hospital Anxiety Scale (HADS anxiety)

iii) Medical Outcome Short Form 36 (SF36)

iv) Life orientation test (LOT), a measure of optimism

v) Beck Depression Inventory (BDI)

In addition to the psychosocial measures outlined here that were included in both the baseline and the six month questionnaire, the following four other additional measurements were used in the six month follow up questionnaire:

i) Social network

ii) Social support

iii) Cook and Medley Hostility scale

iv) Health locus of control

Details of the telephone interview, method of scoring and the postal questionnaire psychometric measurements used have already been described in Chapter 4 (Method of SIS study). At 6 months, all participants were sent the questionnaire along with an explanatory letter regardless if they had been contactable by telephone or not. After one week, all those who failed to complete and return the questionnaire were sent two further serial reminder letters each. Patients who were classified as non-responders were mostly those who were uncontactable due to having moved in the interim or having gone abroad for a significant part of the year. Three participants refused to take part in the follow up citing dissatisfaction with clinical treatment at the tertiary hospital caring for them. One participant passed away within the six month period following a cardiac procedure.

8.3 Results

8.3.1 Description of the sample

70 of the 88 patients were interviewed at 6 months, and 66 completed the questionnaire measures. 77 (88.5%) patients completed either or both sets of questionnaire measures. The interval between the original study and the follow-up period averaged 29 weeks and 4 days (SD 45.1 days). A table of the characteristics of the participants obtained at the 6 month assessment is shown next (Table 8.1), according to demographic, clinical, health behaviours and emotional factors.

Table 8.1 Basic demographic and psychosocial characteristics of patient sample at 6 months

Characteristics at 6 months		Frequency N	Percentage %
Demographic factors			
Gender:	Male	51	66.2
	Female	26	33.8
Marital Status:	Married	31	40.3
	Single/other	46	59.7
Ethnicity:	Non White	20	26.0
	White	57	74.0
Educational Attainment (Secondary and above)		40	51.9
Household income (<£20,000)		46	60.5

Characteristics at 6 months	Frequency N	Percentage %
Clinical Factors		
CAD positive (definite CAD)	49	63.6
CAD negative (not significant CAD)	28	36.4
Personal history of CAD (cardiac events, treatment)	14	18.2
Previous MI	12	18.1
Diabetes	13	18.6
Angina symptoms present	35	45.5
Clinical management		
Reassurance	10	14.7
Medical	30	44.1
PCI/Surgery	28	41.2
Health Behaviour		
Smoker current	16	21.1
Emotional factors		
History affective disorder	14	18.2
Depression level high (BDI score ≥10)	32	42.7
Anxiety level high (HADa score ≥8)	28	36.4

The average age of the sample at 6 months follow up was 62.3 years (ranging from 37 years, to 82 years; SD 9.1). The table highlights that the sample was predominantly male (66.2%) and white (74%), and over half the sample were not married (59.7%). This is interesting in light of the fact that social support plays an

important role both in the development and prognosis of CAD. Better prognosis is found in those with greater social support, in terms of emotional or practical support, that may be provided by a spouse (Orth-Gomer & Udon, 1990) and the benefits seen are greater in men than in women (Orth-Gomer et al., 2000).

51.9% had achieved an educational level of secondary schooling and above, but almost two thirds of the sample (60.5%) had an annual household income of less than £20,000. This high percentage may reflect the large proportion that had retired, were on sick leave, or on benefits following unemployment due to chronic medical conditions, all of which occur more commonly in the older population sample. In the literature there are consistent relationships described between social class, socio-economic status, and CAD prognosis (Hemingway & Marmot, 1999).

Clinically, it is of note that of the sample with suspected CAD at the outset, almost half the sample (45.5%) experienced regular frequent angina symptoms at 6 months after the initial study was carried out. Only under a fifth of the sample had established cardiac risk factors, such as diabetes or a previous history of CAD. After angiography was performed, 63.6% of the sample had definite CAD i.e. one or more coronary vessels demonstrating 50% or more stenosis, suggesting a small but significant proportion that has silent ischaemia in everyday life that may be undetected until angiography confirms vessel disease. Clinical management was divided almost equally between medication (44.1%) and an interventional procedure (41.2%). This may indicate that advances in sophistication of medical care allow the clinician to identify disease in the coronary arteries at an early enough stage to warrant conservative management and obviate the need for surgical intervention like PCI.

Despite only 18.2 % of the sample having a history of an affective disorder, 42.7% of the participants scored highly ($\geq$ 10) on the BDI scale at six months. In

addition, 36.4% of the sample scored highly on the HADS scale at six months. The literature indicates that anxiety can independently predict CAD prognosis (Kubzansky et al., 1998; Lane et al., 2001).

8.3.2 Experience over the follow-up period

Readmission to hospital for cardiac problems and recurrence of symptoms was explored in this sample of patients at 6 months follow up. These data were collected during the telephone interview and so are available from 70 patients. Of these, 9 patients (12.9%) were readmitted, and 22 patients (31.4%) had recurrent symptoms. 28 patients (40%) had one or both.

Table 8.2 below compares patients with CAD and no CAD, and Table 8.3 compares patients managed differently in the hospital following the result of the diagnostic coronary angiogram. These comparisons were made using repeated measures analysis of variance, with group as the between-person and time as the within-person variable.

The results of the analyses are interesting in that they highlight two main points. Firstly, there is no real change in psychological distress or quality of life over the 6 months. On average, people report the same problems on follow-up. There were no significant effects of time or group by time interactions for any variable. Reassurance about their condition or surgical intervention appears to make little difference to emotional or physical adaptation over the next 6 months. Secondly, there is no difference in response depending on whether or not people had diagnosed CAD. One might have expected the non-CAD group to do better perhaps, after they had been reassured that they did not have heart disease. However, these participants do not show

any greater improvement in distress, or any reduced risk of symptom recurrence. It may be that the numbers in the sample were too small to detect any significant differences in response. Alternatively, the follow up time may have been too short at six months. It would be beneficial to repeat the study at 12 months or at 5 years as in previous follow up studies on larger cohorts (Frasure-Smith et al., 1995; Lesperance et al., 2002).

Table 8.2 6 month changes in relation to CAD status

	Group	Baseline	6 months	p group by time effect
Depression	CAD	9.67 ± 6.5	8.28 ± 8.0	0.50
	No CAD	10.30 ± 8.6	9.76 ± 9.1	
Anxiety	CAD	5.7 ± 3.2	6.0 ± 3.5	0.09
	No CAD	8.8 ± 4.3	6.9 ± 4.3	
Physical health status (SF36)	CAD	62.4 ± 19.5	65.1 ± 21.8	0.85
	No CAD	64.4 ± 21.6	68.9 ± 21.6	
Mental health status (SF36)	CAD	66.8 ± 20.9	69.3 ± 21.4	0.97
	No CAD	68.2 ± 19.2	70.6 ± 18.3	
Readmission	CAD		6 (13.6%)	0.80
	No CAD		3 (11.5%)	
Symptom recurrence	CAD		15 (34.1%)	0.53
	No CAD		7 (26.9%)	
Readmission / recurrence	CAD		18 (40.9%)	0.84
	No CAD		10 (38.5%)	

As far as clinical management is concerned, it could be expected there would be some changes at 6 months follow up. It might be expected that there would be a difference in both the physical and emotional adaptation, between a patient who has undergone a prolonged hospital stay for a coronary artery by pass graft (CABG) operation versus a patient discharged on the same day with reassurance after a normal coronary angiogram. The differences relating to management are summed up in Table 8.3.

Table 8.3 6 month changes in relation to clinical management

	Group	Baseline	6 months	p group by time effect
Depression	PCI	8.4 ± 5.6	6.6 ± 3.8	0.9
	Medication	11.7 ± 8.3	10.4 ± 8.5	
	Reassurance	12.4 ± 11.8	11.4 ± 13.8	
Anxiety	PCI	5.2 ± 3.1	5.5 ± 3.1	0.4
	Medication	6.4 ± 3.0	6.3 ± 3.6	
	Reassurance	10.0 ± 3.4	8.8 ± 4.7	
Physical health status (SF36)	PCI	63.1 ± 20.1	68.5 ± 29.1	0.9
	Medication	58.3 ± 16.0	62.5 ± 18.3	
	Reassurance	66.2 ± 30.4	68.8 ± 29.1	
Mental health status (SF36)	PCI	69.8 ± 20.7	73.0 ± 20.1	0.9
	Medication	61.9 ± 19.0	65.3 ± 20.1	
	Reassurance	68.2 ± 19.1	68.8 ± 23.4	

	Group	Baseline	6 months	p group by time effect
Readmission	PCI		5 (18.5%)	0.16
	Medication		3 (11.1%)	
	Reassurance		0 (0%)	
Symptom recurrence	PCI		11 (40.7%)	0.13
	Medication		8 (29.6%)	
	Reassurance		1 (12.5%)	
Readmission / recurrence	PCI		13 (48.1%)	0.10
	Medication		11 (40.7%)	
	Reassurance		1 (12.9%)	

The results were disappointing. The only difference in repeated measures analysis of variance was in anxiety, where the main effect of group was significant ($p = 0.008$). This is not a trend over time, but a general difference between groups that was present at both time points. It shows that the reassurance group had higher anxiety than the others, and this persisted at 6 months. It may be that the more anxious or worried people interpreted innocuous symptoms as life threatening chest pain and despite the normal angiogram failed to be reassured due to fixed beliefs about their presumed ill health (Cheng et al., 2003). The finding of the group with no significant CAD having higher anxiety at both time points is not surprising. Several studies have found that anxiety, depression and bodily concerns e.g. chest pain correlate with global frequency or intensity ratings of angina (Young et al., 1980, Costa et al., 1985; Carney et al., 1992). Studies have shown that patients with a tendency to anxiety, depression, and general

neuroticism are more likely to complain of chest pains, convince the clinician to carry out angiography and this may explain why often, eventually no significant CAD is found (Carney et al., 1991).

Aside from this, there were no group or group by time interactions. It is, however, interesting that none of the patients that were managed by reassurance only were readmitted and only one patient in this group had any symptom recurrence. Unfortunately, the difference was not significant, due to small numbers. But presumably, this reflects the fact that clinicians were correct in their final diagnosis following angiography and appropriately gave this particular group of people reassurance in that they are at low risk for future problems.

8.3.3 Predictors of recurrence of symptoms and hospitalisation

The question investigated in this section here was whether factors measured at the time of the study predicted hospitalisation or the recurrence of symptoms over the 6 month follow up period. The analysis involved 3 stages:

a) testing the bivariate association (e.g. the association between beta blocker use and symptom recurrence)

b) testing the significant associations after controlling for age and gender

c) putting all the significant effects from stage b) into a multivariate analysis, to see whether they are independent of each other. The possible predictors included demographic and clinical factors, baseline quality of life and HRV measures. The findings are shown in Table 8.4.

Table 8.4 Predictors of symptom recurrence and readmission

Factor		N (%) or mean with recurrent symptoms	p	Odds ratio (O.R) adjusted for age and gender (95% C.I.)	p
Symptom recurrence					
Marital status	Married	9/42 (21.4%)	0.037*	1	
	Unmarried	13/28 (46.4%)		3.45 (1.05 – 11.3)	0.041*
Physical health status (SF36)	No symptoms	67.5 (18.9)	0.003*	1	
	Symptoms	52.3 (19.0)		0.97 (0.94 – 0.99)	0.016*
History of depression	No	15/58 (25.9%)	0.04*	1	
	Yes	7/12 (58.3%)		3.0 (0.77 – 12.02)	0.11
Beta blocker use	Yes	10/20 (50.0%)	0.05	1	
	No	12/50 (24.0%)		0.43 (0.14 – 1.38)	0.16
Readmission					
History of CAD	No	5/58 (8.6%)	0.04*	1	0.01*
	Yes	4/12 (33.3%)		12.9 (1.83 – 91.4)	
Physical health status	No admission	64.7 (19.7)	0.027*	1	0.071
	Readmission	49.0 (18.2)		0.97 (0.93 – 1.0)	
NN day mean	No admission	890.8 (119.2)	<0.001*	1	0.002*+
	Readmission	722.0 (88.6)		0.98 (0.97 – 0.99)	
NN night mean	No admission	1030.6 (142.7)	<0.001*	1	0.003*
	Readmission	825.2 (104.1)		10.99 (0.98 – 1.0)	
RMSSD day mean	No admission	23.6 (9.4)	0.005*	1	0.011*
	Readmission	13.8 (4.4)		0.78 (0.64 – 0.94)	
RMSSD night	No admission	31.4 (15.2)	0.04*	1	0.022*
Mean	Readmission	19.6 (6.3)		0.87 (0.77 – 0.98)	

+ Additional adjustment for beta blockade *Significant difference, $p < 0.05$.

Symptom recurrence: The results show that symptom recurrence at 6 months follow up was predicted by marital status and physical health status at baseline. Patients who were married and had good physical health status at baseline were less likely to have a

recurrence of symptoms after multivariate analysis. 40.9 % patients with recurrence of symptoms were married compared to 59.1% of those who were not married ($\chi^2 = 4.9$, p = 0.03). After regression analysis in which age and gender were included, marital status was found to be predictive of symptoms recurrence (Odds Ratio (O.R) 3.45; C.I 1.1 – 11.3; p = 0.04). This once more supports the findings of how social support in terms of having a spouse (Chandra et al., 1983; Coyne et al., 2001), or a close confidant (Dickens et al., 2004), is associated with a beneficial outcome post MI. In terms of physical health, those who experienced a recurrence of symptoms scored significantly lower on the SF36 combined physical health status at baseline, with a mean of 52.3 ± 19.0 SD in this group versus 67.5 ± 19.0 SD in the group who were symptom free at 6 months (p = 0.003). Symptom recurrence was also more common in patients who were not taking beta blockers and had a history of depression, but these effects were not significant once age and gender were taken into account. In the multivariate analysis, the only factor that remained significant after adjustment for age and gender, marital status, history of depression and beta blocker medication, was the SF36 physical health status measure (O.R 0.96, C.I 0.93 – 0.995; p = 0.03).

Readmission: Readmission was associated with a prior history of CAD (previous cardiac events or treatment), with physical health status on the SF36 (though not after adjustment for age and gender), and most interestingly with significantly higher heart rates. The mean normal to normal (NN) interval was significantly shorter both in the day and at night in patients who were readmitted, and these effects remained significant after adjustment for age, gender and beta blockade. In addition patients who were readmitted at 6 months were more likely to show a significantly reduced HRV (RMSSD) both in the day and at night.

The findings from the SIS study, in which reduced HRV and higher HR predicted readmission for further cardiac events (after adjustment for relevant covariates), supports earlier findings relating reduced HRV and long term cardiac mortality in cardiac patients (Carney et al., 1995; Stein et al., 1999). One potential reason for readmission may be that the higher HR and the reduction in HRV correlated with an increased sympathetic or decreased vagal input, which may predispose the patient to cardiac arrhythmias or ischaemia necessitating hospital readmission.

8.3.4 Predictors of quality of life and emotional state at 6 months

The measures used in these analyses are the physical health status measure from the SF36, BDI depression and HAD anxiety. For these measures, we have the baseline assessment as well, so the question is what other factors predict 6 month levels independently of baseline levels.

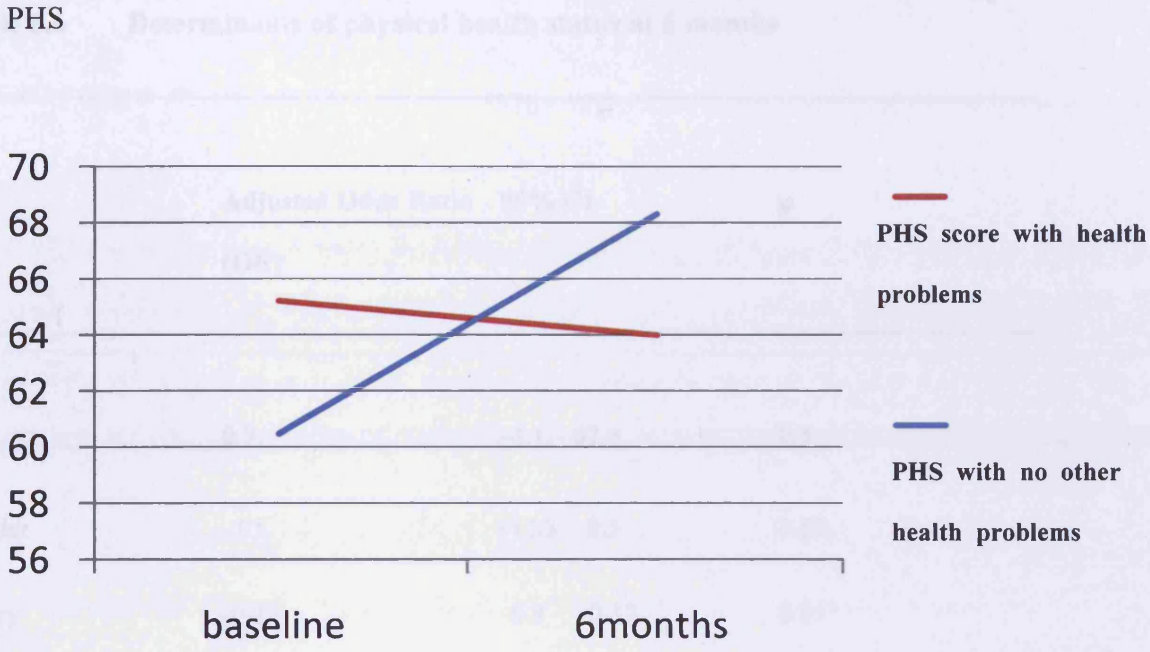
Physical health status (SF36): Changes in physical health were not predicted by any of the demographic variables. There was however, a significant interaction between time and the presence of non-cardiovascular health problems ($p = 0.02$). The results are shown in Table 8.5 and Figure 8.1. These illustrate that people with non-cardiac health problems did not show any improvement in physical health status over the follow-up period, while those with no other health problems did show an improvement. This effect remained significant in linear regression on 6 month physical health status scores, with age, gender and baseline score as covariates ($p = 0.049$). It would be expected that other co-morbidities such as obesity, osteoarthritis would affect the patient's physical health status regardless of cardiac function.

Table 8.5 Change of physical health status at 6 months

	Other current health problems	Mean	SD	p
Physical health status BASELINE	Yes	65.2	21.9	0.02*
	No	60.5	18.6	
Physical health status 6 months	Yes	64.0	23.0	
	No	68.3	20.4	

*Significant difference, $p < 0.05$.

Figure 8.1 Change in PHS score over 6 months in relation to other current health problems



6 months physical health status was also predicted by worry as assessed with the DRM (see Table 8.6). Patients who reported more worry during the sampling day had worse physical health status at 6 months, and this was independent of baseline physical health status, age, gender, CAD status, and readmission and recurrence in the multivariate analysis ($t = -2.21$; $p = 0.032$). This has not been shown before, and so the DRM appears to be providing unique data.

6 month physical health status was also predicted by the cortisol slope over the day. Participants with a steeper cortisol slope showed significantly greater improvements in physical health status ($t = 2.75$; $p = 0.009$) independently of baseline physical health status, age, gender, CAD status, BMI, smoking, symptom recurrence, and

readmission (Table 8.6). Variation in cortisol rhythms has been observed in some disease states and may be related to health outcomes.

Table 8.6 Determinants of physical health status at 6 months

	Adjusted Odds Ratio (OR)	95% CI	p
Age	0.7	-4.1 – 62.6	0.5
Gender	-.05	-12.3 – 8.5	0.62
Worry	-0.22	-8.8 – -0.37	0.03*
Readmission at 6 months	-0.11	-20.3 – 6.3	0.3
Recurrence of symptoms	-.03	-11.2 – 8.7	0.8
Physical health status at baseline	0.55	0.3 – 0.84	<0.01*
Cortisol slope	0.3	1.0 – 0.4	0.09*

*Significant difference, $p < 0.05$.

Depression: Changes in depression were not predicted by any demographic variables. A history of depressive illness was predictive, but perhaps not in the way that might have been expected. People with a history of depression had higher BDI scores at baseline,

coming down at 6 months. So history of depressive illness predicted improvement in BDI score rather than deterioration. A reason for the improved BDI score at 6 months may be because 85.3% of the sample of patients who had medication or a surgical intervention was reassured by the definite diagnosis and corrective treatment procedure. Alternatively, the remaining 14.7% of patients who had normal coronary angiograms were appropriately reassured of their disease free state in the follow up period which may account for the improved BDI level at 6 months. There was no relationship with the DRM after baseline depression was taken into account. Neither were there any significant relationships seen between changes in depression and the HRV indices, which is surprising given that much of the existing literature described a strong association between depression and altered autonomic control (Carney et al., 2000).

Anxiety: Changes in anxiety were not predicted by any of the demographic variables and nor by any of the clinical or treatment variables. There were no significant relationships seen between changes in anxiety and the HRV indices. A reason for the lack of finding of an association between with anxiety and depression with any of the HRV indices may be due to the fact that these patients had not undergone a full blown cardiac event with subsequent damage to the myocardium and consequent electrical instability and altered HRV. A reason for the lack of finding of an association between with anxiety and depression with changes in physical health status, is again possibly due to the fact these patients had not had a full MI, or cardiac complications, with the attendant emotional aftermath of a significant cardiac event and reduced patient confidence in terms of physical capabilities. In addition, the sample size may have been too small to detect any differences in any of the variables tested. The BDI and HAD anxiety scales may not have been sensitive enough to detect mood changes in this population over a 6 month period.

To summarise this section, the key findings were that physical health status at 6 months was predicted by worry ($p = 0.032$), physical health status at baseline ($p = <0.01$) and cortisol slope over the day ($p = 0.009$), after adjustments for potential confounders.

8.4 Discussion of results

This section shall discuss the results relating mainly to the findings of the predictors of the clinical factors; namely symptom recurrence in patients and readmission in patients at 6 months, as well as discuss the findings pertinent to the predictors of quality of life and emotional state at 6 months.

The predictors of recurrence of symptoms and hospitalisation were physical health status measure and heart rate and HRV respectively after adjustments were made for confounders in multivariate analysis. With regards to symptom recurrence, in multivariate analysis physical health status measure was the only predictive factor after adjustment for age, gender, marital status, history of depression and beta blockers. This could be due to the fact that those with poorer physical health status had more severe cardiac disease inadequately treated either with medication or interventional procedure and thus experienced more clinical symptoms at 6 months. This supports the finding that physical functioning has been shown to be affected the most in post MI patients at 3 months (Failde et al., 2006) and 12 months (Van Jaarsveld et al,. 2001; Mendes de Leon et al., 1998).

With regards to readmission, reduced HRV and higher HR, but none of the socio-demographic variables or psychological factors, predicted readmission. Other studies that have examined cardiac patients have shown altered HRV to be related to cardiac

events. Reduction of HRV and higher heart rates have been shown to be a predictor of cardiac events in a wide spectrum of patients, ranging from post MI (Kleiger et al., 1987; Bigger et al., 1992) to unstable angina patients (Lanza et al., 2006) to those additionally with stable heart disease (Van Boven et al., 1998). In a large prospective multicentre trial study by Lanza et al. (2006), 543 patients with unstable angina and preserved left ventricular function (LVF), underwent 24 hour ECG holter monitoring within 24 hours of hospital admission. Amongst the tested variables were the time domain and frequency domain HRV variables. Primary end points were in hospital and six-month total and cardiac deaths. Results suggested that a low HRV, as detected on holter monitoring started within 24 hours after admission for unstable angina, are predictors of in-hospital and medium-term mortality in patients with unstable angina and preserved LV function. In our study, several of the HRV indices (NN, NNSD, LF, and LF/HF ratio) were significantly associated with readmission at six months. The association between a reduced HRV in several of the indices and higher heart rates in post MI patients have been further supported in a variety of other studies. Kleiger et al. (1987), followed up 808 post MI patients and found a relative risk of mortality being 5.3 times higher in the reduced HRV group even after adjusting for clinical, demographic factors and ejection fraction (EF). Bigger et al. (1992) followed up 715 patients post MI for four years and found that after adjustment for age, New York Heart Association functional class and EF the association between mortality and total power, ULF, and VLF remained significantly strong and LF and HF remained only moderately strongly associated with mortality.

Of the quality of life measures, physical health status at 6 months was predicted by those who had other current health problems and worry as measured by the DRM. People who are more worried or anxious over the DRM day may have a tendency to be excessively fearful or cautious about resumption of physical activity or an increase of physical activity following a new diagnosis of cardiac disease (Day et al., 2005; Petrie et

al., 1998). This particular illness belief may partly explain the body of literature, which shows how anxiety has a unique contribution in predicting cardiac mortality and morbidity (Shen et al., 2008; Strik et al., 2003). Furze et al. (2005) carried out a prospective follow-up study over 1 year, of 133 people with angina, and found that patients with more misconceived or maladaptive beliefs were more anxious or worried and physically limited than were people with fewer such beliefs, with significant differences in physical functioning. It was a change in angina beliefs more so than actual change in angina frequency over 1 year that was the most significant predictor for physical functioning at follow-up, after controlling for the effects of demographic variables and the outcome variable at baseline. The DRM could be applied to such patients so that moods are easily and quickly identified using a relatively efficient method and could be potentially corrected by cognitive behavioural therapy within the context of a cardiac rehabilitation programme.

There were no significant associations with any of the HRV indices in the analysis of predictors of emotional adaptation and physical health at 6 months. This finding is a contradiction to a significant number of studies linking depression and other emotions to altered autonomic control (Carney et al., 2000, 2001; Kim et al., 2005, Kawachi et al., 1995, McCraty et al., 1995, Sloan et al., 1994; Rechlin et al., 1994). HRV would be expected to predict greater physical health status given that amounts of RR variability and slower fluctuations are significantly associated with physical activity (Bernardi et al., 1996). Exercise is known to benefit cardiac health by improving autonomic control. In the study by Rosenwinkel et al. (2001) exercise training has been shown to be associated with a relative enhancement of vagal tone, improved heart rate recovery after exercise, and reduced morbidity in patients with cardiovascular disease.

A possible explanation for discrepancies between this study and established literature findings is that many of the studies in the existing literature focused on patients who already had a full blown coronary event and not simply just angina symptoms or accompanying positive cardiac investigations only.

Finally, 6 month physical health status was predicted by cortisol slope over the day. Studies have related cortisol slope to physical activity in healthy adults. Ice et al. (2005) carried out a study which examined factors associated with cortisol level and slope in healthy older adults. Forty-eight older adults (mean age 76.4 ± 5.8 SD years) were interviewed regarding health, stress, affect, and social networks. Participants collected saliva over a three day period while keeping a record of their emotions and activities. In multivariate models, affect was no longer significantly associated with cortisol as in univariate models, and amongst other factors, age ($p < 0.001$), physical activity ($p = 0.017$), and hours slept ($p < 0.001$) predicted cortisol slope. There is less established in the current literature relating cortisol slope as a predictor of physical health status in cardiac patients.

To conclude, to address the questions asked at the beginning of the chapter, it appears that psychological distress (anxiety and depression) changes little over the 6 months following investigation and hospital management. There were no changes in emotional distress of the participants associated with the actual diagnosis (definite CAD or not). However, there were differences found relating to method of management (PCI, reassurance only, or medical management). As expected, none of the patients who were reassured were readmitted although, interestingly, it was this group that showed significantly higher anxiety scores than the others and this effect persisted at 6 months follow up.

HR, HRV, cortisol slope and mood measures were amongst the factors assessed at time 1 (i.e. baseline) that predicted clinical outcomes (in terms of readmission and recurrence of symptoms), psychological distress, and quality of life, (physical health status) at 6 months.

Clinically, symptom recurrence at 6 months was more likely to be seen in those who were unmarried and in those with poorer physical health status on the SF36 measurements, while readmission at 6 months was associated with a reduced HRV and a higher heart rate.

Of the quality of life measures, impaired physical health status at 6 months was predicted by physical health at baseline, worry as measured by the DRM, and patients who had a steeper cortisol slope. Interestingly there was a lack of association between the psychological measures of anxiety and depression over the 6 months and any of the HRV variables.

Chapter 9: Long term adaptation to CAD

9.1 General overview

This chapter and chapter 10 describes two sets of findings from the ACCENT (Acute Coronary Syndrome, Emotion and Trigger) study which focuses on psychosocial factors influencing adaptation to established CAD. The ACCENT study involved 295 ACS patients admitted to four London hospitals, recruited between 2001 – 2004 on the basis of standard symptomatic, electrocardiograph and biochemical (troponin T) criteria. Patients were excluded if they had co-morbid conditions that might influence mood, neuroendocrine function or cardiac enzymes. They underwent a structured interview on an average of 2.56 days after admission, in which exposure to possible triggers (physical exertion, smoking, sexual activity, cocaine, marijuana, anger, stress and depression) were assessed in the two hours prior to symptom onset, and in various control periods. The new statistical technique of case-crossover analysis developed for studying transient acute exposures was used.

Findings from the ACCENT study, concerning triggering of ACS, have been described in section Chapter 1.2. Briefly, some of the results from the data set in the study suggested that the relative risk of ACS onset is raised after physical exertion or anger in the hours before symptom onset compared with no physical activity or no anger respectively (Steptoe et al., 2006). The effects of triggering have been observed not only in acute MI but other types of ACS (Strike & Steptoe, 2005). Also observed was that episodes of acute depression are associated with increased risk (Steptoe et al., 2006). The relative risk of ACS after moderate or severe depression in the two hours before symptom onset compared with no depression was 4.94 (C.I. 3.03 to 7.57). This result is

interesting in light of the evidence that depression is a risk factor for the long term development of CAD (Hemingway and Marmot, 1999), and that depression post MI is associated with increased morbidity and mortality (Van Melle, 2004).

The causal sequence linking acute depression with ACS onset is uncertain. Depression may increase risk of plaque disruption and subsequent thrombosis, but alternatively, negative mood may be because of inflammation.

Depression after an acute cardiac event may impair the rehabilitation processes post MI, and reduce the likelihood of returning to work (Soderman et al., 2003), which is a functional marker of adaptation. Depression also impairs physical and emotional adaptation to ACS in the long term leading to an overall reduced quality of life (Beck et al., 2001; Welin et al., 2000; Wiklund et al., 1989).

The SIS study (described in chapters 4-8) was carried out on patients with suspected cardiac disease who had not yet had a cardiac event like an MI or ACS. In contrast to the ACCENT study, psychosocial factors were examined that may influence or trigger cardiac ischaemia during everyday life hassles and strains, which may eventually over a period of time, lead to ACS in the long term via psychobiological processes. Other than the investigation of acute triggering just prior to an MI, the ACCENT study described in this chapter also allowed investigation of psychosocial factors affecting the long term adaptation to ACS. Patients were followed up both at one year and three years by both telephone interview and self-report questionnaire, to examine the influence of depression and other psychosocial factors on their long term clinical and psychological adaptation to the ACS event.

Whilst one set of findings from the ACCENT data set relate to aetiology of possible triggers of ACS (which is not presented here), here I present analyses that relate to prognosis *after* the ACS event, in particular, emotional and physical adaptation in the

recovery phase after hospitalisation, and to see if any of these factors are associated with the initial trigger of the event. This may elucidate the casual direction of the linking pathway between depression and CAD, i e. does depression lead to physiological changes and behavioural changes to cause an increased risk of coronary events, or is the converse a possibility, i.e. does the acute coronary event itself lead to changes that cause depression and other emotional and physical symptomatology?

These analyses of the ACCENT study were carried out to answer two questions:

Firstly, what are the clinical and psychological factors that may determine return to work in these patients? It has been recently described in the literature that a proportion of ACS patients develop difficulties in long term adaptation in psychosocial functioning, with regards to return to work, specifically at 1 year post ACS. We evaluated the prevalence of return to work at one year in this set of patients and investigated what the clinical and psychosocial predictors of return to work were, as an indicator of adaptation to ACS in the long term.

Secondly, can triggers of acute cardiac events predict the type of adaptation made by the patient in the long term? I have analysed how emotional and physical factors associated with the acute triggering of an ACS may relate to emotional and physical adaptation in the long term at one year and three year follow up, and specifically, whether the particular type of trigger (emotional or physical) could differentially predict the emotional and physical adaptation at three years.

Chapter 9 will begin with a description of the method of the ACCENT study followed by the results and conclusion from the one year follow up regarding return to work. Chapter 10 will describe the results and conclusion from both the one year and three year follow up regarding adaptation and quality of life after ACS.

9.2 Psychological and clinical predictors of return to work after acute coronary syndrome

9.2.1 Introduction

It has been estimated that some 90 million working days are lost annually within the European Union because of CAD morbidity (Leal et al., 2006). Returning to work after acute coronary events not only has economic benefits to the individual and community, but improves morale and the quality of life of patients and their families.

It is well established that returning to work is not a simple function of clinical status, but is influenced by demographic, social and psychological factors. Patients' perceptions of their illness and disability appear to be important predictors (Petrie et al., 1996; Mittag et al., 2001). Emotional responses such as depressed mood may also be significant, although results have been inconsistent (Petrie et al., 1996; Mittag et al., 2001 ; Mayou, 1984). Much of the data relating psychological factors with return to work was collected in the 1970's and 1980's, when clinical management of acute coronary syndrome (ACS) was very different to the present day (Mayou, 1984; Cay et al., 1973; Maeland et al., 1987; Stern et al., 1977). Developments in the management of ACS including thrombolysis, revascularisation and early mobilisation have dramatically changed patients' experience and expectations (Bertrand et al., 2002; Ryan et al., 1999), and it is not clear whether early emotional responses to ACS continue to be related to re-employment in the modern era.

This analysis investigated predictors of failure to return to work, and specifically the role of the emotional responses such as depressed mood that are the focus of my thesis. The findings have recently been published (Bhattacharyya et al., 2007).

9.2.2 Methods

Patients

The participants in this study were the 155 patients who were in paid employment at the time of ACS, out of a total of 295 patients admitted to four hospitals in the London area between 2001 and 2004, and recruited as part of an investigation of emotional and behavioural triggers of cardiac events (ACCENT study; Strike et al., 2006). They were selected on the following criteria: a diagnosis of ACS based on the presence of chest pain with verification by diagnostic electrocardiographic (ECG) changes (new ST elevation >0.2mV in 2 contiguous leads V1,V2,V3 and >0.1mV in 2 contiguous other leads, ST depression >0.1mV in 2 contiguous leads in the absence of QRS confounders, new left bundle branch block or dynamic T wave inversion in more than one lead) and / or cardiac enzyme changes (troponin T measurement >0.01 ug/l or a creatine kinase measurement more than twice the upper range of normal for the measuring laboratory). Patients were aged from 18-90 years, were able to recall the time of onset of symptoms, and did not to have co-morbid conditions that might influence either symptom presentation, mood or troponin positivity (Ammann et al., 2004). Patients were excluded if they had severe psychiatric illness or cognitive decline impairing ability to complete measures, and if they could not speak English. The study was approved by the medical research ethics committees of University College Hospital, St George's Hospital, Southend Hospital and Kingston Hospital, and all patients gave written consent.

Measures

Admission notes and ECG's were assessed by a cardiologist and scrutinized for presentation as ST elevation myocardial infarction (STEMI), non-ST elevation myocardial infarction (NSTEMI), or unstable angina (UA). The troponin T (86% of cases) and creatine kinase (79% of cases) levels measured during the admission and the

presence of arrhythmia and heart failure were recorded. We computed composite risk scores based on the algorithm developed in the Global Registry of Acute Coronary Events (GRACE) study (Beck et al., 1988). This uses nine measures (age, history of congestive heart failure, history of MI, systolic blood pressure and heart rate on admission, ST segment depression on ECG, initial serum creatinine, elevated cardiac enzymes and no in-hospital percutaneous coronary intervention) to define risk of 6-month post discharge death applicable to all types of ACS. Information was obtained from medical notes about cardiovascular disease history and medication pre-admission, and about the management of the ACS. Management strategies were classified as medical, percutaneous coronary intervention (PCI), or coronary artery bypass graft (CABG). Smoking, alcohol consumption, and physical activity were assessed using standard measures (Strike et al., 2006).

Patients were given a set of questionnaires while in hospital, and this was completed 7-10 days post-admission. Depressive symptoms were assessed using the Beck Depression Inventory, (Beck et al., 1988) a 21-item measure that has been widely used for the assessment of symptoms in cardiac patients. Each item is rated from 0-3, so total scores can range from 0-63, with higher values indicating greater depression. The internal consistency (Cronbach α) in this study was 0.88.

Socio-economic status (SES) was defined by two measures: educational attainment and a social deprivation index. The latter assessed access to resources based on four criteria: living in a crowded household (defined as one or more persons per room), renting as opposed to owning a home, not having use of a motor vehicle (car or van), and living on state benefits. Patients were classified as a low deprivation (negative on all items), medium deprivation (1 positive), and high deprivation (2 - 4 positive). Previous history of depression was measured as the use of antidepressant medication at

the time of hospital admission, and by asking patients to estimate whether they had been moderately or severely depressed at any time over the past 6 months.

Information concerning return to work was obtained during a telephone interview with each patient, carried out 12-13 months post-discharge. Patients were asked if they had started work again, and whether they were working full-time or part-time. Information about attendance at rehabilitation was also obtained during these interviews, and the recurrence of cardiac disease (defined as a further ACS requiring hospital admission and treatment, or recurrence of chest pain leading to revascularisation) was recorded. I was not involved in the recruitment of the original sample. However, I carried out most of the 12 month follow-up assessments, and a proportion of the 36 month assessments.

Statistical analysis

Twelve month data were obtained from 126 (81.2%) of patients. The patients included in this analysis did not differ from those who were lost to follow-up in age, gender, ethnicity, marital status, educational attainment, smoking, body mass index (BMI), alcohol consumption, physical activity, type of ACS, previous cardiovascular history, or BDI. However, patients lost to follow-up tended to be more socially deprived ($p = 0.01$) and had lower GRACE risk scores ($p = 0.042$) than those included in the study. Patients who did and did not return to work by 12 months were compared on socio-demographic, clinical and psychological factors using χ^2 statistics for categorical variables and analysis of variance for continuous measures. All tests were two sided. The factors that were significantly associated with return to work in univariate analysis were entered into a multiple logistic regression. Odds ratios (O.R) adjusted for all other factors are presented together with 95% confidence intervals (C.I.).

9.2.3 Results

One hundred and one (80.2%) patients were working at 12 months following ACS, of whom 64 (63.4%) were working full-time, and 37 (36.6%) part-time. The interval between ACS and restarting work averaged 3.4 months, ranging from less than one month to 11 months. Patients who did and did not return to work did not differ in gender distribution, age, ethnicity, educational qualifications, social deprivation scores, or marital status (Table 9.1). There were also no associations with lifestyle factors such as smoking, BMI, and alcohol consumption, but patients who were physically inactive prior to ACS were less likely to return to work.

Table 9.1 Characteristics of patients working and not working at 12 months

		Working (n = 101)	**Not working (n = 25)**	**p**
Gender	Men	89 (88.1%)	22 (88.0%)	0.98
	Women	12 (11.9%)	3 (12.0%)	
Age (years)		54.5 ± 8.2	55.9 ± 9.8	0.47
Ethnicity	White	87 (86.9%)	20 (80.0%)	0.44
	Other	14 (13.1%)	5 (20.0%)	
Educational qualifications	None	37 (36.6%)	12 (48.0%)	0.49
	Primary	24 (23.8%)	6 (24.0%)	
	Secondary	40 (39.6%)	7 (28.0%)	

		Working (n = 101)	Not working (n = 25)	p
Social deprivation	Low	57 (56.4%)	10 (40.0%)	0.13
	Medium	26 (25.7%)	8 (32.0%)	
	High	18 (17.5%)	7 (28.0%)	
Marital status	Married	75 (75.3%)	17 (68.0%)	0.53
	Not married	26 (25.7%)	8 (32.0%)	
Smoking status	Current	47 (46.5%)	16 (64.0%)	0.18
	Ex/non-smoker	54 (53.5%)	9 (36.0%)	
Body mass index	(kg/m^2)	27.5 ± 4.3	27.9 ± 4.5	0.65
Physical activity	None	53 (53.0%)	18 (72.0%)	0.055
	Low	29 (29.0%)	2 (8.0%)	
	≥ 2 times/week	18 (18.0%)	5 (20.0%)	
Alcohol (units/week)		12.0 ± 15.9	11.2 ± 14.3	0.83

The clinical features of patients who were working and not working after 12 months are summarised in Table 9.2. Returning to work was unrelated to the type of ACS, number of vessels diseased, and previous myocardial infarction. Patients with low GRACE risk scores were more likely to return to work. Fewer patients who were working at 12 months had experienced arrhythmia (4 *vs* 24%) or heart failure (5 *vs* 16%)

on admission than those who failed to resume work. There was no association with whether the ACS was managed medically, or with percutaneous coronary intervention (PCI), or coronary by pass graft intervention (CABG). Patients who experienced recurrence of cardiovascular problems leading to readmission or revascularisation, were less likely than others to be working at 12 months. There were no associations with risk factors or medication before admission, or with attendance at cardiac rehabilitation.

Self-reports of moderate to severe symptoms of depression over the 6 months before admission, were not related to the likelihood that patients would be working at 12 months (Table 9.2). Eight patients were taking antidepressant medication at the time of admission; half of these patients were not working at 12 months, compared with 82.2% of those who were not taking antidepressants. Additionally, BDI scores measured 7-10 days post-admission were 36% lower in patients who returned to work compared with those who were not working ($p = 0.018$). The timing of return to work, and whether patients resumed full, or lighter, part-time duties were not predicted by psychological state or clinical factors at the time of admission.

Table 9.2 Clinical features of patients working and not working at 12 months

		Working (n = 101)	**Not working (n = 25)**	**p**
ACS type	STEMI	66 (65.3%)	18 (72.0%)	0.53
	NSTEMI / UA	35 (34.7%)	7 (28.0%)	
N vessels diseased		1.71 ± 0.79	1.76 ± 0.88	0.78
Previous ACS	Yes	7 (6.9%)		0.85
	No	94 (93.1%)	2 (8.0%)	
			23 (92.0%)	
GRACE risk score		81.8 ± 20.1	90.0 ± 21.0	0.072

		Working (n = 101)	Not working (n = 25)	p
Heart failure	Yes	5 (5.0%)	4 (16.0%)	0.055
	No	96 (95.0%)	21 (84.0%)	
Arrhythmia on admission	Yes	4 (4.0%)	6 (24.0%)	0.004*
	No	97 (96.0%)	19 (76.0%)	
Clinical management	Medical	24 (24.7%)	6 (24.0%)	0.50
	PCI	59 (60.8%)	13 (52.0%)	
	CABG	14 (14.4%)	6 (24.0%)	
Recurrence (readmission, revascularisation)	Yes	34 (33.7%)	14 (58.3%)	0.026*
	No	67 (66.3%)	10 (41.7%)	
Attendance at cardiac rehabilitation	Yes	72 (71.3%)	20 (87.0%)	0.12
	No	29 (28.7%)	3 (13.0%)	
Diabetes pre-admission	Yes	9 (8.9%)	3 (12.0%)	0.64
	No	92 (91.1%)	22 (88.0%)	
Hypertension pre-admission	Yes	36 (35.6%)	11 (44.0%)	0.44
	No	65 (64.4%)	14 (56.0%)	
Statin use pre-admission	Yes	9 (8.9%)	1 (4.0%)	0.42
	No	92 (91.1%)	24 (96.0%)	
Moderate/severe depression (6 months)	Yes	28 (27.7%)	10 (40.0%)	0.23
	No	73 (72.3%)	15 (60.0%)	
Antidepressant use pre-admission	Yes	4 (4.0%)	4 (16.0%)	0.027*
	No	97 (96.0%)	21 (84.0%)	

*Significant difference, $p < 0.05$.

The multiple regression analysis of predictors of return to work at 12 months is summarised in Table 9.3. The factors that emerged as independent predictors were arrhythmia during admission, recurrent cardiac events, and BDI score following

admission. Thus patients who experienced arrhythmia (p = 0.030) and recurrent cardiac events (p = 0.025) were substantially less likely than others to be working 12 months after ACS. The BDI effect indicates that for every unit increase in BDI depression score following admission, there was a 10% reduction in the likelihood of returning to work by 12 months (p = 0.032).

Table 9.3 Determinants of return to work 12 months after an ACS

	Adjusted odds ratio	95% C.I.	p
Age	0.91	(0.31 to 2.66)	0.87
Gender (M/F)	1.77	(0.19 to 16.0)	0.63
GRACE score	0.98	(0.93 to 1.03)	0.38
Arrhythmia	0.09	(0.01 to 0.79)	0.030*
Heart failure	1.19	(0.12 to 11.4)	0.88
Recurrence	0.25	(0.01 to 0.84)	0.025*
Antidepressant use pre-admission	0.62	(0.01 to 28.7)	0.81
BDI following admission	0.90	(0.82 to 0.99)	0.032*

*Significant difference, p < 0.05.

9.3 Discussion

A total of 80% of patients in this study had resumed work 12 months after admission for an ACS. This is comparable with the rates of 78-83% recorded in other recent studies (Soejima et al., 1999; Soderman et al., 2003; Boudrez & de Backer, 2000). Return to work was predicted by clinical factors on admission, by cardiovascular complications during the intervening 12 months, and by depressive symptoms measured in the days following admission. Demographic factors, preadmission risk profile, attendance at rehabilitation were not predictive.

This study showed that clinical markers of ACS severity were predictors of subsequent return to work. The significance of clinical indicators has been limited in past studies, with few associations being observed (Petrie et al., 1996; Soejima et al., 1999; Soderman et al., 2003). Neither ACS type, elevated cardiac enzymes, nor number of diseased vessels predicted resumption of work in the present study. However, in univariate analyses, patients who resumed work were less likely to have experienced cardiac arrhythmia in hospital, with near significant effect for heart failure and the GRACE index. The GRACE index has been found to predict mortality in the 6 months following ACS (Eagle et al., 2002), a result that has been independently replicated (Hamalainen et al., 2004). Interestingly, the method of management of ACS was also unrelated to work resumption, with similar rates among patients treated medically or with PCI and CABG. This endorses the view that when used appropriately, surgical and interventional procedures have favourable effects on long term adaptation and recovery.

We observed a robust association between depressed mood during hospitalisation for ACS and return to work 12 months later. The effect was independent of demographic and clinical markers, and of depression prior to ACS (Table 9.3). These

results add to the evidence for adverse effects of depressive responses to ACS. Other early phase psychological factors are also important predictors, including patients' understanding of their illness (cognitive representation), (Petrie et al., 1996) and physicians' and patients' expectations of disability.

Work resumption was not predicted by age, gender or SES, in contrast with studies in the 1970's and 1980's (Mital et al., 2004). These differences may relate to changes in social expectations and in working practices. During periods of relatively high unemployment (as were present 20 years ago), competition for jobs is great, so lower SES patients with limited skills may be disadvantaged. The physical exertion required in lower SES occupations has also diminished markedly over recent decades because of mechanisation, so returning to work is not prevented by physical incapacity. In the past, it may also have been more acceptable for women, especially if married, to not return to paid employment (Mital et al., 2004). We found that patients with higher social deprivation scores were more likely to be lost to follow-up. It is conceivable that this biased the findings relating return to work with SES. However, patients who were lost to follow-up also had lower GRACE scores than those studied at 12 months. This suggests that lower SES patients with mild ACS were particularly at risk of withdrawing from the study. The reason is probably that these individuals had resumed work and were not available for interview. The 12 month telephone interviews were mostly carried out on weekdays during the working day and evening, and these individuals may not have been at home during these times. Their exclusion is likely to have reduced rather than increased the proportion of lower SES patients who had restarted work, so will not have biased results against finding an association between lower SES and failing to return to work.

The absence of a relationship between return to work and attending cardiac rehabilitation is intriguing. The rehabilitation classes offered to patients varied by hospital, so no standard schedule was involved. Previous studies have found that attendance at rehabilitation does not predict return to work unless the programme is specifically focused on resumption of work and related activities (Soderman et al., 2003).

9.4 Strengths and limitations

The strengths of this study include its prospective design of a cohort of patients hospitalised for ACS, the inclusion of different types of ACS which is more appropriate to the current era of medicine as up-to-date categorisation have been used and characterisation of patients in terms of multivariate clinical risk. The BDI scale was used to assess depressive symptoms, which is a well established validated scale, used in previous studies on cardiac patients (Buchanan et al., 1993; Frasure-Smith et al., 1997).

This study also has a number of limitations. Data were not collected from a consecutive series of ACS admissions, since patients were excluded if they were not able to recall the time of onset of symptoms, and if they had co-morbid conditions that might influence symptom presentation or mood. The reason is that the analysis was carried out in the context of a larger study of emotional and behavioural triggers of ACS (Strike et al., 2006). Consequently, the study included a higher proportion of STEMI than NSTEMI/UA and a greater number of men than women compared with recent cohorts (Eagle et al., 2002; Hasdai et al., 2002). We did not assess clinical depression, since our concern was with depressed mood, and this was assessed by questionnaire. However, there is evidence that even moderate depressed mood in cardiac patients is associated

with adverse outcomes (Jiang et al., 2003). The response rate was good (81.2%), but the loss of 18.8% might have influenced the pattern of results. The information we collected on type of occupation was not sufficiently detailed for analysis, but is known to relate to return to work (Gehring et al., 1988). The associations we observed with clinical and psychological factors all concerned return to work, rather than timing of return or whether patients resumed full or part-time work; larger samples may be required to investigate these aspects fully. Additionally, unmeasured factors may have acted as confounds of the association between depressed mood and failure to return to work. Finally, assessment of return to work was based on self-report. Although it is unlikely that patients would report they were in paid employment when they were not (and vice versa), their recollection of the timing of return to work may have not been completely accurate. This may be one reason why depression soon after hospitalisation did not predict the timing of resumption of work.

Chapter 10: The long term effects of acute triggers of ACS on adaptation and quality of life

10.1 Introduction

The purpose of this analysis was to discover whether the experience of acute physical and emotional triggers predicts long term adaptation independently of clinical and socio-demographic factors. The literature on acute triggers has been focused almost exclusively, on whether they stimulate the onset of ACS, and on the underlying biological mechanisms. The possibility that the experience of an acute emotional or physical trigger might have long term effects on adaptation has not been addressed. We therefore followed up the cohort of the ACS patients in the ACCENT study previously described in section 9.2.2, in which acute triggering by physical exertion and emotional factors had previously been assessed (Strike et al., 2006), and predicted that patients who had experienced triggers would show impaired quality of life 12 and 36 months later, compared with patients without triggers. Emotional responses such as anxiety and depression in the days following ACS are known to influence later quality of life, the likelihood of returning to work, and emotional well-being (Bhattacharyya & Steptoe, 2007; Lane et al., 2001; Mayou et al., 2000). Anxiety in hospital was therefore taken into account in the analysis.

Additionally, we hypothesised that emotional and physical triggers might have different associations with long term outcomes. We reasoned that physical exertion during the hazard period could lead to nervousness about physical activity, leading to physical de-conditioning, impaired vitality and fatigue. Emotional triggers could elicit preoccupation with negative emotional experiences, and be associated with impaired

long term mental well-being. We therefore tested for differential prediction of mental and physical quality of life from emotional and physical exertion triggers.

10.2 Methods

Patients

The patients were 295 men and women aged 18-90 years admitted with ACS to one of four hospitals in the London area. (ACCENT study; Strike et al., 2006). Patients were included in the study on the same criteria as the one year follow up study described in section 9.2.2. Symptom onset occurred while sleeping in 38 patients, so 257 patients provided information about triggering of ACS.

Measures

Information about cardiovascular history, psychiatric history, clinical factors during admission and management was obtained from medical notes as described in section 9.2.2.

Procedure and assessment of triggers

Patients were invited to take part as soon as possible after admission to hospital. The study was explained verbally and a patient information sheet was provided, and written consent was obtained. A total of 375 patients were potentially eligible for the study; of these, 48 patients (12.8%) were discharged or transferred to other hospitals before the interview could take place, and further 32 patients (8.5%) refused. The interviews were carried out an average 2.56 ± 1.5 days after admission, with 95% being completed within 5 days of admission.

The structured triggering interview was based on the procedures used in the Onset and SHEEP studies (Mittleman et al., 1995; Moller et al., 1999; Mittleman et al., 1993). Patients were asked in detail, about the circumstances surrounding the onset of acute symptoms. Vigorous physical exertion was defined as activity of at least 6 metabolic equivalents (METS), as used in earlier studies. In the light of this literature, we specifically focused on physical exertion within 1 hour of symptom onset (Mittleman et al., 1993; Willich et al., 1993; Hallqvist et al., 2000). The assessment of negative emotional states enquired about the occurrence of anger, stress and depression or sadness within 2 hours of symptom onset (Mittleman et al., 1995; Moller et al., 1999; Steptoe et al., 2006), and patients reporting moderate or intense emotional states were categorised into the emotional trigger group. Activity and emotion over additional periods were assessed for case-crossover analyses described elsewhere (Steptoe et al., 2006).

After the interview was completed, patients were given a questionnaire that they completed and returned 7-10 days post-admission. Socio-economic status (SES) and depression were assessed as in the previous study described in section 9.2.2. Anxiety was measured using the anxiety scale from the Hospital Anxiety and Depression (HADS) scale (Zigmond & Snaith, 1983), a widely used measure suitable for medical patients (Herrmann, 1997). Scores can range from 0 – 21, and patients were classified as moderately or severe anxious if their ratings exceeded the recognised threshold (≥ 8).

12 and 36 month assessments

Patients were reassessed 12 and 36 months after discharge by telephone interview and questionnaire. Mental well-being was assessed using the HAD anxiety scale and the mental health scale from the Short Form 36 (SF36) health status measure (Ware et al., 1992). This consists of 5 items related to anxiety and depression (see appendix 11). Physical health status was assessed using the SF36 physical health summary scale. This

combines scores on four of the SF36 scales (physical function, role limitations due to physical problems, pain and general health perception). Additionally, we used the vitality scale from the SF36 as an additional measure of physical health status. Each of the SF36 measures was scaled from 0-100, with 100 indicating the best possible quality of life. Cronbach α scores for the SF36 scales ranged from 0.81-0.90. Patients also provided information about whether they had experienced any recurrence of cardiac symptoms over the follow-up period.

Statistical analysis

194 of the 257 (75.5%) patients were reassessed at 12 months, and 160 (62.2%) at 36 months. Non-respondents either could not be traced, refused to be reassessed, or were deceased. Patients who completed the 12 month assessment did not differ from those who failed to take part in gender, ACS type, medical history, the occurrence of emotional and physical triggers, or in anxiety in hospital. However, non responders were significantly younger (57.6 *vs* 61.2 years, $p = 0.024$), had higher social deprivation scores ($p = 0.041$) and lower scores on the Grace index of clinical risk ($p = 0.040$), indicating that younger, less affluent patients with less severe ACS were lost to follow-up.

These analyses use a combined emotional trigger variable, composed of patients who reported stress, anger or depressed mood during the hazard period. Physical exertion triggering was indexed by the one hour exertion measure described by Strike et al. (2006). Patients who experienced emotion prior to the ACS event were placed in an 'emotion trigger group' and those that did not experience an emotional trigger were placed in a 'non emotion trigger' group. The two groups were compared using t-tests for continuous and χ^2 tests for categorical variables.

The relationship between emotional and physical triggers and mental well-being and physical health status at 12 and 36 months, was assessed with multiple regression analyses, on the two dependent variables concerned with mental well-being: anxiety (HADS) and mental health (SF36) and the two dependent variables concerned with physical function: vitality, and physical health scores (SF36). Along with the measures of triggers, age, gender, SES, Grace risk score, anxiety in hospital, history of clinical depression and recurrence of symptoms were entered as covariates in all analyses, so these analyses were controlled for factors that potentially confound associations. Additional covariates were included in particular analyses, based on their associations with the specific outcome measures. Results are presented with regression coefficients (B) and 95% confidence intervals (C.I.).

10.3 Results

Seventy two (37.5%) patients experienced acute emotional distress during the 2 hour trigger period preceding ACS onset, while 11 (5.9%) reported physical exertion. 2.6% of patients reported both physical exertion and emotional stress. The negative emotional states included acute anger (16.3%), stress (27.9%), and depression and sadness (16.3%). The characteristics of patients with emotional triggers are detailed in Table 10.1. Emotional trigger patients were significantly younger than those with no emotional triggers, and tended to be more socially deprived ($p = 0.083$). There were no differences in other socio-demographic factors, clinical indicators, treatment plan, cardiovascular history, lifestyle or history of clinical depression. Anxiety levels in hospital were moderately elevated, but did not differ between groups. In the proportion

of patients who reported symptom recurrence over the 12 month period there was no difference between the groups.

Table 10.1 Socio-demographic and clinical characteristics of ACS patients

		Emotional trigger group (n = 72)	**No emotional trigger group (n = 120)**	**p**
Gender	Men	56 (77.8%)	93 (77.5%)	0.96
	Women	16 (22.2%)	27 (22.5%)	
Age (yrs)		59.0 ± 10.2	62.5 ± 11.6	0.034*
Ethnicity	Non-white	6 (8.3%)	18 (15.0%)	0.18
Social deprivation	Low	29 (40.3%)	60 (50.0%)	0.083
	Medium	19 (26.4%)	34 (28.3%)	
	High	24 (33.3%)	26 (21.7%)	
ACS type	STEMI	53 (73.6%)	82 (68.3%)	0.52
GRACE score		92.3 ± 23.5	98.7 ± 28.1	0.11
N vessels diseased		1.76 ± 0.82	1.81 ± 0.81	0.70
Treatment	Medical	17 (23.9%)	38 (31.7%)	0.23
	PCI	45 (63.4%)	66 (55.0%)	
	CABG	9 (12.7%)	16 (13.3%)	
Previous ACS		6 (8.3%)	13 (10.9%)	0.63
Diabetic		10 (13.9%)	12 (10.0%)	0.48
Aspirin pre-admission		9 (12.5%)	24 (20.0%)	0.24

	Emotional trigger group (n = 72)	No emotional trigger group (n = 120)	p
Beta blockers pre-admission	13 (18.1%)	20 (16.8%)	0.85
Current smokers	32 (44.4%)	52 (43.3%)	0.88
Body mass index	27.5 ± 4.5	26.8 ± 4.4	0.33
Physical activity Sedentary	43 (59.7%)	74 (62.2%)	0.12
Low activity	21 (29.2%)	22 (18.5%)	
High activity	8 (11.1%)	23 (19.3%)	
History of depression	13 (18.1%)	21 (17.5%)	0.92
Anxiety in hospital	6.11 ± 3.5	5.43 ± 4.2	0.30
Symptom recurrence (12months)	9 (13.4%)	27 (23.9%)	0.09

*Significant difference, $p < 0.05$.

10.3.1 Triggers and mental well-being at 12 months

Anxiety on the HAD scale averaged a score of 6.24 ± 4.5 at 12 months, and 32.5% of patients scored above the threshold for moderate or severe anxiety. Scores on the SF36 mental health scale averaged 71.6 ± 20.9. Both anxiety and mental health scores were significantly correlated with anxiety in hospital ($r = 0.29$ and -0.28 respectively, $p < 0.001$), and with a history of clinical depression ($p < 0.01$). Mental health was poorer in lower SES patients ($p = 0.007$). Anxiety levels at 12 months tended

to be higher in patients who were admitted with an NSTEMI/UA compared with a STEMI ($p = 0.057$). Anxiety and mental health were worse at 12 months in patients who had been prescribed aspirin pre-admission, but were better in those prescribed beta blockers. Recurrence of symptoms over 12 months was strongly associated with both anxiety and poor mental health ($p < 0.0001$).

Emotional triggering was positively associated with anxiety at 12 months independently of age, gender, SES, Grace risk score, ACS type, aspirin and beta blocker medication pre-admission, anxiety in hospital, history of depression, and symptom recurrence ($p < 0.001$, Table 10.2). Additionally, anxiety in hospital, symptom recurrence and prescription of beta blockers pre-admission were independent predictors of 12 month anxiety. Anxiety at 12 months adjusted for covariates averaged 7.32 ± 4.2 in the emotional trigger group, and 5.22 ± 4.2 in the non-trigger group ($p < 0.001$). The odds ratio for having an anxiety score above the clinical threshold was 6.24 (C.I. 2.4 to 15.7, $p < 0.001$), for patients reporting emotional triggers versus no triggers after adjustment for covariates.

Similar patterns were recorded for the SF36 mental health scale, with positive associations between emotional triggering and poor mental health independently of age, gender, social deprivation, grace risk score, ACS type, pre-admission medication, anxiety in hospital, depression history and symptom recurrence ($B = -7.18$, C.I. -13.4 to -0.97, $p < 0.001$). Mean adjusted scores were 67.8 ± 21.9 in the emotional trigger and 74.9 ± 27.2 in the no trigger patients. Physical exertion during trigger period was not associated with the 12 month mental health score.

Table 10.2 Predictors of 12 month anxiety

	Regression coefficient (B) (95% C.I.)	p
Age	0.028 (-0.08 to 0.14)	0.61
Gender	0.119 (-1.36 to 1.60)	0.87
Social deprivation	0.002 (-0.73 to 0.73)	0.99
Grace risk score	-0.013 (-1.36 to 1.60)	0.57
ACS type	-0.590 (-1.93 to 0.75)	0.39
Aspirin pre-admission	-1.439 (-3.19 to 0.31)	0.11
Beta blockers pre-admission	2.198 (0.55 to 3.85)	0.009*
Anxiety in hospital	0.246 (0.09 to 0.41)	0.003*
History of depression	1.427 (-0.06 to 2.92)	0.060
Symptom recurrence	4.400 (2.77 to 6.03)	0.001*
Emotional triggering of ACS	2.097 (0.85 to 3.34)	0.001*

*Significant difference, $p < 0.05$.

10.3.2 Triggering and physical health status at 12 months

The SF36 physical health status (PHS) scores averaged 63.2 ± 26.2 at 12 months, while the physical vitality score averaged 55.7 ± 21.7. Physical health status at 12 months was worse in socially deprived patients and in those who experienced symptom recurrence. Additionally, physical activity habits before ACS were associated with

physical health status at 12 months (mean PHS scores 58.7, 68.7 and 72.3 for inactive, low activity and high activity groups respectively, adjusted for age and gender, p = 0.011).

Exertion during the trigger period was predicted by lower physical health status scores at 12 months, independently of age, gender, social deprivation, Grace risk score, ACS type, anxiety in hospital, history of depression, and physical activity levels (B = -16.5, C.I.-33.0 to -0.44, p = 0.044). However, when symptom recurrence was added to the model, the association was no longer significant (p = 0.064). Mean scores adjusted for covariates were 50.8 ± 24 in the exertion, and 65.6 ± 26.1 in the no exertion group. By contrast, vitality at 12 months was predicted by exertion during the trigger period independently of all covariates (p = 0.019, Table 10.3). Physical vitality scores adjusted for covariates averaged 41.8 ± 28.4 in the exertion and 57.3 ± 20.6 in the non-exertion groups. Other independent predictors of 12 month vitality were a history of clinical depression and symptom recurrence over the 12 month period. Neither of the physical health measures at 12 months was associated with emotional triggering of ACS.

Table 10.3 Predictors of 12 month physical vitality

	Regression coefficient (B) (95% C.I.)	p
Age	-0.016 (-0.59 to 0.56)	0.96
Gender	-4.601 (-12.58 to 3.38)	0.26
Social deprivation	-1.839 (-5.79 to 2.17)	0.36
Grace risk score	-0.018 (-0.26 to 0.22)	0.88
ACS type	3.791 (-3.49 to 11.07)	0.31
Anxiety in hospital	-0.627 (-1.49 to 0.23)	0.15
History of depression	-10.70 (-18.70 to -2.71)	0.009*
Symptom recurrence	-14.08 (-22.90 to -5.26)	0.002*
Physical exertion triggering of ACS	-15.45 (-28.35 to -2.56)	0.019*

*Significant difference, $p < 0.05$.

10.3.3 Triggering and adaptation at 36 months

HAD anxiety score averaged 5.52 ± 4.2 at 36 months, while the SF36 mental health scale averaged 72.7 ± 27.2, and the physical health status measure averaged 48.1 ± 19.7. Anxiety at 36 months was no longer related to ACS type or medication pre-admission, but it was predicted by symptom recurrence over the 3 years period ($p < 0.001$). Emotional triggering continued to be a predictor of anxiety at 36 months independently of age, gender, social deprivation, Grace risk score, anxiety in hospital,

history of depression and symptom recurrence (Table 10.4). Other independent predictors were anxiety in hospital and symptom recurrence. Mean levels of anxiety at 36 months adjusted for covariates, were 6.22 ± 4.6 for the emotional trigger and 4.76 ± 3.9 for the non-trigger patients. Similarly, mental health scores at 36 months were predicted by emotional triggering independently of covariates (adjusted means 69.0 ± 20.0 and 76.7 ± 21.5 for emotional trigger and no trigger groups, $p = 0.047$).

Physical health status was associated with triggering by physical exertion, but was not predicted by emotional triggering (Table 10.4). Patients who exerted themselves physically during the one hour before ACS onset had substantially lower physical health status scores at 3 years (adjusted means 31.5 ± 11.5) than those who had not been physically active (mean 50.1± 20.9, $p = 0.019$). The other independent predictor of physical health status at 36 months was symptom recurrence. Vitality scores at 36 months were not predicted by physical or emotional triggers.

Table 10.4 Predictors of anxiety and physical health status at 36 months

	Regression coefficient (B) (95% C.I.)	p
HAD anxiety (36 months)		
Age	0.016 (-3.03 to 6.56)	0.83
Gender	0.397 (-1.28 to 2.80)	0.64
Social deprivation	0.231 (-0.66 to 1.12)	0.61
Grace risk score	-0.013 (-0.07 to 0.41)	0.64
Anxiety in hospital	0.305 (0.12 to 0.49)	0.002*
History of depression	1.300 (-0.48 to 3.08)	0.15
Symptom recurrence	2.993 (1.08 to 4.91)	0.002*
Emotional triggering of ACS	1.465 (0.01 to 2.92)	0.049*
SF36 physical health status (36 months)		
Age	0.228 (-0.53 to 0.99)	0.55
Gender	-3.188 (-12.24 to 5.87)	0.49
Social deprivation	-1.804 (-6.59 to 2.98)	0.46
Grace risk score	-0.225 (-.52 to 0.07)	0.14
Anxiety in hospital	0.086 (-0.92 to 1.09)	0.87
History of depression	-8.657 (-18.15 to 0.84)	0.074
Symptom recurrence	-12.41 (-22.58 to -2.23)	0.017*
Physical exertion triggering of ACS	-18.61 (-34.04 to -3.18)	0.019*

*Significant difference, $p < 0.05$.

10.4 Discussion

The purpose of this study was to discover whether acute triggering of ACS has long term implications for adaptation and quality of life. We discovered that mental well-being at 12 and 36 months was predicted by the presence of acute emotional stress in the 2 hours before symptom onset. The effect was substantial, with the odds of HADS anxiety above the clinical threshold being 6 times greater in patients who experienced emotional triggering, after adjustment for socio-demographic factors such as age, gender and SES, clinical risk as defined by the GRACE risk score, type of ACS, medication, anxiety in hospital, history of depression and symptom recurrence. Effects persisted at 36 months, and were confirmed with 2 independent measures of mental well-being. Emotional triggers were not associated with long term physical health status. Conversely, physical exertion during the hour before symptom onset predicted reduced physical health status at 12 and 36 months, but was not related to mental well-being.

These findings suggest that acute triggers do have long term consequences for adaptation and quality of life in cardiac patients, with differential responses depending on whether patients experience a physical or emotional trigger. The absence of cross-influences between the physical and emotional domains adds credence to the findings, indicating that they are not due to the experience of triggers stimulating generalised impairment in quality of life.

It should be noted that both physical health status and mental well-being were markedly impaired on average both at 12 and 36 months. SF36 physical health status scores averaged 63.2 and 48.1 at the two time points, while 32.5% and 30% respectively scored above the threshold for moderate anxiety. However, there was wide variation in

these responses, with some patients showing very little impairment in quality of life at follow up.

Anxiety and mental health score at 12 months following hospital discharge were positively associated with anxiety measured 7-10 days after hospitalisation, and with a history of clinical depression. These results confirm previous findings that psychological distress following hospitalisation for ACS predicts poor mental health longitudinally (Lane et al., 2001; Beck et al., 2001). Anxiety at 12 months was also higher in those admitted with NSTEMI/UA rather than a STEMI. This may be because of the uncertain prognosis of unstable angina or the more aggressive clinical treatment of STEMI's, that may lead to more complete symptom relief and sense of cure. Mental health at 12 months was also poorer in lower SES patients, as has frequently been described in the past (Lorant et al., 2003). Interestingly, the use of beta blockers prior to ACS was an independent predictor of lower anxiety 12 months later. The explanation is not clear. Patients who were prescribed beta blockers were no less likely to report emotional triggers or physical exertion than others, but it is possible that the intensity of the experience was attenuated. Symptom recurrence was a strong predictor of quality of life both at 12 and 36 months, presumably because patients who experienced symptoms were more worried that they might suffer a new cardiac event (Heller et al., 1997).

Physical health status at 12 months was predicted by lower SES, sedentary behaviour prior to ACS onset, and symptom recurrence. The association between physical exertion during the hour before symptom onset, and later physical health status, was not as strong as the relationship between emotional triggering and mental well-being. The probable reason is that this analysis had limited power, since only 5.9% patients' reported physical exertion during the hazard period. Nonetheless, effects were

significant and persisted at 36 months, when a 19-point difference in SF36 physical health status scores was observed between exertion and non-exertion groups.

The long term impact with physical exertion during the trigger period may again be due to patients' attributions. Patients who believe their ACS was triggered by physical exertion may become reluctant to become active in the future, fearing a recurrence. This will lead to inactivity and de-conditioning, so that sense of vitality and ability to carry out every day physical task will be impaired. This process is of considerable clinical concern, since regular physical activity following ACS is important to future cardiac health, and will increase confidence in ability to resume work and normal activities (Balady at al., 2007).

10.5 Strengths and limitations

The strengths of this study include its prospective design, the use of systematic measures to assess triggering and later quality of life and, as in chapter 9, the inclusion of different type of ACS and the characterisation of patients in terms of multivariate clinical risk.

The study has a number of limitations. It involved a relatively young sample of patients (mean age 61.2 years), with a higher proportion of STEMI than NSTEMI/UA and a greater number of men than women compared with recent cohort studies (Hasdai et al., 2002). Exclusion of patients with co-morbidities likely to influence symptom presentation or mood may have restricted the sample to individuals with lower risk profiles. Patients in the study had to recall a specific time of onset, so the ACS events were not representative of all emergency cardiac admissions and there was the potential

for recall bias. Because of the limited sample size, it was not possible to investigate the intensity of triggers experiences. Emotional experiences during the 2 hours before symptom onset varied from moderate to very intense, and this could have contributed to the likelihood of later poor mental well-being. There were too few patients reporting both physical exertion and emotional stress to analyse separately, but they may be a particularly vulnerable subset. Additionally, we lost 24.5% of patients to 12 months follow up. Younger, lower SES patients were less likely to be included in follow up assessment, but crucially, trigger and non trigger patients were not differentially retained in the study. Nevertheless, the pattern of results might have been different in patients who were not included in follow up.

Chapter 11: Discussion

11.1 Mood in relation to CAD

My thesis presents three studies that address different aspects of the relationship between emotional factors and coronary artery disease (CAD).

The three studies were carried out with the following aims:

a) To evaluate the influence of emotional triggers on cardiac health acutely, on a moment to moment basis, in daily life.

b) To evaluate the influence of emotional acute triggers on the long term adaptation after an established coronary event or procedure, in terms of psychological adaptation and functional recovery.

c) To understand the psychophysiological basis for such effects.

In general, results from these studies suggest that psychological factors relate directly to physiological responses (heart rate variability and neuroendocrine function), relevant to the onset of acute cardiac events in patients with suspected CAD. Additionally, acute emotional triggers of acute coronary syndrome (ACS) have been found to relate to later adaptation and quality of life in established ACS patients. I will discuss these findings in turn, in relation to the hypotheses described in chapter 3.

An overview of the key relationships are discussed and illustrated in Figure 11.1.

SIS study: influence of emotional factors on cardiac health in daily life.

* In patients with definite CAD, depressed mood was associated with decreased high frequency and increased low frequency heart rate variability (HRV), suggestive of parasympathetic withdrawal. This was not true of the non-CAD patients, though in the complete sample, greater parasympathetic control (increased high and decreased low frequency power) was present in patients reporting more positive affect (PA).

* The cortisol slope over the day was flatter in patients with CAD who were more depressed.

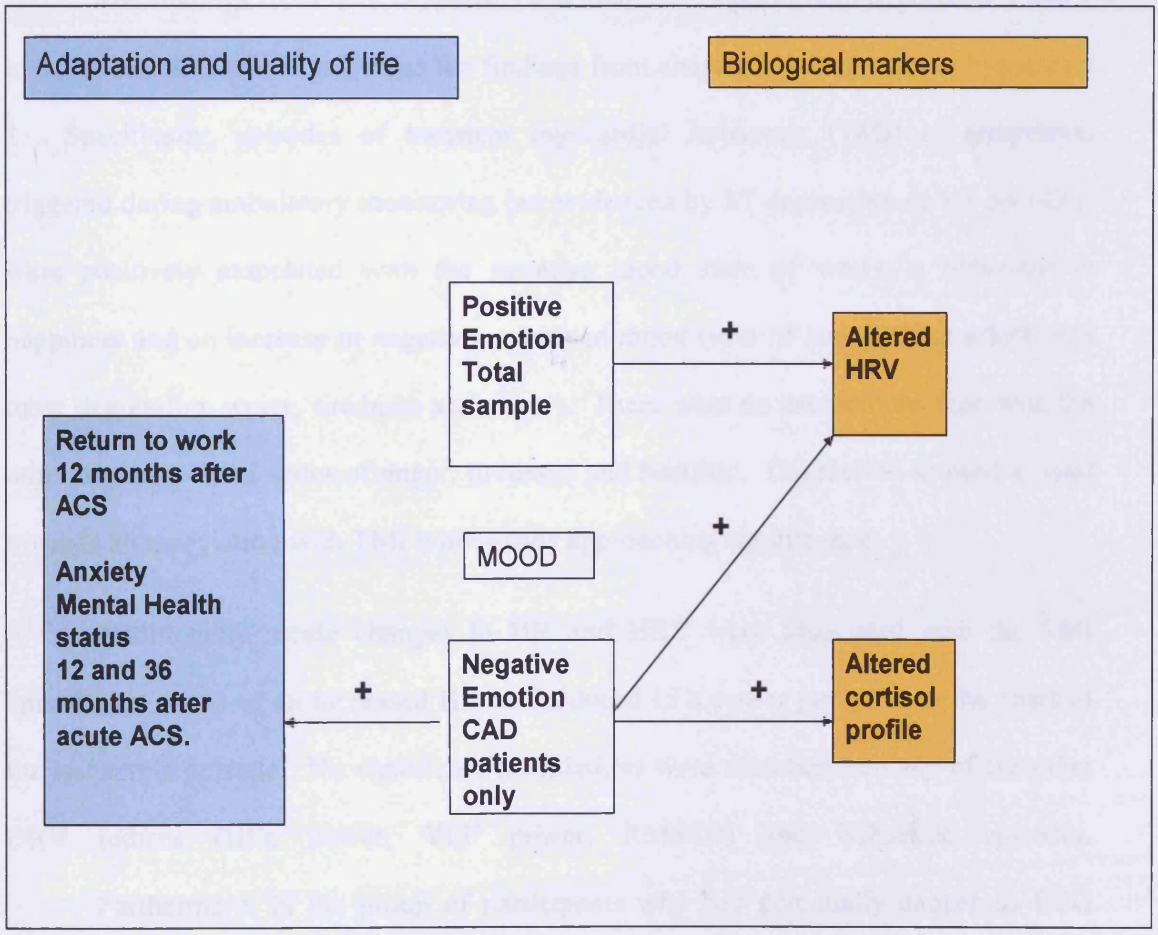
* Episodes of transient ischaemia and/or arrhythmia were also associated with increased negative affect (NA), but their incidence was low in the sample, primarily because most patients were medicated with beta blockers.

ACCENT studies: influence of emotional factors on later adaptation to ACS

* Failure to resume work was associated with cardiac factors on admission (heart failure, arrhythmia), cardiac complications during the intervening months, and depression scores during hospitalisation. It was not related to age, gender, socio-economic status, type of ACS, cardiac history, acute clinical management, or type D personality. In multivariate analyses, the likelihood of returning to work was negatively associated with depression independently of clinical and demographic factors.

* Emotional triggers predicted elevated anxiety and poor mental health status at 12 months independently of age, gender, socio-economic status, ACS presentation, pre-admission medication, anxiety in hospital, depression history and symptom recurrence. Effects persisted at 36 months. Emotional triggers were not related to physical health status at follow-up. By contrast, impaired physical health status was predicted by vigorous exertion during the trigger period independently of covariates.

Figure 11.1 Overview of the three studies.



11.2 Mood and cardiovascular function: Association between mood and transient myocardial ischaemia and heart rate variability in CAD and non-CAD patients

Hypothesis 1: Episodes of silent myocardial ischaemia or arrhythmia triggered during ambulatory monitoring will be positively associated with negative mood states.

Hypothesis 2: Trait measures of depressed affect as measured by validated scales and moment to moment negative mood states over the day will be associated with reduced heart rate variability.

The findings from both chapters 5 and chapter 7 support both hypothesis 1 and 2 to some extent. I will first discuss the findings from chapter 7, which support hypothesis 1. Specifically, episodes of transient myocardial ischaemia (TMI) or arrhythmia triggered during ambulatory monitoring (as evidenced by ST depression or VT on ECG) were positively associated with the negative mood state of worry, a reduction in happiness and an increase in negative combined mood (sum of less positive affect and more depression, worry, tiredness and anger). There were no associations seen with the other negative mood states of anger, tiredness and hostility. Depression showed a trend towards an association with TMI with results approaching significance.

Additionally, acute changes in HR and HRV were associated with the TMI episodes, in terms of an increased HR and reduced LFn power just prior to the onset of the ischaemic episode. No significant associations were seen between any of the other HRV indices (HFn power, VLF power, RMSSD) and ischaemic episodes.

Furthermore, in the group of participants who had potentially dangerous ECG changes, a significant association was seen between mood and HRV surrounding the TMI episodes; specifically an increase in PA was shown to be associated with a smaller

increase in HR and a reduction in LFn power, in other words, a reduction in sympathetic drive. Significant associations were also seen with negative mood states, since an increase in worry and greater depressed mood was associated with a reduction in IBI (or an increase in HR) and therefore a decrease in parasympathetic drive. The HR and HRV findings relating to these negative mood states are the opposite of the findings related to the positive mood states.

The results from chapter 5 supported hypothesis 2. There are significant associations between mood and HRV, with depressed mood being associated with a reduced HRV in the CAD patient group only, while PA in the total sample of participants was associated with an increased HRV.

The SIS study findings thus support results from previous studies in which negative emotions have been shown to precede the onset of ischaemic episodes. For example, Gullette et al. (1997) showed an association between the negative emotions of tension, frustration, and sadness and an increase in the relative risk of ischaemia in the subsequent hour in CAD patients. There were advantages to the new method used to characterise daily experience over diary studies previously used. By using the DRM, it was possible to carry out a fine tuned analysis of subtle and fluctuating mood changes that occur in daily life, in relation to cardiac episodes. In the analysis of the SIS study, mood was assessed in the 15 minute period prior to the onset of the ischaemic episode, not in the hour before as in the study by Gullette et al. (1997), and participants displayed a significant drop in positive affect, and an increase in worry and combined negative mood (less positive affect/more negative affect) just prior to the onset of the episode. The change in the magnitude of emotion just prior the onset of the ischaemic episode is interesting and has not been shown before. Previous naturalistic studies have also shown various emotions to be related to arrhythmia or ECG changes such as anger (Lampert et

al., 2004), depression, or stress (Bacon et al., 2004; Blumenthal et al., 1992), however unfortunately our study did not show associations with other such negative mood states.

One reason for this may be because of inadequate levels of arousal of such negative emotions during the period of monitoring. The majority of the sample was a retired population. Results obtained may have been different if an employed sample had been recruited, in which there may have been an increased frequency and intensity of emotions to provoke an increase in the frequency and duration of episodes of ischaemia, as found in previous studies (Legault et al., 1995). Another factor influencing the arousal level is the presence of the beta blocker medication taken by the majority of cardiac patients. This may block the sympathetic drive associated with feelings of anger, hostility that can provoke TMI episodes (Krantz, 1987, Ratey, 1992).

These positive associations between emotion and the onset of acute ischaemic episodes leads onto a discussion of the relationship between the onset of ischaemic episodes and the acute changes in heart rate variability (HRV). Previous studies have indicated that TMI episodes are often preceded by changes in the autonomic nervous system (ANS) consistent with vagal withdrawal and ST depression in a variety of subtypes of cardiac patients (Pozzati et al., 1996; Ponikowski et al., 1996).

In the SIS study, a reduction of LFn power and an increase in HR was found in the minutes just prior to the onset of ischaemic episodes with a prompt return to baseline levels afterwards, suggesting a reduction in the balance between sympathetic/parasympathetic drive prior to the onset of the ischaemic episode. No associations were seen with HFn and VLF power. This finding supports a previous study by Kop et al. (2001), which examined the changes in HRV one hour before and after ischaemic events recorded on ambulatory 24 hour ECG's. Kop et al. (2001) found a reduction in LF power prior to the onset of TMI and an increase in HR 60 to 20 minutes

prior to the TMI episode. The SIS study suggested a reduced parasympathetic drive preceding TMI in the minutes before the ischaemic episode, and then a rapid return to the original baseline level. It is feasible that the acute changes indicate a possible vagal withdrawal preceding the onset of TMI, but then a prompt compensatory mechanism of rapidly increasing vagal tone (or decreasing sympathetic tone) to return to the optimal baseline level of HRV functioning, in order to limit the severity of the ischaemic episode.

In the study by Pozzati et al. (1996), reduced HRV was seen in the 5 minutes preceding ischaemic episodes in angina patients, and was thought to be a significant predictor of ischaemic death. Huikuri et al. (1999) proposed that a reduced HRV accelerates the progression of coronary atherosclerosis rather than being a consequence of CAD. This is supported by findings from the SIS study of a reduced HRV, just prior to the ischaemic episodes, which in the long term could lead on to acceleration in atherosclerosis and ischaemic death. Although no significant relationships were found between the group with ECG changes and HRV indices when compared to the remainder of the sample, differences were seen when detailed analysis surrounding each of the individual ischemic episodes were carried out.

So in conclusion, there is a significant association between increased negative mood in the 15 minutes prior to the onset of TMI with changes in HR and HRV shown even more acutely in the few minutes prior to ischaemic episodes. The possibility that mood can influence HRV changes has been suggested by the association between more positive mood and smaller increases in HR and a reduced LFn, independent of medication. The converse was seen with worry and depression. This indicates that a reduction in the sympathetic drive or an increase in vagal tone were associated with positive mood states, and this greater parasympathetic influence may be one biological

mechanism by which positive affect may benefit cardiac health in terms of morbidity and mortality.

Hypothesis 2 is to some extent supported by results from chapter 5; changes in HRV were related to mood as assessed by the DRM, but not when assessed by the BDI. HRV may be influenced more by moment to moment changes in mood, than static traits such as those measured by the BDI. Specifically, results from chapter 5 show that depressed mood was associated with reduced HRV (decreased HF and increased LF power) in CAD patients only. A reduced IBI at night was seen only amongst the CAD patient group. Additionally, positive mood was associated with increased HRV (increased HF and decreased LF power) in the total sample of patients, not just those with CAD. No significant relationships were seen between HRV and depressed mood (as measured by the BDI) in either the total or the CAD patient sample.

The absence of associations between HRV and the BDI scores contrasts with many other studies in which a reduced HRV is associated with depression, as measured by a variety of depression scales (Kim et al., 2005; Moser et al., 1998; Stein et al., 2000; Carney et al., 2001; Yeragani et al., 1993, 1995; Krittayaphong et al., 1997). However, a significant relationship was seen between negative affect, assessed by the DRM, and HRV. It may be that differences were not detected using the BDI, due to inadequate demarcation between those who were depressed, and those who were not. A score of 10 was chosen as the cut-off point, but this meant that a score of 11 would be classified as the 'depressed group', while those scoring 9 would be allocated to the 'non-depressed' group, despite the scores being similar. An alternative grouping would be to divide the two groups in a more extreme way, into those who scored less than 10 on the BDI, as the 'non-depressed' group, and those who scored above 15, as the 'depressed' group. The DRM appears to be a more precise tool for measuring moment to moment changes in

emotions, and possibly more suitable for correlating transient changes in mood with transient cardiac changes. There was a good correlation between high BDI scores and increased scores for negative affect with the DRM.

The findings that depressed mood (measured by the DRM) was related to reductions in HRV in stable CAD patients supports results from previous studies (Carney et al., 1995, 2001; Stein et al., 2000). Earlier work has shown a higher HR to be associated with depression, consistent with altered ANS function in healthy participants but not in cardiac patients. Elevated HR is a risk factor for sudden cardiac death in the general population (Kannel et al., 1987). An elevated HR also increases the risk of progression to atherosclerosis (Palatini et al., 1999), ischaemia (Palatini et al., 1997) and plaque disruption in ACS (Heidland et al., 2001). Findings from the SIS study, of an elevated HR at night in the CAD group only, supports the notion of a reduced parasympathetic tone at night predisposing the group of patients with cardiac disease to cardiac arrhythmia and sudden death. This is a feasible biological mechanism to account for the circadian pattern of MI seen in early morning (Willich et al., 1987, Muller et al., 1989; Krantz et al., 1996).

The fact that depressed affect had a significant association with reduced HRV adds to the evidence that the underlying mechanisms linking depression to CAD, include dysregulation of the cardiac ANS, with an increase in sympathetic tone and/or reduction in vagal tone. The DRM results provide some clarification to the temporal sequence of events preceding TMI, since heightened negative affect was recorded prior to the onset of ischaemic episodes. This suggests that the negative moods may be contributing to the alterations in autonomic control, rather than altered autonomic function leading to negative moods in these cardiac patients. However, it should be emphasised that significant increases in depressed mood did not precede the onset of TMI in the SIS

study. The low levels of depressed mood detected with the DRM may have been responsible for this.

The significant association between positive affect (measured by the DRM) and increased HRV (increased HF and decreased LF power) was found in the complete sample of patients, that is both CAD and non-CAD patients. This finding may be due the numbers in the CAD group being too small, or that the frequency of positive mood being too low in the period of monitoring for an association to be found in the CAD group. The findings support a study by McCraty et al. (1995), which showed that the positive emotion of appreciation was associated with a spectral shift towards MF/HF activity in 24 healthy men and women. The SIS study findings do not, however, fit with the study by Bacon et al. (2004). The latter study showed that higher levels of positive emotion were related to an increase in LF power in 135 CAD patients. There is little evidence in the literature relating positive emotions and HRV, but our results suggest that greater PA may provide protection against adverse cardiac changes by increasing the HRV.

It should be emphasised that interpreting HRV results is not straightforward. The underlying presumption is that a reciprocal sympatho-vagal balance is present, is critical to the cardiac ANS, and can be only be deciphered via these calculations. HF power appears to be a satisfactory measure of vagal control, whereas LF components reflect both sympathetic and parasympathetic modulation, and these measures are typically taken without taking patterns of respiration into account. In addition, both LF and VLF power are predominantly caused by fluctuations in the vasomotor tone and systemic vascular resistance and are influenced by neural, humoral, endothelial and thermoregulation factors, making interpretation of results difficult. Normalisation of HF and LF power to total variability and/or using a ratio of these two oscillations help to

increase the reliability of spectral parameters reflecting parasympathetic/sympathetic cardiac modulation. However, it can be argued that transforming variables to better correspond to an anticipated physiological response does not necessarily create a more valid measure. Cardiovascular variability should not be considered as definitive quantitative measures of autonomic outflow, due to its complex physiology.

However, in general, the results from chapters 5 and 7 show that negative emotions in daily life are associated with both the onset of TMI and altered HRV. HRV may be a potential biological mechanism by which emotion can relate to cardiac health. The findings also provide further evidence that the DRM may be a useful tool for the characterisation of momentary mood and correlates with the acute cardiac changes.

11.3 Mood and neuroendocrine function

Hypothesis 3 : Episodes of silent myocardial ischaemia or arrhythmia triggered during ambulatory monitoring will be positively associated with lower cortisol awakening response.

Hypothesis 4 : Trait measures of depressed affect as measured by validated scales will be associated with flattened cortisol slopes over the day, and with an exaggerated cortisol waking response in patients with coronary artery disease.

Hypothesis 3 was supported by results from chapter 7; patients who had episodes of ischaemia or arrhythmia had a reduced cortisol awakening response (CAR). Hypothesis 4 was supported by results from chapter 6; participants with CAD exhibited

an increased CAR, independent of depression. Additionally, the patients who were depressed, as measured by the BDI, demonstrated a flatter cortisol slope after adjustment for confounders.

The current literature relating the CAR to negative mood has been mixed and it is difficult to determine the significance of the CAR, as it is a distinct and dynamic part of the circadian cortisol profile, with further work needed to clarify its main role and importance for cardiovascular health. Cross-sectional associations between chronic stress and self-reported depression and an increased CAR are seen in studies by Pruessner et al. (2003), Steptoe et al. (2004), and Schulz et al. (1998).

The SIS study demonstrated an increased CAR in the CAD patient group only, independent of depression. These findings reject the latter part of hypothesis 4. As an increased CAR has been shown to be associated with depression in the literature, it is plausible that an altered CAR response in patients with CAD may be a mediating biological mechanism, which accounts for the prevalence of depression seen in cardiac patients (Nicholson et al., 2006). However, these associations infer no direction as to the causality, that is, depression could cause the altered CAR response by dysregulation of the HPA axis and subsequent elevation of inflammatory markers or adverse haemostatic effects (Girod & Brotman, 2004). Alternatively, the altered CAR response can lead to anti-inflammatory and cytokine effects that may subsequently cause depressed mood (Steptoe & Brydon, 2007).

There is also evidence to suggest that burnout is associated with an attenuated CAR (Pruessner et al., 1999). A reduced CAR is seen to be associated with increasing age and a range of health problems (Kudielka & Kirschbaum, 2003) and negative markers of cardiovascular health, such as intimae media thickness of arteries in females (Eller et al., 2003).

It appears to be an inconsistency that a heightened CAR can be regarded as maladaptive and that a reduced CAR, as associated with burnout (Pruessner et al., 1999), can be seen as maladaptive. Similarly, the SIS findings were, on the one hand showing an increased CAR in the CAD patients, independent of depression and yet on the other hand, showing a reduced CAR in the group of patients displaying ECG changes. Additionally, the mean cortisol values were lower in the group displaying ischaemic changes on ECG, independent of depression. Higher, rather than lower mean cortisol values as in the SIS study, have been shown to be associated with coronary stenosis (Bain et al., 1989). Troxler et al. (1977) found significant correlations between elevated serial plasma cortisol values in the morning and moderate to severe coronary atherosclerosis. One interpretation of such contradictory findings is based on the theory proposed by Adam et al. (2007) in that the CAR is seen as an adaptive response designed to provide the individual with a boost needed to meet the anticipated demands of the day. When this mechanism becomes exhausted over time, by chronic stressful daily events and depression or other mood states in cardiac patients, dysregulation of the HPA ensues.

To account for the SIS study findings, one theory is that the patients at a very early stage of cardiac disease have an increased CAR, independent of depression, to meet the demands of the day. With the daily stresses, strains and negative emotions, an increase in the CAR is seen as the CAR is modulated by anticipatory stressful demands of the day. Over a prolonged period, with accumulative stresses, this disruption of the natural diurnal cortisol rhythm eventually gives rise to long term metabolic disturbances. Eventually, as the regulatory mechanisms fail, the CAR response is no longer elevated, but attenuated in at-risk individuals with consequent ischaemic changes that present on the ECG. These physiological changes encourage advanced cardiac disease and possibly go on to influence mood, particular depression, in established cardiac patients.

Findings from chapter 6 showed an altered cortisol slope to be associated both with depressed mood and heart disease. Specifically, the results support hypothesis 4 in that a flatter cortisol slope was found in only the depressed (as measured by the BDI) CAD patients. This finding was notably absent from the depressed but cardiac disease-free group. The flatter slope was demonstrated by reduced cortisol levels early in the day and increased evening levels amongst the depressed CAD patient group.

These SIS study results relating to the cortisol slope supports much of the previous literature. A flattened slope has been found in association with work/home load stress in a sample of 156 healthy female adults (Adam et al., 2001). A flattened slope has also been found in 156 older adults in another study by Adam et al. (2006), in which feelings of tension and anger were concurrently associated with a flatter diurnal cortisol rhythm mainly resulting from evening cortisol levels.

There have been fewer studies on cortisol measures and mood in cardiac patients. The findings from the SIS study are consistent with some of the results from previous studies. Otte et al. (2004) has shown greater mean urinary cortisol levels over 24 hours in depressed cardiac out-patients compared with non-depressed cardiac out-patients, but no relationship was seen with the cortisol slope in this study. However, in the study by Nijm et al. (2007), 30 CAD patients were found to have a higher 24 hour cortisol secretion and a flattened diurnal slope with significantly higher cortisol values in the evening, compared with clinically healthy controls.

The association of a flatter slope associated with the depressed CAD patient group only found in the cross-sectional analysis does not determine the causal direction between depression and cortisol. There are a number of possible causes of this relationship:

a) Does depression lead to an alteration in the cortisol profile and then onto cardiac ischaemia? It is possible that affect will influence the way these participants cope with stress resulting in a flatter cortisol slope, which has various metabolic, inflammatory, and haemostatic consequences for cardiovascular health over the long term.

b) Do increased cortisol levels found in CAD patients contribute to greater depressive symptoms commonly seen in those with cardiac disease?

c) Is there another unmeasured factor that induces cortisol release in the evening and thereby a flatter slope and depression?

In conclusion, the results add to the evidence that disturbance of the cortisol profile may be the mediating mechanism by which depression is associated with CAD but the causal nature of this relationship has yet to be elucidated in further work.

11.4 Adaptation to ACS

Hypothesis 5 : Acute emotional state during hospitalisation for ACS will predict resumption of work 13 months later independent of both socio-demographic and cardiological variables.

Hypothesis 6 : Acute emotional triggers of ACS are predictive in greater longer term adaptation to ACS. Psychological and physical triggers in the hours immediately before the symptom onset of ACS will differentially predict mental and physical health adaptation 12 and 36 months later.

The results from chapter 9 support hypothesis 5; depression independently predicts return to work, irrespective of any clinical or socio-demographic factors.

Return to work was regarded as a major indicator of success of recovery from acute myocardial infarction in the 1970's and 1980's (Mital et al., 2004; Soderman et al., 2003), but has been relatively neglected over the past decade in favour of more subtle measures of quality of life. However, resumption of work remains an important marker of the success of medical and rehabilitation services in equipping people to maintain economic independence (Boudrez & de Backer, 2000). It cannot be assumed that factors identified over 25 years ago, as predictors of return to work, will be relevant in the modern era. The concept of ACS has evolved and is no longer limited to acute myocardial infarction. Treatment has substantially changed with the use of PCI and thrombolysis, and rapid restoration of activities for patients is encouraged. The average duration of hospitalisation following ACS has reduced substantially and some authorities recommend discharge of patients with uncomplicated ACS within 4 days (Boudrez et al., 1994).

An inconsistent relationship between depressed mood and return to work has been reported in previous investigations. Cross-sectionally, individuals who are not working post-ACS are more depressed than those who are employed (Mital et al., 2004). However, because causal conclusions cannot be drawn from cross-sectional results, it is possible that depression impairs the ability to resume and maintain paid employment. The reverse may also be true since lack of work and unemployment is a strong predictor of depression (Kaul et al., 2004).

An association between depressed mood measured 4-6 months post-discharge and return to work has been described (Cay et al., 1973; Soderman et al., 2003), but depressed mood soon after hospital admission is particularly important for two reasons.

First, clinical depression and dysphoria in the immediate post-ACS period are predictors of cardiovascular morbidity and mortality (Alter et al., 2006). Second, depressed mood can be conveniently measured before patients are discharged, so provides important early information about risks to long term recovery (Dooley et al., 1996). No associations between depression and anxiety measured during hospitalisation and return to work were found by Petrie et al. (1996) and Mayou (1984), though studies have shown positive associations in Sweden and Japan (Soejima et al., 1999; Maeland et al., 1987).

In conclusion, the results indicate that depressed mood in the acute aftermath of ACS admission is a powerful predictor of failure to resume work one year later. Its influence is independent of clinical and demographic factors. Depressed mood is an easily measured and potentially modifiable factor, and is consistently associated with other adverse outcomes in CAD. These data indicate that it is relevant to the resumption of economic activity as well as other aspects of recovery and rehabilitation.

The results from chapter 10 support hypothesis 6. Multivariate analyses revealed that both anxiety at 12 and 36 months were predicted by acute emotional triggering of ACS but not by physical triggering. Physical vitality at 12 months and physical health status at 36 months were predicted by physical triggers but not by emotional triggers of ACS.

The mechanisms through which emotional triggers predict later mental well-being are not certain. The association is not due to emotional trigger patients being more distressed in hospital or having a worse psychiatric history. It is conceivable that some unmeasured factors were related both to emotional triggering and later impaired well-being, but a wide range of socio-demographic and clinical cardiological factors were tested. One possibility is that the experience of ACS is more distressing in patients who report emotional triggers. The Psychobiology Group at UCL have previously found that

intense fear of dying was greater among patients who experience emotional stress in the two hours before symptom onset (Whitehead et al., 2005). Retrieval of emotional memories is influenced by the emotional context at the time of memory consolidation (Buchanan, 2007) so stress during the trigger period may contribute to the development of post-traumatic symptoms, leading to impaired mental well-being.

Alternatively, patients may attribute their ACS to stress and negative emotions, and become worried that similar occurrences will trigger future cardiac events. Cardiac patients develop cognitive models of the causes of their illness, in which stress often figures prominently (Cameron et al., 2005). Vulnerable individuals may have poor coping resources leading to preoccupation with emotional state and vigilance for the recurrence of situations and feelings they believe would provoke new cardiac illness. Causal attributions have previously been related to other outcomes in coronary heart disease, including maladaptive health behaviours (Day et al., 2005; Martin et al., 2005).

These data suggest that acute triggers have long term clinical and psychological ramifications beyond the first major concern about avoiding future ACS. Greater attention to understanding patients' views of the immediate causes of their cardiac events may lead to wider recognition of the importance of triggers. For example, there is evidence that triggering by physical exertion is reduced in those who are usually physically active (Servoss et al., 2002). Therefore, the appropriate response to triggering by physical exertion is to engage in a regular activity program, and not become more sedentary. Similarly, some patients have maladaptive beliefs about the need to avoid excitement in their lives and this is shown to predict later poor quality of life (Furze et al., 2005). Programmes to educate patients in developing an understanding that emotional upset and distress are inevitable and rarely lead to ACS could prove valuable, although stress management methods may be required for patients with inappropriate

emotional expression (Tofler & Muller, 2006). By identifying differential predictors of adaptation, cardiac rehabilitation programmes could focus more effectively on optimizing quality of life and well-being for individuals.

11.5 General study limitations

SIS study

11.5.1 SIS study - General

A limitation of the SIS study is the relatively small sample size, although it is comparable with many previous investigations of TMI, HRV, and cortisol in everyday life (see chapter 2). The study also has no age and sex matched healthy controls free from cardiac disease and medication. Such a control group may have confirmed our findings, showing that effects were specific to people being investigated for heart disease, and that fewer associations between mood and biological markers would have occurred in healthy individuals.

However, I felt that a more interesting comparison could be made with participants who have normal coronary arteries, despite being in the same clinical situation as the CAD patients. In our study, a proportion of the sample had normal coronary arteries forming a natural control group. When analysing the influence of negative emotion on biological markers, findings are difficult to interpret because medications such as beta blockers have such profound effects on biological responses, such as HR, HRV and TMI. In addition, being investigated clinically for a serious condition such as CAD may have an impact on psychological state.

Of the total sample recruited, 68.2 % were male, 31.8 % were female and only 16.5 % were diabetic. It would have been interesting to recruit a wider range of ethnic groups, a larger percentage of women and participants with a greater range of cardiac risk factors, but such individuals did not attend the outpatient clinics from which I recruited. In the SIS study, all patients were recruited from teaching hospitals so there was no expected difference in the types of patients that were recruited to all three hospitals. However, it should be remembered that there is a possibility that more cases of chest pain are likely to be invasively managed in these types of hospitals and so the patients may not be representative of general cardiac population. This is because in tertiary hospitals there is a wider range of operating theatres and advanced surgical equipment, which may influence the decision making processes of the clinician and lower the threshold for invasive methods of treatment (for example angiography, percutaneous coronary intervention) than in a district general hospital.

11.5.2 Questionnaire

With any questionnaire data, there is a possibility of self-report bias, as people may respond in the way that they would like themselves to be perceived, particularly when measuring health behaviours. There is also the possibility of interpretation bias in the meanings of words. Measurements of trait affect were made using a well-validated BDI scale. An alternative method to assessing depression could have been by structured clinical interview. Measures of hostility and anger were omitted from the baseline questionnaire due to space limitations and the requirement to restrict the questionnaire to an acceptable length. There is well established evidence relating hostility to the development of CAD (Barefoot et al., 1983). These emotions were, however, measured by the DRM but were reported at generally a low frequency and intensity.

11.5.3 Clinical aspects

Ejection fraction

I did not collect data on ejection fraction (EF). The EF is the fraction of blood pumped out of a ventricle with each heart beat. Studies have shown that HRV is reduced in those individuals with a reduced EF, that is those patients with poor left ventricular function (LVF) or heart failure (Nolan et al., 1998). Although, the participants were screened for exclusion of chronic disease or cardiac failure, objective measurements of cardiac status using the EF would have confirmed this. Unfortunately, the three hospitals varied in their reporting of ejection fraction data within the angiogram report.

ECG

I chose to use 3 channel, 6 patient cable lead instead of a 12 patient cable lead in the interest of balancing the highest probability of detecting ischaemic episodes on the ECG recording, versus the acceptability and comfort of wearing the number of electrodes for 24 hours. The ECG monitor was lightweight to carry on a belt, but awkward to wear at night time. A minority of participants developed an allergic skin reaction to the electrode gel pads, despite purchase of a specific type for sensitive skin ('skin sensor' pads) and two participants' electrodes were displaced during recordings by their daily physical activity. Fortunately, with these cases, ECG information was still available from the remaining electrodes.

Use of beta blocker medication

The ECG recordings revealed a lower frequency of ST ischaemic episodes than would be expected for patients with symptoms awaiting an angiogram. Of the SIS study sample, only nine people had ST depression or TMI on ECG. One reason may be that 67% of the sample was on beta blocker medication, which leads to an increase in the

parasympathetic drive, reduction in blood pressure, and prevents cardiac ischaemia. To increase the frequency of detection of ischaemic changes and HRV, it may have been better to increase the length of the monitoring period to 48 hours but this would be less acceptable to the patients. An alternative would have been to recruit the participants off cardiac medication like beta blockers; however, this would have been not ethically acceptable. The TMI studies of post MI patients have been with patients who are medication-free (Barry et al., 1998, Gabbay et al., 1996, Krantz et al., 1994, Gullette et al. 1997), but these studies were carried out in the late 1980's and 1990's, and ethical guidelines have changed since then. All patients recruited in the study were suspected of CAD, awaiting confirmatory angiography, and hence put on beta blocker medication to reduce the frequency of angina symptoms, control risk factors, and reduce the risk of a full blown cardiac event prior to the angiogram.

HRV measures

There are multiple measures of HRV that are available and a selection of time and frequency domain measures were used to reflect a range of HRV measures that would be consistent with each other. The Task Force (1996) recommendations state that for 24 hour ECG recordings, the results of time domain measures are equivalent to those of frequency domain measures. A limitation in the findings of the SIS study is that the effects described in the frequency domain, for example a reduction in LF prior to the ischaemic episodes, are not supported by consistent findings in the time domain measures, such as RMSSD. This may be due to the small sample size. Although there is good evidence relating alteration in HRV with development of CAD and prognosis post MI, when interpreting these HRV measures, it must be remembered that the relative contributions of sympathetic and parasympathetic activity to these HRV indices cannot be precisely specified as they are influenced by other physiological factors. In contrast

to healthy people, in HRV studies of cardiac patients, HF power can be confounded by non-respiratory arrhythmia thus exaggerating the magnitude of HF and thus not reflect vagal moderation of HR (Stein et al., 1999).

Definition of CAD

Another slight limitation with this study was the exact definition of the groups 'CAD positive' and 'CAD negative'. CAD positive patients were those defined as having symptoms, positive tests and an angiogram showing one or more vessels stenosed at greater than 50%. Other participants showed angiogram findings of only mild atheroma, or two or three diseased vessels. With a larger sample, it would have been feasible to classify these findings according to the number of diseased vessels. A proportion of the sample did not eventually undergo an angiogram procedure due to not having any further symptoms or changing their mind about having the procedure done. If these patients had no prior history of CAD and declined the procedure, it was assumed they were CAD negative. There is a possibility that including them in the data set may have overestimated the number of CAD negative people. Additionally, the CAD positive patients did not necessarily consist of the same group of patients who exhibited ECG ischaemic changes.

A proportion of patients were found to have normal angiogram results despite reporting symptoms of chest pain or undergoing positive exercise tests or a positive myocardial perfusion scan. Whilst this is not a limitation to the study, it highlights how variable the sensitivity and specificity of the exercise ECG treadmill tests (ETT) and myocardial perfusion scans are (Fleischmann et al., 1998; Marwick et al., 1992).

11.5.4 Physical activity

In order to assess the relative impact of affective states on cardiac function, the effect of physical activity needs to be statistically controlled, as everyday physical activity has been associated with ischaemic episodes (Gullette et al., 1997; Gabbay et al., 1996). Time constraints have prevented physical activity from being taken into account in this study in the analysis of ischaemic changes. However, these analyses are planned for the near future. Actogram data will be used to statistically control for physical activity and it is possible that the association between negative mood and ischaemic ECG changes will be accentuated independent of physical activity. Additionally, the DRM did provide data regarding activity and mood throughout the monitoring period, which will be used to confirm findings on the actogram in future analyses.

11.5.5 DRM

The new DRM tool, whilst having the advantages of reducing participant burden in the study and not missing important incidents in the day, is dependent on accurate recall of activities and emotional experiences. It has been argued that affective experience as assessed by the DRM is less dependent on comparison standards and global prototypic evaluations than by questionnaire measures (Kahneman et al., 2004). For example, when people are asked to make global judgements such as how much they enjoy spending time with their children, they make prototypical positive evaluations. However, the DRM reveals that the time actually spent with children is often not rated as enjoyable or satisfying on a day to day basis, and that other activities are rated far more positively (Kahneman et al., 2006). It is possible that the interaction with the interviewer (researcher) face to face will have influenced affective descriptions for certain activities (for example, argument with spouse, school run with child).

Although, the DRM burdened the participants less than studies using diary methods (Gullette et al., 1997; Gabbay et al., 1996), the one hour DRM interview was found to be time consuming, laborious and repetitive by some of the participants. An alternative method of carrying out the DRM would be for an on-line computer questionnaire in which the participants completed it in their own time and with no influence from the interviewer.

A longer ECG recording or DRM interview assessing mood over 48 hours may have picked up more changes in HRV with relation to various emotions. In addition, because of the simultaneous occurrences of multiple activities during daily life, particularly those activities being reported together (for example, cooking with friends), it may be difficult to specify independent emotional triggers relating to HRV. Another limitation to the study is that DRM analyses on data concerning activities and social interaction measures have not been carried out. All the analyses are based on mood, but the DRM also provides rich data on how people spent their time, and how they felt when they were involved in different activities.

11.5.6 Cortisol

Salivary sampling of cortisol nine times over a 24-hour period is satisfactory and was acceptable to the majority of patients. However, it would have been interesting to have taken samples on more than one day to assess the CAR on two consecutive mornings, to measure the consistency of the diurnal pattern. Discrepancies can occur between studies measuring cortisol values and depression, as depressed individuals may be less inclined to accurately adhere to protocols. There was an absence of adherence monitoring of the salivary cortisol sampling. While the actigraph can confirm to a high degree, the time of awakening, there is no comparable assessment of whether the saliva

sample was collected within the appropriate time periods and whether the patient stayed in bed for the first sample of the day. An alternative approach would be to place the salivette in a MemsCap bottle which records the date/time of opening, and thereby provides a better index of adherence than self-report.

It has also been shown that a potential confounding factor for the CAR is sensitivity to light (Clow et al., 2004). These samples were collected from participants across a whole range of seasons in which the different environmental exposure to light for the participants may have affected the results.

A strength of the study is that patients were studied prior to a diagnosis of CAD, so both investigator and research participant were blind to the final diagnosis of their symptoms. However, each of these patients was being referred for cardiac catheterization which may have affected mood prior to this procedure. It could be anticipated that some degree of anxiety or stress was in process, causing the associated neuroendocrine activation. For others, it may be reassuring that something active was being done about their problem. So despite not knowing the angiogram results, it is not guaranteed that mood was unaffected prior to knowledge of actual disease, in these patients with suspected CAD.

ACCENT study

11.5.7 Follow up

A satisfactory follow up rate is important to ensure the findings are not biased and are representative across the patient sample. For instance, it is possible that the more depressed people after an MI declined follow up and dropped out of the study. If so, analysis of the remaining sample may have underestimated the effect that depression has

on cardiac prognosis. Follow up of patients proved to be particularly difficult, especially as the time from the initial phase of the study had increased. A substantial proportion of the patients had either passed away from cardiac or non-cardiac causes or moved address. A few participants declined to take part in further follow up or had difficulty completing the questionnaire due to increasing ill health. Following up non respondents was addressed by searching computerised patient records at the hospital of their original admission for ACS.

11.5.8 Return to work

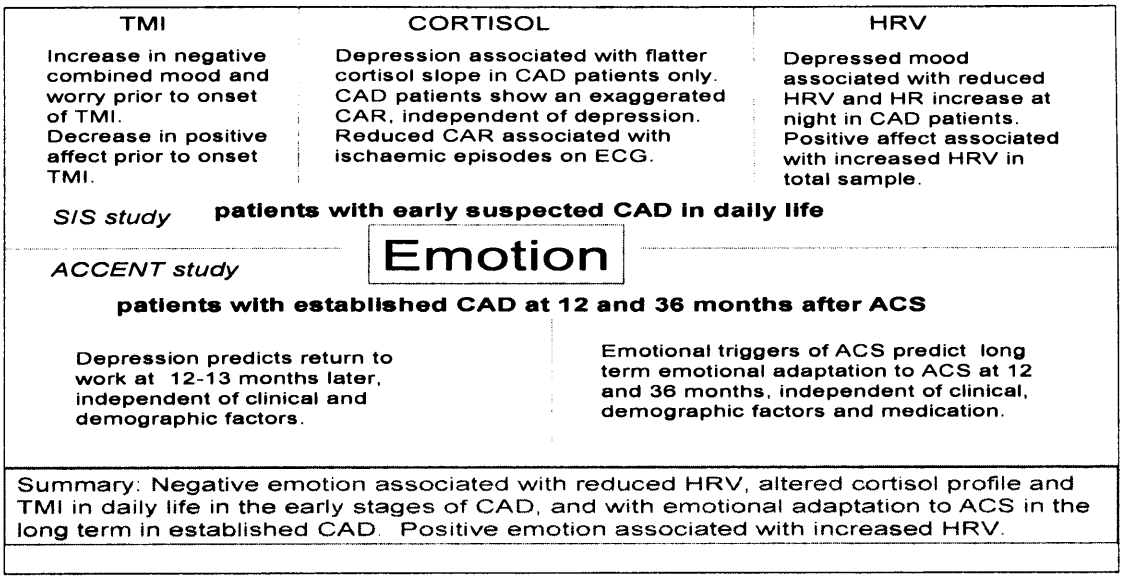
In the return to work analysis, the main outcome measure was whether participants were working or not at 12 months follow up. Information was collected about whether the participants' level of work commitments had changed because of the ACS, and about exactly when they returned to work. These factors were not associated with depression in hospital, but the quality of data was somewhat suspect. Patients were asked about timing at 12 months, and they may not accurately have recalled exactly when they resumed work. It should also be emphasised that the return to work measure was self-reported, and I was not able to corroborate it with objective measures.

11.5.9 Triggering of ACS

All patients' description of possible triggers in the hour or two prior to the MI were self-reported with no objective outside verification, for example, by a spouse. In addition, only a very small number of physical exertion trigger cases were reported and so this may have biased results in the follow up analysis of emotional and physical triggers of ACS and later adaptation.

11.6 Key message

Figure 11.2: Key messages



11.7 Future plans

To build on the present findings from these three studies, I would like to focus on a number of areas.

The SIS study utilised cross-sectional data and therefore associations between mood and reduced HRV and ischaemic episodes cannot infer causality and a preferable methodology is follow up longitudinal studies or case-control designs.

It would be interesting to repeat the study with a much larger sample of patients and comparable healthy participants and analyse the associations between a wider range of variables (time and frequency domains) and the specific emotions as assessed by the DRM.

I think it would be interesting to further our study by analysing different types of CAD patients; that is comparing HRV changes associated with ischaemia and mood in these SIS patients with established CAD patients post ACS or after cardiac surgery or patients with congestive heart failure. HRV changes may only occur in specific types / subgroups of cardiac patients and not others. Additionally, gender differences (Thayer et al., 1996) and ethnicity differences (Liao et al., 1995; Wang et al., 2005) in HRV have been found, and this is an area to explore further.

It would be interesting to further examine the cohort of patients in the SIS study prospectively, to see if reduced HRV associated with negative affect in daily life in the participants predicts cardiac mortality/morbidity at one or three year follow up, although this study may not have a big enough patient sample to show any statistical differences.

As differing symptoms (cognitive versus somatic) of depression were found to differentially relate to variables of HRV (De Jonge et al., 2007); an intervention trial could be undertaken in which the patient group who showed an increase in depressive symptoms could be recruited and divided into two groups. One group could undertake a 12 week course of antidepressant treatment and another group could undergo cognitive behavioural therapy. HRV and cortisol measures could be assessed along with DRM mood after 3 months to see if there is any improvement in HRV or cortisol profiles.

The cortisol diurnal profile was analysed in relation to mood as measured by the BDI but not related to the mood profile as measured by the DRM in the day. Previous studies have examined cortisol profiles in relation to daily negative events in predominantly healthy people. In the study by Peeters et al. (2003), patients with a major depressive disorder were investigated by ESM. In contrast to healthy participants, the depressed group showed a blunted response to daily negative events. In a study by Smyth et al. (1998), increased negative affect in response to current daily stress or

anticipated stress was associated with elevated cortisol levels and conversely, increased positive affect was associated with decreased cortisol levels. It would be interesting to analyse associations between cortisol values and the cortisol awakening response and aggregate scores of specific emotional states as measured by the DRM in daily life, in both cardiac patients and age and sex matched healthy controls from a GP database.

The HPA response to daily stressors over a long period of time remains to be demonstrated. Whilst there have been plenty of cross-sectional studies linking cortisol to mood and stress in daily life, there have been few prospective studies determining whether daily emotional stress predicts future health outcomes. Negative affect may mediate the association seen between stress and cortisol, either by affect influencing the perception of daily events or being related to a heightened physiological effect of stress (Van Eck et al., 1996, Smyth et al., 1998). Two questionnaires were completed-the first just before the interview and the second at 6 months. To detect any longer term adaptation after the CAD diagnosis, the SIS study patients could be followed up prospectively at one year and three years by repeat questionnaire, along with the measurements of related physiological correlates such as the ANS, and salivary cortisol assessment. This would show whether repeated daily alterations in the HRV indices or cortisol slope over time are associated with an alteration in trait BDI score with a consequent long term effect on cardiovascular health, in terms of new cardiac events or re-admission or change in quality of life.

Finally, the SIS study investigated temporal variation in HRV, cortisol and mood across the day, focusing on differences between depressed and non-depressed individuals and between groups of CAD and non-CAD patients. However, all the results from the SIS study so far, are based on between-person analyses. DRM analyses could include the relationship between the patient's activities and who they were with at the time of the

ischaemic episode. These data lend themselves well to within-person analyses using multilevel modelling, looking at co-variation between mood, activities and physiology.

11.8 Clinical implications

The clinical implications of identifying emotional stimuli as triggers of ACS either at an early stage of CAD before an MI has occurred, or at an advanced stage of disease in which patients have been hospitalised for ACS, are related both to prognosis and prevention. From the prognostic perspective, emotional triggering may imply a special vulnerability to interpersonal events, which places certain types of patients at high risk.

A range of clinical management strategies can be directed against the risk of triggering of ACS, by reducing exposure to known emotional or physical triggers in daily life, either in patients with early suspected CAD or in patients recovering from an ACS event. Precautions could be taken that heighten alertness to high risk situations to ameliorate the impact of these triggers. A good example is regular physical exercise training for reducing the risk of triggering by physical exertion (Willich et al., 1993; Mittleman et al., 1993). The onset of ACS during vigorous exercise is greatly lessened in people who are physically fit and exercise regularly.

Prevention of emotional triggering is more difficult than physical triggers. This is because the absolute rates are of low intensity especially in daily life. So even in high risk cases, the chances of a trigger stimulus actually inducing an ACS on any particular occasion are low. Informing patients about the possible dangers of emotional triggers must be handled delicately, since it is important not to give the impression that all

excitement and intense emotion should be avoided (for example, attending a football match), or that the patient should withdraw into a restricted style of living (Thompson et al., 2000). Patients should be reassured that the absolute risk levels are low even though relative risk may be high.

Nevertheless, there are cognitive behavioural therapies that can assist people with the inappropriate or excessive expression of emotions, such as anxiety, worry, and distress. High levels of worry predicted a worse physical health status at 6 months independently of covariates (chapter 8 SIS study 6 month follow up results) whereas anxiety at both 12 and 36 months was predicted by emotional triggering of ACS. Anxiety management programmes can help people escape from the cycle of negative thoughts, identify unreasonable fears and encourage a more realistic appraisal of the situation with its probable risks, and replace it with more measured methods of coping. Similarly, stress management training can help people cope with apparently overwhelming demands by more effective time management, prioritising, and reappraisal of the importance of different pressures. A study by Blumenthal et al. (2002) was carried out in which 94 male CAD out-patients were randomly assigned to a stress management programme, exercise regime, or usual care. After 5 years, stress management was associated with a significant reduction in clinical CAD events compared with usual care over each of the first two years and after five years.

Pharmacological methods may also be appropriate, including beta blockers. Depressed mood has been associated with reduced HRV. Activity induced changes in the sympatho-vagal balance have been implicated in triggering of ischaemia. The SIS study showed a reduced frequency of ischaemic episodes possibly due to patients being on beta blocker medication. Beta blockade may thus, in theory, be beneficial in treatment by reducing cardiac demand. Reduction of the sympathetic drive by beta

blockers may also attenuate the natural haemodynamic responses evoked by anxiety or panic. However, the use of pharmacological methods requires fuller evaluation; while some studies suggest that emotional triggering is less common in patients taking beta blockers (Culic et al., 2004), this is not a universal finding (Strike et al., 2006).

11.9 Conclusion

In combination, the SIS study and the two studies from the ACCENT study add to the literature relating emotional factors to cardiac health. They suggest that negative emotions in daily life as measured by a new tool, the DRM, and negative trait affect contribute both to the onset of acute cardiac events in susceptible patients and that negative emotions are related to impaired long term adaptation following ACS.

The studies indicate that the pathophysiological processes underlying emotional triggering include the neuroendocrine and autonomic processes stimulating rhythm disturbances, which may promote plaque rupture, thrombosis formation, and cardiac ischaemia.

The results from these studies promises important insight into the timing of acute cardiac events and implications for rapid recovery after ACS, opening up possibilities for new methods of clinical management. The effectiveness of such techniques in clinical practice remains to be demonstrated empirically. By further understanding how emotional factors relate to cardiac health, clinicians can risk-stratify psychologically vulnerable individuals and apply a more individually tailored management programme (both pharmacological and non pharmacological). Focusing on the psychological

environment of the patient in addition to treating the standard biological risk factors will ultimately provide greater benefit to the patients' cardiac health and well being.

REFERENCES

Aardal-Eriksson, E., Eriksson, T. E., & Thorell, L. H. (2001). Salivary cortisol, posttraumatic stress symptoms, and general health in the acute phase and during 9-month follow-up. *Biol.Psychiatry, 50,* 986-993.

Adam, E. K. & Gunnar, M. R. (2001). Relationship functioning and home and work demands predict individual differences in diurnal cortisol patterns in women. *Psychoneuroendocrinology, 26,* 189-208.

Adam, E. K., Hawkley, L. C., Kudielka, B. M., & Cacioppo, J. T. (2006). Day-to-day dynamics of experience--cortisol associations in a population-based sample of older adults. *Proc.Natl.Acad.Sci.U.S.A, 103,* 17058-17063.

Adam, T. C. & Epel, E. S. (2007). Stress, eating and the reward system. *Physiol Behav., 91,* 449-458.

Ahern, D. K., Gorkin, L., Anderson, J. L., Tierney, C., Hallstrom, A., Ewart, C. et al. (1990). Biobehavioral variables and mortality or cardiac arrest in the Cardiac Arrhythmia Pilot Study (CAPS). *Am.J Cardiol., 66,* 59-62.

Albert, C. M., Chae, C. U., Rexrode, K. M., Manson, J. E., & Kawachi, I. (2005). Phobic anxiety and risk of coronary heart disease and sudden cardiac death among women. *Circulation, 111,* 480-487.

Allan, J. L., Johnston, D. W., Johnston, M., & Mant, D. (2007). Depression and perceived behavioral control are independent predictors of future activity and fitness after coronary syndrome events. *J.Psychosom.Res., 63,* 501-508.

Allgulander, C. & Lavori, P. W. (1991). Excess mortality among 3302 patients with 'pure' anxiety neurosis. *Arch.Gen.Psychiatry, 48,* 599-602.

Alter, D. A., Venkatesh, V., & Chong, A. (2006). Evaluating the performance of the Global Registry of Acute Coronary Events risk-adjustment index across socio-economic strata among patients discharged from the hospital after acute myocardial infarction. *Am.Heart J., 151,* 323-331.

Ammann, P., Pfisterer, M., Fehr, T., & Rickli, H. (2004). Raised cardiac troponins. *BMJ, 328,* 1028-1029.

Anda, R., Williamson, D., Jones, D., Macera, C., Eaker, E., Glassman, A. et al. (1993). Depressed affect, hopelessness, and the risk of ischemic heart disease in a cohort of U.S. adults. *Epidemiology, 4,* 285-294.

Angerer, P., Siebert, U., Kothny, W., Muhlbauer, D., Mudra, H., & von Schacky, C. (2000). Impact of social support, cynical hostility and anger expression on progression of coronary atherosclerosis. *J.Am.Coll.Cardiol., 36,* 1781-1788.

Antelmi, I., de Paula, R. S., Shinzato, A. R., Peres, C. A., Mansur, A. J., & Grupi, C. J. (2004). Influence of age, gender, body mass index, and functional capacity on heart rate variability in a cohort of subjects without heart disease. *Am.J.Cardiol., 93,* 381-385.

Ariyo, A. A., Haan, M., Tangen, C. M., Rutledge, J. C., Cushman, M., Dobs, A. et al. (2000). Depressive symptoms and risks of coronary heart disease and mortality in elderly Americans. Cardiovascular Health Study Collaborative Research Group. *Circulation, 102,* 1773-1779.

Aromaa, A., Raitasalo, R., Reunanen, A., Impivaara, O., Heliovaara, M., Knekt, P. et al. (1994). Depression and cardiovascular diseases. *Acta Psychiatr.Scand.Suppl, 377,* 77-82.

Aronow, W. S. & Ahn, C. (1998). Risk factors for new coronary events in older African-American men and women. *Am.J.Cardiol., 82,* 902-904.

Bacon, S. L., Watkins, L. L., Babyak, M., Sherwood, A., Hayano, J., Hinderliter, A. L. et al. (2004). Effects of daily stress on autonomic cardiac control in patients with coronary artery disease. *Am.J.Cardiol., 93,* 1292-1294.

Bacon, S. L., Ring, C., Hee, F. L., Lip, G. Y., Blann, A. D., Lavoie, K. L. et al. (2006). Hemodynamic, hemostatic, and endothelial reactions to psychological and physical stress in coronary artery disease patients. *Biol.Psychol., 71,* 162-170.

Bain, R. J., Poeppinghaus, V. J., Jones, G. M., & Peaston, M. J. (1989). Cortisol level predicts myocardial infarction in patients with ischaemic chest pain. *Int.J.Cardiol., 25,* 69-72.

Balady, G. J., Williams, M. A., Ades, P. A., Bittner, V., Comoss, P., Foody, J. M. et al. (2007). Core components of cardiac rehabilitation/secondary prevention programs: 2007 update: a scientific statement from the American Heart Association Exercise, Cardiac Rehabilitation, and Prevention Committee, the Council on Clinical Cardiology; the Councils on Cardiovascular Nursing, Epidemiology and Prevention, and Nutrition, Physical Activity, and Metabolism; and the American Association of Cardiovascular and Pulmonary Rehabilitation. *Circulation, 115,* 2675-2682.

Balog, P., Janszky, I., Leineweber, C., Blom, M., Wamala, S. P., & Orth-Gomer, K. (2003). Depressive symptoms in relation to marital and work stress in women with and without coronary heart disease. The Stockholm Female Coronary Risk Study. *J.Psychosom.Res., 54,* 113-119.

Barefoot, J. C., Dahlstrom, W. G., & Williams, R. B., Jr. (1983). Hostility, CHD incidence, and total mortality: a 25-year follow-up study of 255 physicians. *Psychosom.Med., 45,* 59-63.

Barefoot, J. C., Dodge, K. A., Peterson, B. L., Dahlstrom, W. G., & Williams, R. B. (1989). The Cook-Medley Hostility Scale - Item Content and Ability to Predict Survival. *Psychosomatic Medicine, 51,* 46-57.

Barefoot, J. C., Larsen, S., von der, L. L., & Schroll, M. (1995). Hostility, incidence of acute myocardial infarction, and mortality in a sample of older Danish men and women. *Am.J.Epidemiol., 142,* 477-484.

Barefoot, J. C. & Schroll, M. (1996). Symptoms of depression, acute myocardial infarction, and total mortality in a community sample. *Circulation, 93,* 1976-1980.

Barefoot, J. C., Helms, M. J., Mark, D. B., Blumenthal, J. A., Califf, R. M., Haney, T. L. et al. (1996). Depression and long term mortality risk in patients with coronary artery disease. *Am.J.Cardiol., 78,* 613-617.

Barefoot, J. C. (1997). Depression and coronary heart disease. *Cardiologia, 42,* 1245-1250.

Barlow, D. H. & Campbell, L. A. (2000). Mixed anxiety-depression and its implications for models of mood and anxiety disorders. *Compr.Psychiatry, 41,* 55-60.

Barnett, A. G. & Dobson, A. J. (2005). Excess in cardiovascular events on Mondays: a meta-analysis and prospective study. *J.Epidemiol.Community Health, 59,* 109-114.

Barnett, R. C., Steptoe, A., & Gareis, K. C. (2005). Marital-role quality and stress-related psychobiological indicators. *Ann.Behav.Med., 30,* 36-43.

Barry, J., Selwyn, A. P., Nabel, E. G., Rocco, M. B., Mead, K., Campbell, S. et al. (1988). Frequency of ST-segment depression produced by mental stress in stable angina pectoris from coronary artery disease. *Am.J.Cardiol., 61,* 989-993.

Bass, C. & Mayou, R. (2002). Chest pain. *BMJ, 325,* 588-591.

Beck, A. T., Steer, R. A., & Garbin, M. G. (1988). Psychometric Properties of the Beck Depression Inventory - 25 Years of Evaluation. *Clinical Psychology Review, 8,* 77-100.

Beck, C. A., Joseph, L., Belisle, P., & Pilote, L. (2001). Predictors of quality of life 6 months and 1 year after acute myocardial infarction. *Am.Heart J., 142,* 271-279.

Behar, S., Halabi, M., Reicher-Reiss, H., Zion, M., Kaplinsky, E., Mandelzweig, L. et al. (1993). Circadian variation and possible external triggers of onset of myocardial infarction. SPRINT Study Group. *Am.J.Med., 94,* 395-400.

Berkman, L. F. & Syme, S. L. (1979). Social networks, host resistance, and mortality: a nine-year follow-up study of Alameda County residents. *Am.J.Epidemiol., 109,* 186-204.

Berkman, L. F., Leosummers, L., & Horwitz, R. I. (1992). Emotional Support and Survival After Myocardial-Infarction - A Prospective, Population-Based Study of the Elderly. *Annals of Internal Medicine, 117,* 1003-1009.

Berkman, L. F. (1995). The role of social relations in health promotion. *Psychosom.Med., 57,* 245-254.

Berkman, L. F., Blumenthal, J., Burg, M., Carney, R. M., Catellier, D., Cowan, M. J. et al. (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. *JAMA, 289,* 3106-3116.

Bernardi, L., Valle, F., Coco, M., Calciati, A., & Sleight, P. (1996). Physical activity influences heart rate variability and very-low-frequency components in Holter electrocardiograms. *Cardiovasc.Res., 32,* 234-237.

Bertrand, M. E., Simoons, M. L., Fox, K. A., Wallentin, L. C., Hamm, C. W., McFadden, E. et al. (2002). Management of acute coronary syndromes in patients presenting without persistent ST-segment elevation. *Eur.Heart J., 23,* 1809-1840.

Bhagwagar, Z., Hafizi, S., & Cowen, P. J. (2003). Increase in concentration of waking salivary cortisol in recovered patients with depression. *Am.J.Psychiatry, 160,* 1890-1891.

Bhattacharyya, M. R., Perkins-Porras, L., Whitehead, D. L., & Steptoe, A. (2007). Psychological and clinical predictors of return to work after acute coronary syndrome. *Eur.Heart J., 28,* 160-165.

Bhattacharyya, M. R. & Steptoe, A. (2007). Emotional triggers of acute coronary syndromes: strength of evidence, biological processes, and clinical implications. *Prog.Cardiovasc.Dis., 49,* 353-365.

Bigger, J. T., Jr., Fleiss, J. L., Steinman, R. C., Rolnitzky, L. M., Kleiger, R. E., & Rottman, J. N. (1992). Correlations among time and frequency domain measures of heart period variability two weeks after acute myocardial infarction. *Am.J.Cardiol., 69,* 891-898.

Bigger, J. T., Jr., Rolnitzky, L. M., Steinman, R. C., & Fleiss, J. L. (1994). Predicting mortality after myocardial infarction from the response of RR variability to antiarrhythmic drug therapy. *J.Am.Coll.Cardiol., 23,* 733-740.

Billing, E., Bar-On, D., & Rehnqvist, N. (1997). Determinants of lifestyle changes after a first myocardial infarction. *Cardiology, 88,* 29-35.

Birnbaum, Y., Kloner, R. A., Perritt, R., & Poole, K. (1997). Atherosclerotic cardiovascular mortality during the 1992 riots in Los Angeles. *Am.J.Cardiol., 79,* 1155-1158.

Blumenthal, J. A., Barefoot, J., Burg, M. M., & Williams, R. B., Jr. (1987). Psychological correlates of hostility among patients undergoing coronary angiography. *Br.J.Med.Psychol., 60 (Pt 4),* 349-355.

Blumenthal, J. A., Jiang, W., Waugh, R. A., Frid, D. J., Morris, J. J., Coleman, R. E. et al. (1995). Mental Stress-Induced Ischemia in the Laboratory and Ambulatory Ischemia During Daily-Life - Association and Hemodynamic Features. *Circulation, 92,* 2102-2108.

Blumenthal, J. A., Babyak, M., Wei, J., O'Connor, C., Waugh, R., Eisenstein, E. et al. (2002). Usefulness of psychosocial treatment of mental stress-induced myocardial ischemia in men. *Am.J.Cardiol., 89,* 164-168.

Bolger, N., Davis, A., & Rafaeli, E. (2003). Diary methods: Capturing life as it is lived. *Annual Review of Psychology, 54,* 579-616.

Boltwood, M. D., Taylor, C. B., Burke, M. B., Grogin, H., & Giacomini, J. (1993). Anger report predicts coronary artery vasomotor response to mental stress in atherosclerotic segments. *Am.J.Cardiol., 72,* 1361-1365.

Bosma, H., Marmot, M. G., Hemingway, H., Nicholson, A. C., Brunner, E., & Stansfeld, S. A. (1997). Low job control and risk of coronary heart disease in Whitehall II (prospective cohort) study. *BMJ, 314,* 558-565.

Bosma, H., Peter, R., Siegrist, J., & Marmot, M. (1998). Two alternative job stress models and the risk of coronary heart disease. *Am.J.Public Health, 88,* 68-74.

Bosma, H., Stansfeld, S. A., & Marmot, M. G. (1998). Job control, personal characteristics, and heart disease. *J.Occup.Health Psychol., 3,* 402-409.

Bouchard, T. J., Jr. (1994). Genes, environment, and personality. *Science, 264,* 1700-1701.

Boudrez, H., De Backer, G., & Comhaire, B. (1994). Return to work after myocardial infarction: results of a longitudinal population based study. *Eur.Heart J., 15,* 32-36.

Boudrez, H. & De Backer, G. (2000). Recent findings on return to work after an acute myocardial infarction or coronary artery bypass grafting. *Acta Cardiol., 55,* 341-349.

Brantley, P. J., Dietz, L. S., McKnight, G. T., Jones, G. N., & Tulley, R. (1988). Convergence between the Daily Stress Inventory and endocrine measures of stress. *J.Consult Clin.Psychol., 56,* 549-551.

Brink, E., Grankvist, G., Karlson, B. W., & Hallberg, L. R. (2005). Health-related quality of life in women and men one year after acute myocardial infarction. *Qual.Life Res., 14,* 749-757.

Broadley, A. J., Korszun, A., Abdelaal, E., Moskvina, V., Jones, C. J., Nash, G. B. et al. (2005). Inhibition of cortisol production with metyrapone prevents mental stress-induced endothelial dysfunction and baroreflex impairment. *J.Am.Coll.Cardiol., 46,* 344-350.

Brotman, D. J., Girod, J. P., Garcia, M. J., Patel, J. V., Gupta, M., Posch, A. et al. (2005). Effects of short-term glucocorticoids on cardiovascular biomarkers. *J.Clin.Endocrinol.Metab, 90,* 3202-3208.

Brotman, D. J., Golden, S. H., & Wittstein, I. S. (2007). The cardiovascular toll of stress. *Lancet, 370,* 1089-1100.

Brown, A. D. & Garber, A. M. (1998). Cost effectiveness of coronary heart disease prevention strategies in adults. *Pharmacoeconomics., 14,* 27-48.

Brown, D. L. (1999). Disparate effects of the 1989 Loma Prieta and 1994 Northridge earthquakes on hospital admissions for acute myocardial infarction: importance of superimposition of triggers. *Am.Heart J., 137,* 830-836.

Brown, N., Melville, M., Gray, D., Young, T., Munro, J., Skene, A. M. et al. (1999). Quality of life four years after acute myocardial infarction: short form 36 scores compared with a normal population. *Heart, 81,* 352-358.

Brunekreef, B. & Hoek, G. (2002). No association between major football games and cardiovascular mortality. *Epidemiology, 13,* 491-492.

Brydon, L., Edwards, S., Jia, H., Mohamed-Ali, V., Zachary, I., Martin, J. F. et al. (2005). Psychological stress activates interleukin-1beta gene expression in human mononuclear cells. *Brain Behav.Immun., 19,* 540-546.

Buchanan, L. M., Cowan, M., Burr, R., Waldron, C., & Kogan, H. (1993). Measurement of recovery from myocardial infarction using heart rate variability and psychological outcomes. *Nurs.Res., 42,* 74-78.

Buchanan, T. W. (2007). Retrieval of emotional memories. *Psychol.Bull., 133,* 761-779.

Cameron, L. D., Petrie, K. J., Ellis, C., Buick, D., & Weinman, J. A. (2005). Symptom experiences, symptom attributions, and causal attributions in patients following first-time myocardial infarction. *Int.J.Behav.Med., 12,* 30-38.

Camm, A. J., Pratt, C. M., Schwartz, P. J., Al Khalidi, H. R., Spyt, M. J., Holroyde, M. J. et al. (2004). Mortality in patients after a recent myocardial infarction: a randomized, placebo-controlled trial of azimilide using heart rate variability for risk stratification. *Circulation, 109,* 990-996.

Campbell, S., Rocco, M. B., Nabel, E. G., Barry, J., Rebecca, G. S., Deanfield, J. E. et al. (1986). Factors determining the activity of ischemic heart disease. *Am.J.Med., 80,* 9-17.

Carels, R. A., Blumenthal, J. A., & Sherwood, A. (2000). Emotional responsivity during daily life: relationship to psychosocial functioning and ambulatory blood pressure. *International Journal of Psychophysiology, 36,* 25-33.

Carney, R. M., Rich, M. W., teVelde, A., Saini, J., Clark, K., & Freedland, K. E. (1988). The relationship between heart rate, heart rate variability and depression in patients with coronary artery disease. *J.Psychosom.Res., 32,* 159-164.

Carney, R. M., Rich, M. W., Freedland, K. E., Saini, J., teVelde, A., Simeone, C. et al. (1988). Major depressive disorder predicts cardiac events in patients with coronary artery disease. *Psychosom.Med., 50,* 627-633.

Carney, R. M., Freedland, K. E., Smith, L., Lustman, P. J., & Jaffe, A. S. (1991). Relation of depression and mortality after myocardial infarction in women. *Circulation, 84,* 1876-1877.

Carney, R. M., Freedland, K. E., Clark, K. A., Skala, J. A., Smith, L. J., Delamater, A. et al. (1992). Psychosocial adjustment of patients arriving early at the emergency department after acute myocardial infarction. *Am.J.Cardiol., 69,* 160-162.

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. *Am.J.Med., 95,* 23-28.

Carney, R. M., Saunders, R. D., Freedland, K. E., Stein, P., Rich, M. W., & Jaffe, A. S. (1995). Association of depression with reduced heart rate variability in coronary artery disease. *Am.J.Cardiol., 76,* 562-564.

Carney, R. M., Freedland, K. E., Sheline, Y. I., & Weiss, E. S. (1997). Depression and coronary heart disease: a review for cardiologists. *Clin.Cardiol., 20,* 196-200.

Carney, R. M., Freedland, K. E., & Stein, P. K. (2000). Anxiety, depression, and heart rate variability. *Psychosom.Med., 62,* 84-87.

Carney, R. M., Blumenthal, J. A., Stein, P. K., Watkins, L., Catellier, D., Berkman, L. F. et al. (2001). Depression, heart rate variability, and acute myocardial infarction. *Circulation, 104,* 2024-2028.

Carney, R. M., Freedland, K. E., Miller, G. E., & Jaffe, A. S. (2002). Depression as a risk factor for cardiac mortality and morbidity: a review of potential mechanisms. *J.Psychosom.Res., 53,* 897-902.

Carney, R. M., Blumenthal, J. A., Catellier, D., Freedland, K. E., Berkman, L. F., Watkins, L. L. et al. (2003). Depression as a risk factor for mortality after acute myocardial infarction. *Am.J.Cardiol., 92,* 1277-1281.

Carney, R. M. & Freedland, K. E. (2003). Depression, mortality, and medical morbidity in patients with coronary heart disease. *Biol.Psychiatry, 54,* 241-247.

Carney, R. M., Freedland, K. E., & Veith, R. C. (2005). Depression, the autonomic nervous system, and coronary heart disease. *Psychosom.Med., 67 Suppl 1,* S29-S33.

Carney, R. M., Blumenthal, J. A., Freedland, K. E., Stein, P. K., Howells, W. B., Berkman, L. F. et al. (2005). Low heart rate variability and the effect of depression on post-myocardial infarction mortality. *Arch.Intern.Med., 165,* 1486-1491.

Carroll, D., Ebrahim, S., Tilling, K., Macleod, J., & Smith, G. D. (2002). Admissions for myocardial infarction and World Cup football: database survey. *BMJ, 325,* 1439-1442.

Carroll, K., Majeed, A., Firth, C., & Gray, J. (2003). Prevalence and management of coronary heart disease in primary care: population-based cross-sectional study using a disease register. *J.Public Health Med., 25,* 29-35.

Carstensen, L. L., Pasupathi, M., Mayr, U., & Nesselroade, J. R. (2000). Emotional experience in everyday life across the adult life span. *J.Pers.Soc.Psychol., 79,* 644-655.

Case, R. B., Moss, A. J., Case, N., McDermott, M., & Eberly, S. (1992). Living alone after myocardial infarction. Impact on prognosis. *JAMA, 267,* 515-519.

Casscells, W., Hassan, K., Vaseghi, M. F., Siadaty, M. S., Naghavi, M., Kirkeeide, R. L. et al. (2003). Plaque blush, branch location, and calcification are angiographic predictors of progression of mild to moderate coronary stenoses. *Am.Heart J., 145,* 813-820.

Cay, E. L., Vetter, N., Philip, A. E., & Dugard, P. (1972). Psychological reactions to a coronary care unit. *J.Psychosom.Res., 16,* 437-447.

Cay, E. L., Vetter, N. J., & Philips, A. E. (1973). Practical aspects of cardiac rehabilitation: psycho-social factors. *G.Ital.Cardiol., 3,* 646-655.

Cay, E. L., Vetter, N., Philip, A., & Dugard, P. (1973). Return to work after a heart attack. *J.Psychosom.Res., 17,* 231-243.

Chandra, V., Szklo, M., Goldberg, R., & Tonascia, J. (1983). The impact of marital status on survival after an acute myocardial infarction: a population-based study. *Am.J.Epidemiol., 117,* 320-325.

Chaput, L. A., Adams, S. H., Simon, J. A., Blumenthal, R. S., Vittinghoff, E., Lin, F. et al. (2002). Hostility predicts recurrent events among postmenopausal women with coronary heart disease. *Am.J.Epidemiol., 156,* 1092-1099.

Cheng, C., Wong, W. M., Lai, K. C., Wong, B. C., Hu, W. H., Hui, W. M. et al. (2003). Psychosocial factors in patients with noncardiac chest pain. *Psychosom.Med., 65,* 443-449.

Chi, J. S., Poole, W. K., Kandefer, S. C., & Kloner, R. A. (2003). Cardiovascular mortality in New York City after September 11, 2001. *Am.J.Cardiol., 92,* 857-861.

Chi, J. S., Speakman, M. T., Poole, W. K., Kandefer, S. C., & Kloner, R. A. (2003). Hospital admissions for cardiac events in New York City after September 11, 2001. *Am.J.Cardiol., 92,* 61-63.

Chierchia, S., Muiesan, L., Davies, A., Balasubramian, V., Gerosa, S., & Raftery, E. B. (1990). Role of the sympathetic nervous system in the pathogenesis of chronic stable angina. Implications for the mechanism of action of beta-blockers. *Circulation, 82,* II71-II81.

Christensen, J. H., Toft, E., Christensen, M. S., & Schmidt, E. B. (1999). Heart rate variability and plasma lipids in men with and without ischaemic heart disease. *Atherosclerosis, 145,* 181-186.

Clow, A., Thorn, L., Evans, P., & Hucklebridge, F. (2004). The awakening cortisol response: methodological issues and significance. *Stress., 7,* 29-37.

Cohen, S. & Wills, T. A. (1985). Stress, social support, and the buffering hypothesis. *Psychol.Bull., 98,* 310-357.

Cohen, S. (1988). Psychosocial models of the role of social support in the etiology of physical disease. *Health Psychol., 7,* 269-297.

Cohen, S. & Williamson, G. M. (1991). Stress and infectious disease in humans. *Psychol.Bull., 109,* 5-24.

Cohen, S., Kessler, R.C., & Underwood Gordon, L. (Eds.). (1997). *Measuring stress: A guide for health and social scientists.* London: Oxford University Press.

Cohen, S., Doyle, W. J., Skoner, D. P., Rabin, B. S., & Gwaltney, J. M., Jr. (1997). Social ties and susceptibility to the common cold. *JAMA, 277,* 1940-1944.

Cohen, S., Frank, E., Doyle, W. J., Skoner, D. P., Rabin, B. S., & Gwaltney, J. M., Jr. (1998). Types of stressors that increase susceptibility to the common cold in healthy adults. *Health Psychol., 17,* 214-223.

Cohen, S., Doyle, W. J., Turner, R. B., Alper, C. M., & Skoner, D. P. (2003). Emotional style and susceptibility to the common cold. *Psychosom.Med., 65,* 652-657.

Cohen, S. (2004). Social relationships and health. *Am.Psychol., 59,* 676-684.

Colao, A., Pivonello, R., Spiezia, S., Faggiano, A., Ferone, D., Filippella, M. et al. (1999). Persistence of increased cardiovascular risk in patients with Cushing's disease after five years of successful cure. *J.Clin.Endocrinol.Metab, 84,* 2664-2672.

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. *N.Engl.J.Med., 341,* 1351-1357.

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. *Ann.Intern.Med., 132,* 552-555.

Cook W. W and Medley D. M., Proposed hostility and pharisaic-virtue scales for the MMPI, *Journal of Applied Psychology., 38,* 414–418.

Costa, P. T., Zonderman, A. B., Engel, B. T., Baile, W. F., Brimlow, D. L., & Brinker, J. (1985). The relation of chest pain symptoms to angiographic findings of coronary artery stenosis and neuroticism. *Psychosom.Med., 47,* 285-293.

Coyne, J. C., Thompson, R., & Racioppo, M. W. (2001). Validity and efficiency of screening for history of depression by self-report. *Psychol.Assess., 13,* 163-170.

Crowe, J. M., Runions, J., Ebbesen, L. S., Oldridge, N. B., & Streiner, D. L. (1996). Anxiety and depression after acute myocardial infarction. *Heart Lung, 25,* 98-107.

Culic, V., Eterovic, D., Miric, D., Giunio, L., Lukin, A., & Fabijanic, D. (2004). Triggering of ventricular tachycardia by meteorologic and emotional stress: protective effect of beta-blockers and anxiolytics in men and elderly. *Am.J.Epidemiol., 160,* 1047-1058.

Culic, V., Eterovic, D., & Miric, D. (2005). Meta-analysis of possible external triggers of acute myocardial infarction. *Int.J.Cardiol., 99,* 1-8.

Cummins, S. E. & Gevirtz, R. N. (1993). The relationship between daily stress and urinary cortisol in a normal population: an emphasis on individual differences. *Behav.Med., 19,* 129-134.

Curtis, A. L., Bello, N. T., Connolly, K. R., & Valentino, R. J. (2002). Corticotropin-releasing factor neurones of the central nucleus of the amygdala mediate locus coeruleus activation by cardiovascular stress. *J.Neuroendocrinol., 14,* 667-682.

Dargie, H. J., Ford, I., & Fox, K. M. (1996). Total Ischaemic Burden European Trial (TIBET). Effects of ischaemia and treatment with atenolol, nifedipine SR and their combination on outcome in patients with chronic stable angina. The TIBET Study Group. *Eur.Heart J., 17,* 104-112.

Davidson, K. W., Rieckmann, N., & Lesperance, F. (2004). Psychological theories of depression: potential application for the prevention of acute coronary syndrome recurrence. *Psychosom.Med., 66,* 165-173.

Davidson, K. W., Kupfer, D. J., Bigger, J. T., Califf, R. M., Carney, R. M., Coyne, J. C. et al. (2006). Assessment and treatment of depression in patients with cardiovascular disease: National Heart, Lung, and Blood Institute Working Group Report. *Psychosom.Med., 68,* 645-650.

Davies, M. J. (1996). Detecting vulnerable coronary plaques. *Lancet, 347,* 1422-1423.

Davies, M. J. (1996). The contribution of thrombosis to the clinical expression of coronary atherosclerosis. *Thromb.Res., 82,* 1-32.

Davies, R. F., Habibi, H., Klinke, W. P., Dessain, P., Nadeau, C., Phaneuf, D. C. et al. (1995). Effect of amlodipine, atenolol and their combination on myocardial ischemia during treadmill exercise and ambulatory monitoring. Canadian Amlodipine/Atenolol in Silent Ischemia Study (CASIS) Investigators. *J.Am.Coll.Cardiol., 25,* 619-625.

Day, R. C., Freedland, K. E., & Carney, R. M. (2005). Effects of anxiety and depression on heart disease attributions. *Int.J.Behav.Med., 12,* 24-29.

de Clerck, F. (1991). Effects of serotonin on platelets and blood vessels. *J.Cardiovasc.Pharmacol., 17 Suppl 5,* S1-S5.

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. *Psychosom.Med., 69,* 735-739.

Deanfield, J. E., Shea, M., Kensett, M., Horlock, P., Wilson, R. A., de Landsheere, C. M. et al. (1984). Silent myocardial ischaemia due to mental stress. *Lancet, 2,* 1001-1005.

Deanfield, J. E., Detry, J. M., Lichtlen, P. R., Magnani, B., Sellier, P., & Thaulow, E. (1994). Amlodipine reduces transient myocardial ischemia in patients with coronary artery disease: double-blind Circadian Anti-Ischemia Program in Europe (CAPE Trial). *J.Am.Coll.Cardiol., 24,* 1460-1467.

Deanfield, J. E., Detry, J. M., Sellier, P., Lichtlen, P. R., Thaulow, E., Bultas, J. et al. (2002). Medical treatment of myocardial ischemia in coronary artery disease: effect of drug regime and irregular dosing in the CAPE II trial. *J.Am.Coll.Cardiol., 40,* 917-925.

Deedwania, P. C. & Carbajal, E. V. (1990). Prevalence and patterns of silent myocardial ischemia during daily life in stable angina patients receiving conventional antianginal drug therapy. *Am.J.Cardiol., 65,* 1090-1096.

Deedwania, P. C. & Carbajal, E. V. (1990). Silent ischemia during daily life is an independent predictor of mortality in stable angina. *Circulation, 81,* 748-756.

Deedwania, P. C. & Carbajal, E. V. (1992). Role of myocardial oxygen demand in the pathogenesis of silent ischemia during daily life. *Am.J.Cardiol., 70,* 19F-24F.

Deedwania, P. C. (1992). Increased myocardial oxygen demand and ischemia during daily life: resurrection of an age-old concept. *J.Am.Coll.Cardiol., 20,* 1099-1100.

Deedwania, P. C. (1999). Anti-ischemic effects of amlodipine in patients with stable angina pectoris and myocardial ischemia during daily life. Amlodipine Study Group. *Am.J.Cardiol., 83,* 1117-1119.

Deininger, E., Oltmanns, K. M., Wellhoener, P., Fruehwald-Schultes, B., Kern, W., Heuer, B. et al. (2001). Losartan attenuates symptomatic and hormonal responses to hypoglycemia in humans. *Clin.Pharmacol.Ther., 70,* 362-369.

Denollet, J. & De Potter, B. (1992). Coping subtypes for men with coronary heart disease: relationship to well-being, stress and Type-A behaviour. *Psychol.Med., 22,* 667-684.

Denollet, J., Sys, S. U., & Brutsaert, D. L. (1995). Personality and mortality after myocardial infarction. *Psychosom.Med., 57,* 582-591.

Denollet, J., Sys, S. U., Stroobant, N., Rombouts, H., Gillebert, T. C., & Brutsaert, D. L. (1996). Personality as independent predictor of long term mortality in patients with coronary heart disease. *Lancet, 347,* 417-421.

Denollet, J. (1998). Personality and coronary heart disease: The Type-D scale-16 (DS16). *Annals of Behavioral Medicine, 20,* 209-215.

Denollet, J. & Brutsaert, D. L. (1998). Personality, disease severity, and the risk of long term cardiac events in patients with a decreased ejection fraction after myocardial infarction. *Circulation, 97,* 167-173.

Denollet, J., Pedersen, S. S., Vrints, C. J., & Conraads, V. M. (2006). Usefulness of type D personality in predicting five-year cardiac events above and beyond concurrent symptoms of stress in patients with coronary heart disease. *Am.J.Cardiol., 97,* 970-973.

Dias, C. C., Mateus, P., Santos, L., Mateus, C., Sampaio, F., Adao, L. et al. (2005). Acute coronary syndrome and predictors of quality of life. *Rev.Port.Cardiol., 24,* 819-831.

Dickens, C. M., McGowan, L., Percival, C., Douglas, J., Tomenson, B., Cotter, L. et al. (2004). Lack of a close confidant, but not depression, predicts further cardiac events after myocardial infarction. *Heart, 90,* 518-522.

Diener, E. & Emmons, R. A. (1984). The independence of positive and negative affect. *J.Pers.Soc.Psychol., 47,* 1105-1117.

Dobson, A. J., Alexander, H. M., Malcolm, J. A., Steele, P. L., & Miles, T. A. (1991). Heart attacks and the Newcastle earthquake. *Med.J.Aust., 155,* 757-761.

Dockray, S., Bhattacharyya, M. R., Molloy, G. J., & Steptoe, A. (2008). The cortisol awakening response in relation to objective and subjective measures of waking in the morning. *Psychoneuroendocrinology, 33,* 77-82.

Doherty, W. J., Schrott, H. G., Metcalf, L., & Iasiello-Vailas, L. (1983). Effect of spouse support and health beliefs on medication adherence. *J.Fam.Pract., 17,* 837-841.

Dooley, D., Fielding, J., & Levi, L. (1996). Health and unemployment. *Annu.Rev.Public Health, 17,* 449-465.

Dumitrascu, D. L., Hopulele, S., & Baban, A. (1993). Cardiovascular complaints following the uprising of December 1989 in Romania. *Med.War, 9,* 45-51.

Dumville, J. C., Macpherson, H., Griffith, K., Miles, J. N., & Lewin, R. J. (2007). Non-cardiac chest pain: a retrospective cohort study of patients who attended a Rapid Access Chest Pain Clinic. *Fam.Pract., 24,* 152-157.

Eagle, K. A., Berger, P. B., Calkins, H., Chaitman, B. R., Ewy, G. A., Fleischmann, K. E. et al. (2002). ACC/AHA Guideline Update for Perioperative Cardiovascular Evaluation for Noncardiac Surgery--Executive Summary. A report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee to

Update the 1996 Guidelines on Perioperative Cardiovascular Evaluation for Noncardiac Surgery). *Anesth.Analg., 94,* 1052-1064.

Eaker, E. D., Chesebro, J. H., Sacks, F. M., Wenger, N. K., Whisnant, J. P., & Winston, M. (1993). Cardiovascular disease in women. *Circulation, 88,* 1999-2009.

Edwards, S., Evans, P., Hucklebridge, F., & Clow, A. (2001). Association between time of awakening and diurnal cortisol secretory activity. *Psychoneuroendocrinology, 26,* 613-622.

Eller, N. H., Netterstrom, B., & Hansen, A. M. (2003). Cortisol in urine and saliva: relations to the intima media thickness, IMT. Atherosclerosis 159, 175-185. Ref Type: Generic

Emery, C. F., Frid, D. J., Engebretson, T. O., Alonzo, A. A., Fish, A., Ferketich, A. K. et al. (2004). Gender differences in quality of life among cardiac patients. *Psychosom.Med., 66,* 190-197.

Evans, O. & Steptoe, A. (2002). The contribution of gender-role orientation, work factors and home stressors to psychological well-being and sickness absence in male- and female-dominated occupational groups. *Soc.Sci.Med., 54,* 481-492.

Everson, S. A., Lynch, J. W., Chesney, M. A., Kaplan, G. A., Goldberg, D. E., Shade, S. B. et al. (1997). Interaction of workplace demands and cardiovascular reactivity in progression of carotid atherosclerosis: Population based study. *British Medical Journal, 314,* 553-558.

Everson, S. A., Kauhanen, J., Kaplan, G. A., Goldberg, D. E., Julkunen, J., Tuomilehto, J. et al. (1997). Hostility and increased risk of mortality and acute myocardial infarction: the mediating role of behavioral risk factors. *Am.J.Epidemiol., 146,* 142-152.

Failde, I. I. & Soto, M. M. (2006). Changes in Health Related Quality of Life 3 months after an acute coronary syndrome. *BMC.Public Health, 6,* 18.

Fantidis, P., Perez, D. P., Fernandez-Ortiz, A., Carcia-Touchard, A., Alfonso, F., Sabate, M. et al. (2002). Morning cortisol production in coronary heart disease patients. *Eur.J.Clin.Invest, 32,* 304-308.

Ferketich, A. K., Schwartzbaum, J. A., Frid, D. J., & Moeschberger, M. L. (2000). Depression as an antecedent to heart disease among women and men in the NHANES I study. National Health and Nutrition Examination Survey. *Arch.Intern.Med., 160,* 1261-1268.

Fleischmann, K. E., Hunink, M. G., Kuntz, K. M., & Douglas, P. S. (1998). Exercise echocardiography or exercise SPECT imaging? A meta-analysis of diagnostic test performance. *JAMA, 280,* 913-920.

Fogel, J., Fauerbach, J. A., Ziegelstein, R. C., & Bush, D. E. (2004). Quality of life in physical health domains predicts adherence among myocardial infarction patients even after adjusting for depressive symptoms. *J.Psychosom.Res., 56,* 75-82.

Ford, D. E., Mead, L. A., Chang, P. P., Cooper-Patrick, L., Wang, N. Y., & Klag, M. J. (1998). Depression is a risk factor for coronary artery disease in men: the precursors study. *Arch.Intern.Med., 158,* 1422-1426.

Fox, K. M., Mulcahy, D., Findlay, I., Ford, I., & Dargie, H. J. (1996). The Total Ischaemic Burden European Trial (TIBET). Effects of atenolol, nifedipine SR and their combination on the exercise test and the total ischaemic burden in 608 patients with stable angina. The TIBET Study Group. *Eur.Heart J., 17,* 96-103.

Frasure-Smith, N. (1991). In-hospital symptoms of psychological stress as predictors of long term outcome after acute myocardial infarction in men. *Am.J.Cardiol., 67,* 121-127.

Frasure-Smith, N., Lesperance, F., & Talajic, M. (1993). Depression following myocardial infarction. Impact on 6-month survival. *JAMA, 270,* 1819-1825.

Frasure-Smith, N., Lesperance, F., & Talajic, M. (1995). The impact of negative emotions on prognosis following myocardial infarction: is it more than depression? *Health Psychol., 14,* 388-398.

Frasure-Smith, N., Lesperance, F., & Talajic, M. (1995). Depression and 18-month prognosis after myocardial infarction. *Circulation, 91,* 999-1005.

Frasure-Smith, N., Lesperance, F., Prince, R. H., Verrier, P., Garber, R. A., Juneau, M. et al. (1997). Randomised trial of home-based psychosocial nursing intervention for patients recovering from myocardial infarction. *Lancet, 350,* 473-479.

Frasure-Smith, N., Lesperance, F., Juneau, M., Talajic, M., & Bourassa, M. G. (1999). Gender, depression, and one-year prognosis after myocardial infarction. *Psychosom.Med., 61,* 26-37.

Frasure-Smith, N., Lesperance, F., Gravel, G., Masson, A., Juneau, M., Talajic, M. et al. (2000). Depression and health-care costs during the first year following myocardial infarction. *J.Psychosom.Res., 48,* 471-478.

Frasure-Smith, N., Lesperance, F., Gravel, G., Masson, A., Juneau, M., Talajic, M. et al. (2000). Social support, depression, and mortality during the first year after myocardial infarction. *Circulation, 101,* 1919-1924.

Frasure-Smith, N., Lesperance, F., Gravel, G., Masson, A., Juneau, M., & Bourassa, M. G. (2002). Long term survival differences among low-anxious, high-anxious and repressive copers enrolled in the Montreal heart attack readjustment trial. *Psychosom.Med., 64,* 571-579.

Frasure-Smith, N. & Lesperance, F. (2003). Depression--a cardiac risk factor in search of a treatment. *JAMA, 289,* 3171-3173.

Frasure-Smith, N. & Lesperance, F. (2003). Depression and other psychological risks following myocardial infarction. *Arch.Gen.Psychiatry, 60,* 627-636.

Frederickson, B. L. (1998). What good are positive emotions. *Review of general psychology, 2,* 300.

Fredrickson, B. L. & Kahneman, D. (1993). Duration neglect in retrospective evaluations of affective episodes. *J.Pers.Soc.Psychol., 65,* 45-55.

Freedman, J. E. & Loscalzo, J. (2002). Platelet-monocyte aggregates: bridging thrombosis and inflammation. *Circulation, 105,* 2130-2132.

Freedman, S. B. & Wong, C. K. (1998). Triggers of daily life ischaemia. *Heart, 80,* 489-492.

French, D. P., Senior, V., Weinman, J., & Marteau, T. M. (2001). Causal attributions for heart disease: A systematic review. *Psychology & Health, 16,* 77-98.

Friedman, M. & Rosenman, R. H. (1971). Type A Behavior Pattern: its association with coronary heart disease. *Ann.Clin.Res., 3,* 300-312.

Fruergaard, P., Launbjerg, J., Hesse, B., Jorgensen, F., Petri, A., Eiken, P. et al. (1996). The diagnoses of patients admitted with acute chest pain but without myocardial infarction. *Eur.Heart J., 17,* 1028-1034.

Furze, G., Lewin, R. J., Murberg, T., Bull, P., & Thompson, D. R. (2005). Does it matter what patients think? The relationship between changes in patients' beliefs about angina and their psychological and functional status. *J.Psychosom.Res., 59,* 323-329.

Gabbay, F. H., Krantz, D. S., Kop, W. J., Hedges, S. M., Klein, J., Gottdiener, J. S. et al. (1996). Triggers of myocardial ischemia during daily life in patients with coronary artery disease: physical and mental activities, anger and smoking. *J.Am.Coll.Cardiol., 27,* 585-592.

Gallacher, J. E., Yarnell, J. W., Sweetnam, P. M., Elwood, P. C., & Stansfeld, S. A. (1999). Anger and incident heart disease in the caerphilly study. *Psychosom.Med., 61,* 446-453.

Gallo, L. C., Troxel, W. M., Kuller, L. H., Sutton-Tyrrell, K., Edmundowicz, D., & Matthews, K. A. (2003). Marital status, marital quality, and atherosclerotic burden in postmenopausal women. *Psychosom.Med., 65,* 952-962.

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. *Arch.Gen.Psychiatry, 62,* 661-666.

Gehi, A., Haas, D., Pipkin, S., & Whooley, M. A. (2005). Depression and medication adherence in outpatients with coronary heart disease: findings from the Heart and Soul Study. *Arch.Intern.Med., 165,* 2508-2513.

Gehring, J., Koenig, W., Rana, N. W., & Mathes, P. (1988). The influence of the type of occupation on return to work after myocardial infarction, coronary angioplasty and coronary bypass surgery. *Eur.Heart J., 9 Suppl L,* 109-114.

Gellman, M., Spitzer, S., Ironson, G., Llabre, M., Saab, P., DeCarlo, P. R. et al. (1990). Posture, place, and mood effects on ambulatory blood pressure. *Psychophysiology, 27,* 544-551.

George, L. K. & Gwyther, L. P. (1986). Caregiver well-being: a multidimensional examination of family caregivers of demented adults. *Gerontologist, 26,* 253-259.

Gerin, W., Milner, D., Chawla, S., & Pickering, T. G. (1995). Social support as a moderator of cardiovascular reactivity in women: a test of the direct effects and buffering hypotheses. *Psychosom.Med., 57,* 16-22.

Ghiadoni, L., Donald, A. E., Cropley, M., Mullen, M. J., Oakley, G., Taylor, M. et al. (2000). Mental stress induces transient endothelial dysfunction in humans. *Circulation, 102,* 2473-2478.

Gill, T. M. & Feinstein, A. R. (1994). A critical appraisal of the quality of quality-of-life measurements. *JAMA, 272,* 619-626.

Girod, J. P. & Brotman, D. J. (2004). Does altered glucocorticoid homeostasis increase cardiovascular risk? *Cardiovasc.Res., 64,* 217-226.

Glassman, A. H. & Shapiro, P. A. (1998). Depression and the course of coronary artery disease. *Am.J.Psychiatry, 155,* 4-11.

Glassman, A. H., O'Connor, C. M., Califf, R. M., Swedberg, K., Schwartz, P., Bigger, J. T., Jr. et al. (2002). Sertraline treatment of major depression in patients with acute MI or unstable angina. *JAMA, 288,* 701-709.

Goebel, M. U. & Mills, P. J. (2000). Acute psychological stress and exercise and changes in peripheral leukocyte adhesion molecule expression and density. *Psychosom.Med., 62,* 664-670.

Gold, P. W., Goodwin, F. K., & Chrousos, G. P. (1988). Clinical and biochemical manifestations of depression. Relation to the neurobiology of stress (1). *N.Engl.J.Med., 319,* 348-353.

Goodyer, I. M., Herbert, J., Tamplin, A., & Altham, P. M. (2000). Recent life events, cortisol, dehydroepiandrosterone and the onset of major depression in high-risk adolescents. *Br.J.Psychiatry, 177,* 499-504.

Gottdiener, J. S., Krantz, D. S., Howell, R. H., Hecht, G. M., Klein, J., Falconer, J. J. et al. (1994). Induction of silent myocardial ischemia with mental stress testing: relation to the triggers of ischemia during daily life activities and to ischemic functional severity. *J.Am.Coll.Cardiol., 24,* 1645-1651.

Guder, G., Bauersachs, J., Frantz, S., Weismann, D., Allolio, B., Ertl, G. et al. (2007). Complementary and incremental mortality risk prediction by cortisol and aldosterone in chronic heart failure. *Circulation, 115,* 1754-1761.

Gudmundsdottir, H., Johnston, M., Johnston, D., & Foulkes, J. (2001). Spontaneous, elicited and cued causal attributions in the year following a first myocardial infarction. *Br.J.Health Psychol., 6,* 81-96.

Guinjoan, S. M., de Guevara, M. S., Correa, C., Schauffele, S. I., Nicola-Siri, L., Fahrer, R. D. et al. (2004). Cardiac parasympathetic dysfunction related to depression in older adults with acute coronary syndromes. *J.Psychosom.Res., 56,* 83-88.

Gullette, E. C., Blumenthal, J. A., Babyak, M., Jiang, W., Waugh, R. A., Frid, D. J. et al. (1997). Effects of mental stress on myocardial ischemia during daily life. *JAMA, 277,* 1521-1526.

Haas, D. C., Davidson, K. W., Schwartz, D. J., Rieckmann, N., Roman, M. J., Pickering, T. G. et al. (2005). Depressive symptoms are independently predictive of carotid atherosclerosis. *Am.J.Cardiol., 95,* 547-550.

Habib, G. (1997). Reappraisal of the importance of heart rate as a risk factor for cardiovascular morbidity and mortality. *Clin.Ther., 19 Suppl A,* 39-52.

Haines, A., Cooper, J., & Meade, T. W. (2001). Psychological characteristics and fatal ischaemic heart disease. *Heart, 85,* 385-389.

Haines, A. P., Imeson, J. D., & Meade, T. W. (1987). Phobic anxiety and ischaemic heart disease. *Br.Med.J.(Clin.Res.Ed), 295,* 297-299.

Hallqvist, J., Moller, J., Ahlbom, A., Diderichsen, F., Reuterwall, C., & de Faire, U. (2000). Does heavy physical exertion trigger myocardial infarction? A case-crossover analysis nested in a population-based case-referent study. *Am.J.Epidemiol., 151,* 459-467.

Hallstrom, T., Lapidus, L., Bengtsson, C., & Edstrom, K. (1986). Psychosocial factors and risk of ischaemic heart disease and death in women: a twelve-year follow-up of participants in the population study of women in Gothenburg, Sweden. *J.Psychosom.Res., 30,* 451-459.

Hamalainen, H., Maki, J., Virta, L., Keskimaki, I., Mahonen, M., Moltchanov, V. et al. (2004). Return to work after first myocardial infarction in 1991-1996 in Finland. *Eur.J.Public Health, 14,* 350-353.

Harris, T. O., Borsanyi, S., Messari, S., Stanford, K., Cleary, S. E., Shiers, H. M. et al. (2000). Morning cortisol as a risk factor for subsequent major depressive disorder in adult women. *Br.J.Psychiatry, 177,* 505-510.

Hartel, U., Stieber, J., & Keil, U. (1988). Social relations and smoking behavior: results from the first MONICA Survey Augsburg. *Soz.Praventivmed., 33,* 27-31.

Hasdai, D., Behar, S., Wallentin, L., Danchin, N., Gitt, A. K., Boersma, E. et al. (2002). A prospective survey of the characteristics, treatments and outcomes of patients with acute coronary syndromes in Europe and the Mediterranean basin; the Euro Heart Survey of Acute Coronary Syndromes (Euro Heart Survey ACS). *Eur.Heart J., 23,* 1190-1201.

Hayano, J., Yamada, M., Sakakibara, Y., Fujinami, T., Yokoyama, K., Watanabe, Y. et al. (1990). Short- and long term effects of cigarette smoking on heart rate variability. *Am.J.Cardiol., 65,* 84-88.

Hearn, M. D., Murray, D. M., & Luepker, R. V. (1989). Hostility, coronary heart disease, and total mortality: a 33-year follow-up study of university students. *J.Behav.Med., 12,* 105-121.

Heart rate variability: standards of measurement, physiological interpretation and clinical use. Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology (1996). *Circulation, 93,* 1043-1065.

Heidland, U. E. & Strauer, B. E. (2001). Left ventricular muscle mass and elevated heart rate are associated with coronary plaque disruption. *Circulation, 104,* 1477-1482.

Heiser, J. F. & Defrancisco, D. (1976). The treatment of pathological panic states with propranolol. *Am.J.Psychiatry, 133,* 1389-1394.

Heller, R. F., Lim, L., Valenti, L., & Knapp, J. (1997). Predictors of quality of life after hospital admission for heart attack or angina. *Int.J.Cardiol., 59,* 161-166.

Helmers, K. F., Krantz, D. S., Howell, R. H., Klein, J., Bairey, C. N., & Rozanski, A. (1993). Hostility and myocardial ischemia in coronary artery disease patients: evaluation by gender and ischemic index. *Psychosom.Med., 55,* 29-36.

Hemingway, H., Nicholson, A., Stafford, M., Roberts, R., & Marmot, M. (1997). The impact of socio-economic status on health functioning as assessed by the SF-36 questionnaire: the Whitehall II Study. *Am.J.Public Health, 87,* 1484-1490.

Hemingway, H. & Marmot, M. (1999). Evidence based cardiology: psychosocial factors in the aetiology and prognosis of coronary heart disease. Systematic review of prospective cohort studies. *BMJ, 318,* 1460-1467.

Hemingway, H., Whitty, C. J., Shipley, M., Stansfeld, M. S., Brunner, E., Fuhrer, R. et al. (2001). Psychosocial risk factors for coronary disease in White, South Asian and Afro-Caribbean civil servants: the Whitehall II study. *Ethn.Dis., 11,* 391-400.

Herrmann, C. (1997). International experiences with the Hospital Anxiety and Depression Scale--a review of validation data and clinical results. *J.Psychosom.Res., 42,* 17-41.

Hippisley-Cox, J., Fielding, K., & Pringle, M. (1998). Depression as a risk factor for ischaemic heart disease in men: population based case-control study. *BMJ, 316,* 1714-1719.

Holsboer, F. (2001). Stress, hypercortisolism and corticosteroid receptors in depression: implications for therapy. *J.Affect.Disord., 62,* 77-91.

Holt-Lunstad, J., Uchino, B. N., Smith, T. W., Olson-Cerny, C., & Nealey-Moore, J. B. (2003). Social relationships and ambulatory blood pressure: structural and qualitative predictors of cardiovascular function during everyday social interactions. *Health Psychol., 22,* 388-397.

House, J. S., Robbins, C., & Metzner, H. L. (1982). The association of social relationships and activities with mortality: prospective evidence from the Tecumseh Community Health Study. *Am.J.Epidemiol., 116,* 123-140.

House, JS., & Kahn, RL. (1985). Measures and concepts of social support. In S. Cohen & S. L. Syme (Eds.), *Social support and health*, 83–108. New York: Academic Press.

Hughes, J. W., Watkins, L., Blumenthal, J. A., Kuhn, C., & Sherwood, A. (2004). Depression and anxiety symptoms are related to increased 24-hour urinary norepinephrine excretion among healthy middle-aged women. *J.Psychosom.Res., 57,* 353-358.

Huikuri, H. V., Jokinen, V., Syvanne, M., Nieminen, M. S., Airaksinen, K. E., Ikaheimo, M. J. et al. (1999). Heart rate variability and progression of coronary atherosclerosis. *Arterioscler.Thromb.Vasc.Biol., 19,* 1979-1985.

Huikuri, H. V., Makikallio, T., Airaksinen, K. E., Mitrani, R., Castellanos, A., & Myerburg, R. J. (1999). Measurement of heart rate variability: a clinical tool or a research toy? *J.Am.Coll.Cardiol., 34,* 1878-1883.

Ice, G. H. (2005). Factors influencing cortisol level and slope among community dwelling older adults in Minnesota. *J.Cross.Cult.Gerontol., 20,* 91-108.

Ingjaldsson, J. T., Laberg, J. C., & Thayer, J. F. (2003). Reduced heart rate variability in chronic alcohol abuse: relationship with negative mood, chronic thought suppression, and compulsive drinking. *Biol.Psychiatry, 54,* 1427-1436.

Iribarren, C., Sidney, S., Bild, D. E., Liu, K., Markovitz, J. H., Roseman, J. M. et al. (2000). Association of hostility with coronary artery calcification in young adults: the CARDIA study. Coronary Artery Risk Development in Young Adults. *JAMA, 283,* 2546-2551.

Ironson, G., Taylor, C. B., Boltwood, M., Bartzokis, T., Dennis, C., Chesney, M. et al. (1992). Effects of anger on left ventricular ejection fraction in coronary artery disease. *Am.J.Cardiol., 70,* 281-285.

Irvine, J., Basinski, A., Baker, B., Jandciu, S., Paquette, M., Cairns, J. et al. (1999). Depression and risk of sudden cardiac death after acute myocardial infarction: testing for the confounding effects of fatigue. *Psychosom.Med., 61,* 729-737.

Jacob, R. G., Thayer, J. F., Manuck, S. B., Muldoon, M. F., Tamres, L. K., Williams, D. M. et al. (1999). Ambulatory blood pressure responses and the circumplex model of mood: a 4-day study. *Psychosom.Med., 61,* 319-333.

Jain, D., Shaker, S. M., Burg, M., Wackers, F. J., Soufer, R., & Zaret, B. L. (1998). Effects of mental stress on left ventricular and peripheral vascular performance in patients with coronary artery disease. *J.Am.Coll.Cardiol., 31,* 1314-1322.

James, G. D., Yee, L. S., Harshfield, G. A., Blank, S. G., & Pickering, T. G. (1986). The influence of happiness, anger, and anxiety on the blood pressure of borderline hypertensives. *Psychosom.Med., 48,* 502-508.

Jenkinson, C. M., Madeley, R. J., Mitchell, J. R., & Turner, I. D. (1993). The influence of psychosocial factors on survival after myocardial infarction. *Public Health, 107,* 305-317.

Jiang, W., Blumenthal, J. A., Hanson, M. W., Coleman, R. E., O'Connor, C. M., Frid, D. et al. (1995). Relative importance of electrode placement over number of channels in transient myocardial ischemia detection by Holter monitoring. *Am.J.Cardiol., 76,* 350-354.

Jiang, W. & Blumenthal, J. A. (2003). Depression and ischemic heart disease: overview of the evidence and treatment implications. *Curr.Psychiatry Rep., 5,* 47-54.

Jiang, W., Babyak, M. A., Rozanski, A., Sherwood, A., O'Connor, C. M., Waugh, R. A. et al. (2003). Depression and increased myocardial ischemic activity in patients with ischemic heart disease. *Am.Heart J., 146,* 55-61.

Johnston, D. W., Cook, D. G., & Shaper, A. G. (1987). Type A behaviour and ischaemic heart disease in middle aged British men. *Br.Med.J.(Clin.Res.Ed), 295,* 86-89.

Julkunen, J., Salonen, R., Kaplan, G. A., Chesney, M. A., & Salonen, J. T. (1994). Hostility and the progression of carotid atherosclerosis. *Psychosom.Med., 56,* 519-525.

Kahneman, D. (2003). A perspective on judgment and choice: mapping bounded rationality. *Am.Psychol., 58,* 697-720.

Kahneman, D., Krueger, A. B., Schkade, D. A., Schwarz, N., & Stone, A. A. (2004). A survey method for characterizing daily life experience: the day reconstruction method. *Science, 306,* 1776-1780.

Kamarck, T. W., Annunziato, B., & Amateau, L. M. (1995). Affiliation moderates the effects of social threat on stress-related cardiovascular responses: boundary conditions for a laboratory model of social support. *Psychosom.Med., 57,* 183-194.

Kannel WB., & Vokonas, P.S. (1986). Primary risk factors for coronary heart disease in the elderly: The Framingham Study. In N.K. Wegner, C.D Furtberg, & E. Pitt (Eds.), *Coronary heart disease in the elderly* (pp.60-93). New York: Elsevier.

Kannel, W. B., Kannel, C., Paffenbarger, R. S., Jr., & Cupples, L. A. (1987). Heart rate and cardiovascular mortality: the Framingham Study. *Am.Heart J., 113,* 1489-1494.

Kannel, W. B., Wolf, P. A., Castelli, W. P., & D'Agostino, R. B. (1987). Fibrinogen and risk of cardiovascular disease. The Framingham Study. *JAMA, 258,* 1183-1186.

Karasek, R., Baker, D., Marxer, F., Ahlbom, A., & Theorell, T. (1981). Job decision latitude, job demands, and cardiovascular disease: a prospective study of Swedish men. *Am.J.Public Health, 71,* 694-705.

Kark, J. D., Goldman, S., & Epstein, L. (1995). Iraqi missile attacks on Israel. The association of mortality with a life-threatening stressor. *JAMA, 273,* 1208-1210.

Katona, P. G. (1982). Automated control of physiological variables and clinical therapy. *Crit Rev.Biomed.Eng, 8,* 281-310.

Katz, E., Metzger, J. T., Schlaepfer, J., Fromer, M., Fishman, D., Mayer, L. et al. (2005). Increase of out-of-hospital cardiac arrests in the male population of the French speaking provinces of Switzerland during the 1998 FIFA World Cup. *Heart, 91,* 1096-1097.

Katz, E., Metzger, J. T., Marazzi, A., & Kappenberger, L. (2006). Increase of sudden cardiac deaths in Switzerland during the 2002 FIFA World Cup. *Int.J.Cardiol., 107,* 132-133.

Kaufmann, M. W., Fitzgibbons, J. P., Sussman, E. J., Reed, J. F., III, Einfalt, J. M., Rodgers, J. K. et al. (1999). Relation between myocardial infarction, depression, hostility, and death. *Am.Heart J., 138,* 549-554.

Kaul, P., Newby, L. K., Fu, Y., Mark, D. B., Califf, R. M., Topol, E. J. et al. (2004). International differences in evolution of early discharge after acute myocardial infarction. *Lancet, 363,* 511-517.

Kawachi, I., Colditz, G. A., Ascherio, A., Rimm, E. B., Giovannucci, E., Stampfer, M. J. et al. (1994). Prospective study of phobic anxiety and risk of coronary heart disease in men. *Circulation, 89,* 1992-1997.

Kawachi, I., Sparrow, D., Vokonas, P. S., & Weiss, S. T. (1994). Symptoms of anxiety and risk of coronary heart disease. The Normative Aging Study. *Circulation, 90,* 2225-2229.

Kawachi, I., Colditz, G. A., Ascherio, A., Rimm, E. B., Giovannucci, E., Stampfer, M. J. et al. (1994). Prospective study of phobic anxiety and risk of coronary heart disease in men. *Circulation, 89,* 1992-1997.

Kawachi, I., Sparrow, D., Vokonas, P. S., & Weiss, S. T. (1995). Decreased heart rate variability in men with phobic anxiety (data from the Normative Aging Study). *Am.J.Cardiol., 75,* 882-885.

Kawachi, I., Colditz, G. A., Ascherio, A., Rimm, E. B., Giovannucci, E., Stampfer, M. J. et al. (1996). A prospective study of social networks in relation to total mortality and cardiovascular disease in men in the USA. *J.Epidemiol.Community Health, 50,* 245-251.

Kawachi, I., Sparrow, D., Spiro, A., III, Vokonas, P., & Weiss, S. T. (1996). A prospective study of anger and coronary heart disease. The Normative Aging Study. *Circulation, 94,* 2090-2095.

Kelly, W. F., Checkley, S. A., Bender, D. A., & Mashiter, K. (1983). Cushing's syndrome and depression--a prospective study of 26 patients. *Br.J.Psychiatry, 142,* 16-19.

Kennedy, H. L. (1997). Beta blockade, ventricular arrhythmias, and sudden cardiac death. *Am.J.Cardiol., 80,* 29J-34J.

Kiecolt-Glaser, J. K. & Greenberg, B. (1984). Social support as a moderator of the aftereffects of stress in female psychiatric inpatients. *J.Abnorm.Psychol., 93,* 192-199.

Kiecolt-Glaser, J. K., Glaser, R., Cacioppo, J. T., & Malarkey, W. B. (1998). Marital stress: immunologic, neuroendocrine, and autonomic correlates. *Ann.N.Y.Acad.Sci., 840,* 656-663.

Kiecolt-Glaser, J. K. & Glaser, R. (2002). Depression and immune function: central pathways to morbidity and mortality. *J.Psychosom.Res., 53,* 873-876.

Kim, C. K., McGorray, S. P., Bartholomew, B. A., Marsh, M., Dicken, T., Wassertheil-Smoller, S. et al. (2005). Depressive symptoms and heart rate variability in postmenopausal women. *Arch.Intern.Med., 165,* 1239-1244.

King, K. B., Reis, H. T., Porter, L. A., & Norsen, L. H. (1993). Social support and long term recovery from coronary artery surgery: effects on patients and spouses. *Health Psychol., 12,* 56-63.

Kinne, G., Droste, C., Fahrenberg, J., & Roskamm, H. (1999). Symptomatic myocardial ischemia and everyday life: Implications for clinical use of interactive monitoring. *Journal of Psychosomatic Research, 46,* 369-377.

Kirkup, W. & Merrick, D. W. (2003). A matter of life and death: population mortality and football results. *J.Epidemiol.Community Health, 57,* 429-432.

Kirschbaum, C. & Hellhammer, D. H. (1989). Salivary cortisol in psychobiological research: an overview. *Neuropsychobiology, 22,* 150-169.

Kirschbaum, C. & Hellhammer, D. (1989). Response variability of salivary cortisol under psychological stimulation. *J.Clin.Chem.Clin.Biochem., 27,* 237.

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. *Am.J.Cardiol., 59,* 256-262.

Kloner, R. A., Leor, J., Poole, W. K., & Perritt, R. (1997). Population-based analysis of the effect of the Northridge Earthquake on cardiac death in Los Angeles County, California. *J.Am.Coll.Cardiol., 30,* 1174-1180.

Kloner, R. A. (2006). Natural and unnatural triggers of myocardial infarction. *Prog.Cardiovasc.Dis., 48,* 285-300.

Koertge, J., Al Khalili, F., Ahnve, S., Janszky, I., Svane, B., & Schenck-Gustafsson, K. (2002). Cortisol and vital exhaustion in relation to significant coronary artery stenosis in middle-aged women with acute coronary syndrome. *Psychoneuroendocrinology, 27,* 893-906.

Kop, W. J., Verdino, R. J., Gottdiener, J. S., O'Leary, S. T., Bairey Merz, C. N., & Krantz, D. S. (2001). Changes in heart rate and heart rate variability before ambulatory ischemic events(1). *J.Am.Coll.Cardiol., 38,* 742-749.

Kop, W. J., Krantz, D. S., Nearing, B. D., Gottdiener, J. S., Quigley, J. F., O'Callahan, M. et al. (2004). Effects of acute mental stress and exercise on T-wave alternans in patients with implantable cardioverter defibrillators and controls. *Circulation, 109,* 1864-1869.

Krantz, D. S., Schaeffer, M. A., Davia, J. E., Dembroski, T. M., MacDougall, J. M., & Shaffer, R. T. (1981). Extent of coronary atherosclerosis, type A behavior, and cardiovascular response to social interaction. *Psychophysiology, 18,* 654-664.

Krantz, D. S., Contrada, R. J., LaRiccia, P. J., Anderson, J. R., Durel, L. A., Dembroski, T. M. et al. (1987). Effects of beta-adrenergic stimulation and blockade on cardiovascular reactivity, affect, and type A behavior. *Psychosom.Med., 49,* 146-158.

Krantz, D. S., Hedges, S. M., Gabbay, F. H., Klein, J., Falconer, J. J., Merz, C. N. et al. (1994). Triggers of angina and ST-segment depression in ambulatory patients with coronary artery disease: evidence for an uncoupling of angina and ischemia. *Am.Heart J., 128,* 703-712.

Krantz, D. S., Kop, W. J., Gabbay, F. H., Rozanski, A., Barnard, M., Klein, J. et al. (1996). Circadian variation of ambulatory myocardial ischemia. Triggering by daily activities and evidence for an endogenous circadian component. *Circulation, 93,* 1364-1371.

Krantz, D. S., Kop, W. J., Santiago, H. T., & Gottdiener, J. S. (1996). Mental stress as a trigger of myocardial ischemia and infarction. *Cardiol.Clin., 14,* 271-287.

Krantz, D. S., Santiago, H. T., Kop, W. J., Bairey Merz, C. N., Rozanski, A., & Gottdiener, J. S. (1999). Prognostic value of mental stress testing in coronary artery disease. *Am.J.Cardiol., 84,* 1292-1297.

Krantz, D. S. & McCeney, M. K. (2002). Effects of psychological and social factors on organic disease: a critical assessment of research on coronary heart disease. *Annu.Rev.Psychol., 53,* 341-369.

Krittayaphong, R., Light, K. C., Biles, P. L., Ballenger, M. N., & Sheps, D. S. (1995). Increased heart rate response to laboratory-induced mental stress predicts frequency and duration of daily life ambulatory myocardial ischemia in patients with coronary artery disease. *Am.J.Cardiol., 76,* 657-660.

Krittayaphong, R., Cascio, W. E., Light, K. C., Sheffield, D., Golden, R. N., Finkel, J. B. et al. (1997). Heart rate variability in patients with coronary artery disease: differences in patients with higher and lower depression scores. *Psychosom.Med., 59,* 231-235.

Kubzansky, L. D., Kawachi, I., Spiro, A., III, Weiss, S. T., Vokonas, P. S., & Sparrow, D. (1997). Is worrying bad for your heart? A prospective study of worry and coronary heart disease in the Normative Aging Study. *Circulation, 95,* 818-824.

Kubzansky, L. D., Kawachi, I., Weiss, S. T., & Sparrow, D. (1998). Anxiety and coronary heart disease: a synthesis of epidemiological, psychological, and experimental evidence. *Ann.Behav.Med., 20,* 47-58.

Kubzansky, L. D. & Kawachi, I. (2000). Going to the heart of the matter: do negative emotions cause coronary heart disease? *J.Psychosom.Res., 48,* 323-337.

Kubzansky, L. D., Sparrow, D., Vokonas, P., & Kawachi, I. (2001). Is the glass half empty or half full? A prospective study of optimism and coronary heart disease in the normative aging study. *Psychosom.Med., 63,* 910-916.

Kubzansky, L. D. & Thurston, R. C. (2007). Emotional vitality and incident coronary heart disease: benefits of healthy psychological functioning. *Arch.Gen.Psychiatry, 64,* 1393-1401.

Kubzansky, L. D. (2007). Sick at heart: the pathophysiology of negative emotions. *Cleve.Clin.J.Med., 74 Suppl 1,* S67-S72.

Kudielka, B. M. & Kirschbaum, C. (2003). Awakening cortisol responses are influenced by health status and awakening time but not by menstrual cycle phase. *Psychoneuroendocrinology, 28,* 35-47.

Kuper, H., Singh-Manoux, A., Siegrist, J., & Marmot, M. (2002). When reciprocity fails: effort-reward imbalance in relation to coronary heart disease and health functioning within the Whitehall II study. *Occup.Environ.Med., 59,* 777-784.

Kuper, H. & Marmot, M. (2003). Job strain, job demands, decision latitude, and risk of coronary heart disease within the Whitehall II study. *J.Epidemiol.Community Health, 57,* 147-153.

Kupper, N., de Geus, E. J., van den, B. M., Kirschbaum, C., Boomsma, D. I., & Willemsen, G. (2005). Familial influences on basal salivary cortisol in an adult population. *Psychoneuroendocrinology, 30,* 857-868.

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,* 478-484.

Laerum, E., Johnsen, N., Smith, P., & Larsen, S. (1988). Myocardial infarction may induce positive changes in life-style and in the quality of life. *Scand.J.Prim.Health Care, 6,* 67-71.

Laghrissi-Thode, F., Wagner, W. R., Pollock, B. G., Johnson, P. C., & Finkel, M. S. (1997). Elevated platelet factor 4 and beta-thromboglobulin plasma levels in depressed patients with ischemic heart disease. *Biol.Psychiatry, 42,* 290-295.

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. *Am.J.Psychiatry, 139,* 1315-1318.

Lampert, R., Joska, T., Burg, M. M., Batsford, W. P., McPherson, C. A., & Jain, D. (2002). Emotional and physical precipitants of ventricular arrhythmia. *Circulation, 106,* 1800-1805.

Lane, D., Carroll, D., Ring, C., Beevers, D. G., & Lip, G. Y. (2000). Do depression and anxiety predict recurrent coronary events 12 months after myocardial infarction? *QJM., 93,* 739-744.

Lane, D., Carroll, D., Ring, C., Beevers, D. G., & Lip, G. Y. (2001). Mortality and quality of life 12 months after myocardial infarction: effects of depression and anxiety. *Psychosom.Med., 63,* 221-230.

Lane, D., Carroll, D., Ring, C., Beevers, D. G., & Lip, G. Y. (2002). In-hospital symptoms of depression do not predict mortality 3 years after myocardial infarction. *International Journal of Epidemiology, 31,* 1179-1182.

Lane, R. D., Laukes, C., Marcus, F. I., Chesney, M. A., Sechrest, L., Gear, K. et al. (2005). Psychological stress preceding idiopathic ventricular fibrillation. *Psychosom.Med., 67,* 359-365.

Lanza, G. A., Cianflone, D., Rebuzzi, A. G., Angeloni, G., Sestito, A., Ciriello, G. et al. (2006). Prognostic value of ventricular arrhythmias and heart rate variability in patients with unstable angina. *Heart, 92,* 1055-1063.

Lanza, G. A., Sgueglia, G. A., Cianflone, D., Rebuzzi, A. G., Angeloni, G., Sestito, A. et al. (2006). Relation of heart rate variability to serum levels of C-reactive protein in patients with unstable angina pectoris. *Am.J.Cardiol., 97,* 1702-1706.

Lauderdale, D. S., Knutson, K. L., Yan, L. L., Rathouz, P. J., Hulley, S. B., Sidney, S. et al. (2006). Objectively measured sleep characteristics among early-middle-aged adults: the CARDIA study. *Am.J.Epidemiol., 164,* 5-16.

Lauer, M. S. & Froelicher, V. (2002). Abnormal heart-rate recovery after exercise. *Lancet, 360,* 1176-1177.

Leal, J., Luengo-Fernandez, R., Gray, A., Petersen, S., & Rayner, M. (2006). Economic burden of cardiovascular diseases in the enlarged European Union. *Eur.Heart J., 27,* 1610-1619.

Lee, S., Colditz, G., Berkman, L., & Kawachi, I. (2002). A prospective study of job strain and coronary heart disease in US women. *International Journal of Epidemiology, 31,* 1147-1153.

Lee, S., Colditz, G., Berkman, L., & Kawachi, I. (2003). Caregiving to children and grandchildren and risk of coronary heart disease in women. *Am.J.Public Health, 93,* 1939-1944.

Lee, S., Colditz, G. A., Berkman, L. F., & Kawachi, I. (2004). Prospective study of job insecurity and coronary heart disease in US women. *Ann.Epidemiol., 14,* 24-30.

Lefkovits, J., Plow, E. F., & Topol, E. J. (1995). Platelet glycoprotein IIb/IIIa receptors in cardiovascular medicine. *N.Engl.J.Med., 332,* 1553-1559.

Legault, S. E., Joffe, R. T., & Armstrong, P. W. (1992). Psychiatric morbidity during the early phase of coronary care for myocardial infarction: association with cardiac diagnosis and outcome. *Can.J.Psychiatry, 37,* 316-325.

Legault, S. E., Langer, A., Armstrong, P. W., & Freeman, M. R. (1995). Usefulness of ischemic response to mental stress in predicting silent myocardial ischemia during ambulatory monitoring. *Am.J.Cardiol., 75,* 1007-1011.

Legault, S. E., Freeman, M. R., Langer, A., & Armstrong, P. W. (1995). Pathophysiology and Time-Course of Silent-Myocardial-Ischemia During Mental Stress - Clinical, Anatomical, and Physiological Correlates. *British Heart Journal, 73,* 242-249.

Leineweber, C., Kecklund, G., Janszky, I., Akerstedt, T., & Orth-Gomer, K. (2003). Poor sleep increases the prospective risk for recurrent events in middle-aged women with coronary disease. The Stockholm Female Coronary Risk Study. *J.Psychosom.Res., 54,* 121-127.

Leor, J., Poole, W. K., & Kloner, R. A. (1996). Sudden cardiac death triggered by an earthquake. *N.Engl.J.Med., 334,* 413-419.

Leor, J. & Kloner, R. A. (1996). The Northridge earthquake as a trigger for acute myocardial infarction. *Am.J.Cardiol., 77,* 1230-1232.

Lesperance, F., Frasure-Smith, N., Juneau, M., & Theroux, P. (2000). Depression and 1-year prognosis in unstable angina. *Archives of Internal Medicine, 160,* 1354-1360.

Lesperance, F. & Frasure-Smith, N. (2000). Depression in patients with cardiac disease: a practical review. *J.Psychosom.Res., 48,* 379-391.

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,* 1049-1053.

Lesperance, F. & Frasure-Smith, N. (2003). Depression and coronary artery disease: time to move from observation to trials. *CMAJ., 168,* 570-571.

Lesperance, F., Frasure-Smith, N., Theroux, P., & Irwin, M. (2004). The association between major depression and levels of soluble intercellular adhesion molecule 1, interleukin-6, and C-reactive protein in patients with recent acute coronary syndromes. *Am.J.Psychiatry, 161,* 271-277.

Lett, H. S., Blumenthal, J. A., Babyak, M. A., Sherwood, A., Strauman, T., Robins, C. et al. (2004). Depression as a risk factor for coronary artery disease: evidence, mechanisms, and treatment. *Psychosom.Med., 66,* 305-315.

Levy, M. N. (1990). Autonomic interactions in cardiac control. *Ann.N.Y.Acad.Sci., 601,* 209-221.

Liao, D., Barnes, R. W., Chambless, L. E., Simpson, R. J., Jr., 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. Atherosclerosis Risk in Communities. *Am.J.Cardiol., 76,* 906-912.

Liao, D., Cai, J., Barnes, R. W., Tyroler, H. A., Rautaharju, P., Holme, I. et al. (1996). Association of cardiac autonomic function and the development of hypertension: the ARIC study. *Am.J.Hypertens., 9,* 1147-1156.

Libby, P., Ridker, P. M., & Maseri, A. (2002). Inflammation and atherosclerosis. *Circulation, 105,* 1135-1143.

Lichstein, K. L., Stone, K. C., Donaldson, J., Nau, S. D., Soeffing, J. P., Murray, D. et al. (2006). Actigraphy validation with insomnia. *Sleep, 29,* 232-239.

Light, K. C., Dolan, C. A., Davis, M. R., & Sherwood, A. (1992). Cardiovascular responses to an active coping challenge as predictors of blood pressure patterns 10 to 15 years later. *Psychosom.Med., 54,* 217-230.

Lim, L. L., Valenti, L. A., Knapp, J. C., Dobson, A. J., Plotnikoff, R., Higginbotham, N. et al. (1993). A self-administered quality-of-life questionnaire after acute myocardial infarction. *J.Clin.Epidemiol., 46,* 1249-1256.

Lin, L. Y., Wu, C. C., Liu, Y. B., Ho, Y. L., Liau, C. S., & Lee, Y. T. (2001). Derangement of heart rate variability during a catastrophic earthquake: a possible mechanism for increased heart attacks. *Pacing Clin.Electrophysiol., 24,* 1596-1601.

Lipovetzky, N., Hod, H., Roth, A., Kishon, Y., Sclarovsky, S., & Green, M. S. (2004). Heavy meals as a trigger for a first event of the acute coronary syndrome: a case-crossover study. *Isr.Med.Assoc.J., 6,* 728-731.

Lipsitz, L. A. & Goldberger, A. L. (1992). Loss of 'complexity' and aging. Potential applications of fractals and chaos theory to senescence. *JAMA, 267,* 1806-1809.

Litchfield, W. R., Hunt, S. C., Jeunemaitre, X., Fisher, N. D., Hopkins, P. N., Williams, R. R. et al. (1998). Increased urinary free cortisol: a potential intermediate phenotype of essential hypertension. *Hypertension, 31,* 569-574.

Loosen, P. T., Chambliss, B., DeBold, C. R., Shelton, R., & Orth, D. N. (1992). Psychiatric phenomenology in Cushing's disease. *Pharmacopsychiatry, 25,* 192-198.

Lovallo, W. R. (2005). *Stress & Health: Biological and Psychological Interactions.*

Lundberg, U., Fredrikson, M., Wallin, L., Melin, B., & Frankenhaeuser, M. (1989). Blood lipids as related to cardiovascular and neuroendocrine functions under different conditions in healthy males and females. *Pharmacol.Biochem.Behav., 33,* 381-386.

Lupien, S. J. & McEwen, B. S. (1997). The acute effects of corticosteroids on cognition: integration of animal and human model studies. *Brain Res.Brain Res.Rev., 24,* 1-27.

Lynch, J., Krause, N., Kaplan, G. A., Salonen, R., & Salonen, J. T. (1997). Workplace demands, economic reward, and progression of carotid atherosclerosis. *Circulation, 96,* 302-307.

Maclure, M. (1991). The case-crossover design: a method for studying transient effects on the risk of acute events. *Am.J.Epidemiol., 133,* 144-153.

Maclure, M. & Mittleman, M. A. (2000). Should we use a case-crossover design? *Annu.Rev.Public Health, 21,* 193-221.

Madjirova, N. P., Tashev, T. G., Delchev, N. N., & Bakalova, R. G. (1995). Interrelationship between cortisol levels in plasma and the circadian rhythm of temperature, pulse and blood pressure in depressed patients with good and disturbed sleep. *Int.J.Psychophysiol., 20,* 145-154.

Maeland, J. G. & Havik, O. E. (1987). Psychological predictors for return to work after a myocardial infarction. *J.Psychosom.Res., 31,* 471-481.

Maeland, J. G. & Havik, O. E. (1989). After the myocardial infarction. A medical and psychological study with special emphasis on perceived illness. *Scand.J.Rehabil.Med.Suppl, 22,* 1-87.

Makikallio, T. H., Huikuri, H. V., Hintze, U., Videbaek, J., Mitrani, R. D., Castellanos, A. et al. (2001). Fractal analysis and time- and frequency-domain measures of heart rate variability as predictors of mortality in patients with heart failure. *Am.J.Cardiol., 87,* 178-182.

Makikallio, T. H., Huikuri, H. V., Makikallio, A., Sourander, L. B., Mitrani, R. D., Castellanos, A. et al. (2001). Prediction of sudden cardiac death by fractal analysis of heart rate variability in elderly subjects. *J.Am.Coll.Cardiol., 37,* 1395-1402.

Malliani, A., Lombardi, F., Pagani, M., & Cerutti, S. (1994). Power spectral analysis of cardiovascular variability in patients at risk for sudden cardiac death. *J.Cardiovasc.Electrophysiol., 5,* 274-286.

Marco, C. A. & Suls, J. (1993). Daily stress and the trajectory of mood: spillover, response assimilation, contrast, and chronic negative affectivity. *J.Pers.Soc.Psychol., 64,* 1053-1063.

Markovitz, J. H. & Matthews, K. A. (1991). Platelets and coronary heart disease: potential psychophysiologic mechanisms. *Psychosom.Med., 53,* 643-668.

Martin, R., Johnsen, E. L., Bunde, J., Bellman, S. B., Rothrock, N. E., Weinrib, A. et al. (2005). Gender differences in patients' attributions for myocardial infarction: implications for adaptive health behaviors. *Int.J.Behav.Med., 12,* 39-45.

Marwick, T. H., Lafont, A., Go, R. T., Underwood, D. A., Saha, G. B., & MacIntyre, W. J. (1992). Identification of recurrent ischemia after coronary artery bypass surgery: a comparison of positron emission tomography and single photon emission computed tomography. *Int.J.Cardiol., 35,* 33-41.

Mason, J. W. (1968). A review of psychoendocrine research on the pituitary-adrenal cortical system. *Psychosom.Med., 30,* Suppl-607.

Matsuo, T., Suzuki, S., Kodama, K., & Kario, K. (1998). Hemostatic activation and cardiac events after the 1995 Hanshin-Awaji earthquake. *Int.J.Hematol., 67,* 123-129.

Matthews, K. A., Weiss, S. M., Detre, T., Dembroski, T. M., Falkner, B., Manuck, S. B., & Williams, R. B. (1986). *Handbook of stress, reactivity, and cardiovascular disease.* New York: Wiley.

Matthews, K., Schwartz, J., Cohen, S., & Seeman, T. (2006). Diurnal cortisol decline is related to coronary calcification: CARDIA study. *Psychosom.Med., 68,* 657-661.

Matthews, K. A. & Gump, B. B. (2002). Chronic work stress and marital dissolution increase risk of posttrial mortality in men from the Multiple Risk Factor Intervention Trial. *Arch.Intern.Med., 162,* 309-315.

Matthews, K. A., Gump, B. B., Harris, K. F., Haney, T. L., & Barefoot, J. C. (2004). Hostile behaviors predict cardiovascular mortality among men enrolled in the Multiple Risk Factor Intervention Trial. *Circulation, 109,* 66-70.

Mayou, R., Foster, A., & Williamson, B. (1978). Psychosocial adjustment in patients one year after myocardial infarction. *J.Psychosom.Res., 22,* 447-453.

Mayou, R. (1979). Psychological reactions to myocardial infarction. *J.R.Coll.Physicians Lond, 13,* 103-105.

Mayou, R. (1984). Prediction of emotional and social outcome after a heart attack. *J.Psychosom.Res., 28,* 17-25.

Mayou, R. A., Gill, D., Thompson, D. R., Day, A., Hicks, N., Volmink, J. et al. (2000). Depression and anxiety as predictors of outcome after myocardial infarction. *Psychosom.Med., 62,* 212-219.

McCraty, R., Atkinson, M., Tiller, W. A., Rein, G., & Watkins, A. D. (1995). The effects of emotions on short-term power spectrum analysis of heart rate variability. *Am.J.Cardiol., 76,* 1089-1093.

McEwen, B. S. (2000). Allostasis and allostatic load: implications for neuropsychopharmacology. *Neuropsychopharmacology, 22,* 108-124.

McEwen, B. S. (2000). Protective and damaging effects of stress mediators: central role of the brain. *Prog.Brain Res., 122,* 25-34.

McEwen, B. S. (2008). Central effects of stress hormones in health and disease: Understanding the protective and damaging effects of stress and stress mediators. *Eur.J.Pharmacol., 583,* 174-185.

Meade, T. W., Ruddock, V., Stirling, Y., Chakrabarti, R., & Miller, G. J. (1993). Fibrinolytic activity, clotting factors, and long term incidence of ischaemic heart disease in the Northwick Park Heart Study. *Lancet, 342,* 1076-1079.

Medalie, J. H., Snyder, M., Groen, J. J., Neufeld, H. N., Goldbourt, U., & Riss, E. (1973). Angina pectoris among 10,000 men. 5 year incidence and univariate analysis. *Am.J.Med., 55,* 583-594.

Medalie, J. H. & Goldbourt, U. (1976). Angina pectoris among 10,000 men. II. Psychosocial and other risk factors as evidenced by a multivariate analysis of a five year incidence study. *Am.J.Med., 60,* 910-921.

Meisel, S. R., Kutz, I., Dayan, K. I., Pauzner, H., Chetboun, I., Arbel, Y. et al. (1991). Effect of Iraqi missile war on incidence of acute myocardial infarction and sudden death in Israeli civilians. *Lancet, 338,* 660-661.

Melanson, E. L. (2000). Resting heart rate variability in men varying in habitual physical activity. *Med.Sci.Sports Exerc., 32,* 1894-1901.

Meltzer, H. (1989). Serotonergic dysfunction in depression. *Br.J.Psychiatry Suppl,* 25-31.

Mendes de Leon, C. F., Kop, W. J., de Swart, H. B., Bar, F. W., & Appels, A. P. (1996). Psychosocial characteristics and recurrent events after percutaneous transluminal coronary angioplasty. *Am.J.Cardiol., 77,* 252-255.

Mendes de Leon, C. F., Krumholz, H. M., Vaccarino, V., Williams, C. S., Glass, T. A., Berkman, L. F. et al. (1998). A population-based perspective of changes in health-related quality of life after myocardial infarction in older men and women. *J.Clin.Epidemiol., 51,* 609-616.

Mendes de Leon, C. F., Czajkowski, S. M., Freedland, K. E., Bang, H., Powell, L. H., Wu, C. et al. (2006). The effect of a psychosocial intervention and quality of life after acute myocardial infarction: the Enhancing Recovery in Coronary Heart Disease (ENRICHD) clinical trial. *J.Cardiopulm.Rehabil., 26,* 9-13.

Meredith, I. T., Broughton, A., Jennings, G. L., & Esler, M. D. (1991). Evidence of a selective increase in cardiac sympathetic activity in patients with sustained ventricular arrhythmias. *N.Engl.J.Med., 325,* 618-624.

Middleton, RA., & Byrd, E.K. (1996). Psychosocial factors and hospital readmission status of older persons with cardiovascular disease. *Journal of applied rehabilitation counseling, 27,* 3-10.

Mihatov, S., Bergovec, M., Prpic, H., Heitzler, V. N., Batarelo, V., Rogan, S. et al. (1995). Incidence and hospital mortality of acute coronary artery disease among civilians in Zagreb during air-raid alarms. *Acta Med.Croatica, 49,* 49-52.

Miller, G. E., Cohen, S., & Herbert, T. B. (1999). Pathways linking major depression and immunity in ambulatory female patients. *Psychosom.Med., 61,* 850-860.

Miller, G. E., Dopp, J. M., Myers, H. F., Stevens, S. Y., & Fahey, J. L. (1999). Psychosocial predictors of natural killer cell mobilisation during marital conflict. *Health Psychol., 18,* 262-271.

Miller, T. Q., Smith, T. W., Turner, C. W., Guijarro, M. L., & Hallet, A. J. (1996). A meta-analytic review of research on hostility and physical health. *Psychol.Bull., 119,* 322-348.

Mital, A., Desai, A., & Mital, A. (2004). Return to work after a coronary event. *J.Cardiopulm.Rehabil., 24,* 365-373.

Mittag, O., Kolenda, K. D., Nordman, K. J., Bernien, J., & Maurischat, C. (2001). Return to work after myocardial infarction/coronary artery bypass grafting: patients' and physicians' initial viewpoints and outcome 12 months later. *Soc.Sci.Med., 52,* 1441-1450.

Mittleman, M. A., Maclure, M., Tofler, G. H., Sherwood, J. B., Goldberg, R. J., & Muller, J. E. (1993). Triggering of acute myocardial infarction by heavy physical exertion. Protection against triggering by regular exertion. Determinants of Myocardial Infarction Onset Study Investigators. *N.Engl.J.Med., 329,* 1677-1683.

Mittleman, M. A., Maclure, M., Sherwood, J. B., Mulry, R. P., Tofler, G. H., Jacobs, S. C. et al. (1995). Triggering of acute myocardial infarction onset by episodes of anger. Determinants of Myocardial Infarction Onset Study Investigators. *Circulation, 92,* 1720-1725.

Mittleman, M. A., Mintzer, D., Maclure, M., Tofler, G. H., Sherwood, J. B., & Muller, J. E. (1999). Triggering of myocardial infarction by cocaine. *Circulation, 99,* 2737-2741.

Moller, J., Hallqvist, J., Diderichsen, F., Theorell, T., Reuterwall, C., & Ahlbom, A. (1999). Do episodes of anger trigger myocardial infarction? A case- crossover analysis in the Stockholm Heart Epidemiology Program (SHEEP). *Psychosomatic Medicine, 61,* 842-849.

Moller, J., Hessen-Soderman, A. C., & Hallqvist, J. (2004). Differential misclassification of exposure in case-crossover studies. *Epidemiology, 15,* 589-596.

Moller, J., Theorell, T., de Faire, U., Ahlbom, A., & Hallqvist, J. (2005). Work related stressful life events and the risk of myocardial infarction. Case-control and case-crossover analyses within the Stockholm heart epidemiology programme (SHEEP). *J.Epidemiol.Community Health, 59,* 23-30.

Monk, T. H., Fookson, J. E., Moline, M. L., & Pollak, C. P. (1985). Diurnal variation in mood and performance in a time-isolated environment. *Chronobiol.Int., 2,* 185-193.

Moser, M., Lehofer, M., Hoehn-Saric, R., McLeod, D. R., Hildebrandt, G., Steinbrenner, B. et al. (1998). Increased heart rate in depressed subjects in spite of unchanged autonomic balance? *J.Affect.Disord., 48,* 115-124.

Mulcahy, D., Keegan, J., Cunningham, D., Quyyumi, A., Crean, P., Park, A. et al. (1988). Circadian variation of total ischaemic burden and its alteration with anti-anginal agents. *Lancet, 2,* 755-759.

Muller, J. E., Tofler, G. H., & Stone, P. H. (1989). Circadian variation and triggers of onset of acute cardiovascular disease. *Circulation, 79,* 733-743.

Musselman, D. L., Tomer, A., Manatunga, A. K., Knight, B. T., Porter, M. R., Kasey, S. et al. (1996). Exaggerated platelet reactivity in major depression. *Am.J.Psychiatry, 153,* 1313-1317.

Musselman, D. L. & Nemeroff, C. B. (2000). Depression really does hurt your heart: stress, depression, and cardiovascular disease. *Prog.Brain Res., 122,* 43-59.

Naghavi, M., Libby, P., Falk, E., Casscells, S. W., Litovsky, S., Rumberger, J. et al. (2003). From vulnerable plaque to vulnerable patient: a call for new definitions and risk assessment strategies: Part I. *Circulation, 108,* 1664-1672.

Nash, I. S., Curtis, L. H., & Rubin, H. (1999). Predictors of patient-reported physical and mental health 6 months after percutaneous coronary revascularization. *Am.Heart J., 138,* 422-429.

Nelson, J. C. & Davis, J. M. (1997). DST studies in psychotic depression: a meta-analysis. *Am.J.Psychiatry, 154,* 1497-1503.

Niaura, R. & Goldstein, M. G. (1992). Psychological factors affecting physical condition. Cardiovascular disease literature review. Part II: Coronary artery disease and sudden death and hypertension. *Psychosomatics, 33,* 146-155.

Niaura, R., Todaro, J. F., Stroud, L., Spiro, A., III, Ward, K. D., & Weiss, S. (2002). Hostility, the metabolic syndrome, and incident coronary heart disease. *Health Psychol., 21,* 588-593.

Nicholson, A., Kuper, H., & Hemingway, H. (2006). Depression as an aetiologic and prognostic factor in coronary heart disease: a meta-analysis of 6362 events among 146 538 participants in 54 observational studies. *Eur.Heart J., 27,* 2763-2774.

Nijm, J., Kristenson, M., Olsson, A. G., & Jonasson, L. (2007). Impaired cortisol response to acute stressors in patients with coronary disease. Implications for inflammatory activity. *J.Intern.Med., 262,* 375-384.

Nolan, J., Batin, P. D., Andrews, R., Lindsay, S. J., Brooksby, P., Mullen, M. et al. (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,* 1510-1516.

Orth-Gomer, K. & Unden, A. L. (1990). Type A behavior, social support, and coronary risk: interaction and significance for mortality in cardiac patients. *Psychosom.Med., 52,* 59-72.

Orth-Gomer, K., Rosengren, A., & Wilhelmsen, L. (1993). Lack of social support and incidence of coronary heart disease in middle-aged Swedish men. *Psychosom.Med., 55,* 37-43.

Orth-Gomer, K., Wamala, S. P., Horsten, M., Schenck-Gustafsson, K., Schneiderman, N., & Mittleman, M. A. (2000). Marital stress worsens prognosis in women with coronary heart disease: The Stockholm Female Coronary Risk Study. *JAMA, 284,* 3008-3014.

Ostir, G. V., Markides, K. S., Peek, M. K., & Goodwin, J. S. (2001). The association between emotional well-being and the incidence of stroke in older adults. *Psychosom.Med., 63,* 210-215.

Otte, C., Marmar, C. R., Pipkin, S. S., Moos, R., Browner, W. S., & Whooley, M. A. (2004). Depression and 24-hour urinary cortisol in medical outpatients with coronary heart disease: The Heart and Soul Study. *Biol.Psychiatry, 56,* 241-247.

Owens, M. J. & Nemeroff, C. B. (1994). Role of serotonin in the pathophysiology of depression: focus on the serotonin transporter. *Clin.Chem., 40,* 288-295.

Palatini, P. & Julius, S. (1997). Heart rate and the cardiovascular risk. *J.Hypertens., 15,* 3-17.

Palatini, P. & Julius, S. (1999). The physiological determinants and risk correlations of elevated heart rate. *Am.J.Hypertens., 12,* 3S-8S.

Palatini, P. (1999). Elevated heart rate as a predictor of increased cardiovascular morbidity. *J.Hypertens.Suppl, 17,* S3-10.

Parati, G., Antonicelli, R., Guazzarotti, F., Paciaroni, E., & Mancia, G. (2001). Cardiovascular effects of an earthquake: direct evidence by ambulatory blood pressure monitoring. *Hypertension, 38,* 1093-1095.

Patterson, S. M., Krantz, D. S., Montgomery, L. C., Deuster, P. A., Hedges, S. M., & Nebel, L. E. (1993). Automated physical activity monitoring: validation and comparison with physiological and self-report measures. *Psychophysiology, 30,* 296-305.

Peeters, F., Nicholson, N. A., & Berkhof, J. (2003). Cortisol responses to daily events in major depressive disorder. *Psychosom.Med., 65,* 836-841.

Peeters, F., Berkhof, J., Delespaul, P., Rottenberg, J., & Nicolson, N. A. (2006). Diurnal mood variation in major depressive disorder. *Emotion., 6,* 383-391.

Penninx, B. W., Guralnik, J. M., Mendes de Leon, C. F., Pahor, M., Visser, M., Corti, M. C. et al. (1998). Cardiovascular events and mortality in newly and chronically depressed persons > 70 years of age. *Am.J.Cardiol., 81,* 988-994.

Penninx, B. W., Beekman, A. T., Honig, A., Deeg, D. J., Schoevers, R. A., van Eijk, J. T. et al. (2001). Depression and cardiac mortality: results from a community-based longitudinal study. *Arch.Gen.Psychiatry, 58,* 221-227.

Penninx, B. W., Kritchevsky, S. B., Yaffe, K., Newman, A. B., Simonsick, E. M., Rubin, S. et al. (2003). Inflammatory markers and depressed mood in older persons: results from the Health, Aging and Body Composition study. *Biol.Psychiatry, 54,* 566-572.

Pepine, C. J., Cohn, P. F., Deedwania, P. C., Gibson, R. S., Handberg, E., Hill, J. A. et al. (1994). Effects of treatment on outcome in mildly symptomatic patients with ischemia during daily life. The Atenolol Silent Ischemia Study (ASIST). *Circulation, 90,* 762-768.

Peters, A., von Klot, S., Heier, M., Trentinaglia, I., Hormann, A., Wichmann, H. E. et al. (2004). Exposure to traffic and the onset of myocardial infarction. *N.Engl.J.Med., 351,* 1721-1730.

Peterson, E. D., Shaw, L. J., & Califf, R. M. (1997). Risk stratification after myocardial infarction. *Ann.Intern.Med., 126,* 561-582.

Petrie, K. J., Weinman, J., Sharpe, N., & Buckley, J. (1996). Role of patients' view of their illness in predicting return to work and functioning after myocardial infarction: longitudinal study. *BMJ, 312,* 1191-1194.

Petrie, K. J., Cameron, L. D., Ellis, C. J., Buick, D., & Weinman, J. (2002). Changing illness perceptions after myocardial infarction: an early intervention randomized controlled trial. *Psychosom.Med., 64,* 580-586.

Phillips, D. P. & King, E. W. (1988). Death takes a holiday: mortality surrounding major social occasions. *Lancet, 2,* 728-732.

Phillips, D. P., Liu, G. C., Kwok, K., Jarvinen, J. R., Zhang, W., & Abramson, I. S. (2001). The Hound of the Baskervilles effect: natural experiment on the influence of psychological stress on timing of death. *BMJ, 323,* 1443-1446.

Phillips, D. P., Jarvinen, J. R., Abramson, I. S., & Phillips, R. R. (2004). Cardiac mortality is higher around Christmas and New Year's than at any other time: the holidays as a risk factor for death. *Circulation, 110,* 3781-3788.

Plotsky, P. M., Owens, M. J., & Nemeroff, C. B. (1998). Psychoneuroendocrinology of depression. Hypothalamic-pituitary-adrenal axis. *Psychiatr.Clin.North Am., 21,* 293-307.

Podrid, P. J. (1990). Silent ischemia, ventricular arrhythmia and sudden cardiac death. *J.Am.Coll.Cardiol., 16,* 55-56.

Podrid, P. J., Fuchs, T., & Candinas, R. (1990). Role of the sympathetic nervous system in the genesis of ventricular arrhythmia. *Circulation, 82,* 1103-1113.

Polk, D. E., Cohen, S., Doyle, W. J., Skoner, D. P., & Kirschbaum, C. (2005). State and trait affect as predictors of salivary cortisol in healthy adults. *Psychoneuroendocrinology, 30,* 261-272.

Ponikowski, P., Rosano, G. M., Amadi, A. A., Collins, P., Coats, A. J., Poole-Wilson, P. A. et al. (1996). Transient autonomic dysfunction precedes ST-segment depression in patients with syndrome X. *Am.J.Cardiol., 77,* 942-947.

Poole, W. K., Chi, J. S., Walton, J. D., Kandefer, S., & Kloner, R. A. (2005). Increased cardiovascular mortality associated with the turn of the millennium in Los Angeles County, California. *J.Epidemiol.Community Health, 59,* 205-206.

Potter, E. K. (1982). Angiotensin inhibits action of vagus nerve at the heart. *Br.J.Pharmacol., 75,* 9-11.

Potts, S. G. & Bass, C. M. (1993). Psychosocial outcome and use of medical resources in patients with chest pain and normal or near-normal coronary arteries: a long term follow-up study. *Q.J.Med., 86,* 583-593.

Pozzati, A., Pancaldi, L. G., Di Pasquale, G., Pinelli, G., & Bugiardini, R. (1996). Transient sympathovagal imbalance triggers "ischemic" sudden death in patients undergoing electrocardiographic Holter monitoring. *J.Am.Coll.Cardiol., 27,* 847-852.

Pratt, L. A., Ford, D. E., Crum, R. M., Armenian, H. K., Gallo, J. J., & Eaton, W. W. (1996). Depression, psychotropic medication, and risk of myocardial infarction. Prospective data from the Baltimore ECA follow-up. *Circulation, 94,* 3123-3129.

Pressman, S. D. & Cohen, S. (2005). Does positive affect influence health? *Psychol.Bull., 131,* 925-971.

Pruessner, J. C., Wolf, O. T., Hellhammer, D. H., Buske-Kirschbaum, A., von Auer, K., Jobst, S. et al. (1997). Free cortisol levels after awakening: a reliable biological marker for the assessment of adrenocortical activity. *Life Sci., 61,* 2539-2549.

Pruessner, J. C., Hellhammer, D. H., & Kirschbaum, C. (1999). Burnout, perceived stress, and cortisol responses to awakening. *Psychosom.Med., 61,* 197-204.

Pruessner, M., Hellhammer, D. H., Pruessner, J. C., & Lupien, S. J. (2003). Self-reported depressive symptoms and stress levels in healthy young men: associations with the cortisol response to awakening. *Psychosom.Med., 65,* 92-99.

Radloff, L. S. (1977). The CES-D Scale: A Self-Report Depression Scale for Research in the General Population. *Applied Psychological Measurement, 1,* 385-401.

Ragland, D. R. & Brand, R. J. (1988). Type A behavior and mortality from coronary heart disease. *N.Engl.J.Med., 318,* 65-69.

Ragland, D. R. & Brand, R. J. (1988). Coronary heart disease mortality in the Western Collaborative Group Study. Follow-up experience of 22 years. *Am.J.Epidemiol., 127,* 462-475.

Ratey, J. J., Sorgi, P., O'Driscoll, G. A., Sands, S., Daehler, M. L., Fletcher, J. R. et al. (1992). Nadolol to treat aggression and psychiatric symptomatology in chronic psychiatric inpatients: a double-blind, placebo-controlled study. *J.Clin.Psychiatry, 53,* 41-46.

Rawles, J., Light, J., & Watt, M. (1992). Quality of life in the first 100 days after suspected acute myocardial infarction--a suitable trial endpoint? *J.Epidemiol.Community Health, 46,* 612-616.

Rechlin, T., Weis, M., & Claus, D. (1994). Heart rate variability in depressed patients and differential effects of paroxetine and amitriptyline on cardiovascular autonomic functions. *Pharmacopsychiatry, 27,* 124-128.

Rechlin, T., Weis, M., Spitzer, A., & Kaschka, W. P. (1994). Are affective disorders associated with alterations of heart rate variability? *J.Affect.Disord., 32,* 271-275.

Reed, D., McGee, D., Yano, K., & Feinleib, M. (1983). Social networks and coronary heart disease among Japanese men in Hawaii. *Am.J.Epidemiol., 117,* 384-396.

Rennie, K. L., Hemingway, H., Kumari, M., Brunner, E., Malik, M., & Marmot, M. (2003). Effects of moderate and vigorous physical activity on heart rate variability in a British study of civil servants. *Am.J.Epidemiol., 158,* 135-143.

Roberts, A. D., Wessely, S., Chalder, T., Papadopoulos, A., & Cleare, A. J. (2004). Salivary cortisol response to awakening in chronic fatigue syndrome. *Br.J.Psychiatry, 184,* 136-141.

Rocco, M. B., Campbell, S., Barry, J., Rebecca, G., Nabel, E., Deanfield, J. et al. (1985). Activity of transient myocardial ischemia out of hospital in coronary artery disease and implications for management. *Am.J.Cardiol., 56,* 191-221.

Rosengren, A., Tibblin, G., & Wilhelmsen, L. (1993). Low systolic blood pressure and self perceived wellbeing in middle aged men. *BMJ, 306,* 243-246.

Rosengren, A., Hawken, S., Ounpuu, S., Sliwa, K., Zubaid, M., Almahmeed, W. A. et al. (2004). Association of psychosocial risk factors with risk of acute myocardial infarction in 11119 cases and 13648 controls from 52 countries (the INTERHEART study): case-control study. *Lancet, 364,* 953-962.

Rosenman, R. H., Brand, R. J., Jenkins, D., Friedman, M., Straus, R., & Wurm, M. (1975). Coronary heart disease in Western Collaborative Group Study. Final follow-up experience of 8 1/2 years. *JAMA, 233,* 872-877.

Rosenwinkel, E. T., Bloomfield, D. M., Arwady, M. A., & Goldsmith, R. L. (2001). Exercise and autonomic function in health and cardiovascular disease. *Cardiol.Clin., 19,* 369-387.

Ross, R. (1999). Atherosclerosis is an inflammatory disease. *Am.Heart J., 138,* S419-S420.

Rottenberg, J., Chambers, A. S., Allen, J. J., & Manber, R. (2007). Cardiac vagal control in the severity and course of depression: The importance of symptomatic heterogeneity. *J.Affect.Disord.*.

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

Rozanski, A., Blumenthal, J. A., Davidson, K. W., Saab, P. G., & Kubzansky, L. (2005). The epidemiology, pathophysiology, and management of psychosocial risk factors in cardiac practice: the emerging field of behavioral cardiology. *J.Am.Coll.Cardiol., 45,* 637-651.

Ruberman, W., Weinblatt, E., Goldberg, J. D., & Chaudhary, B. S. (1984). Psychosocial influences on mortality after myocardial infarction. *N.Engl.J.Med., 311,* 552-559.

Rugulies, R. (2002). Depression as a predictor for coronary heart disease. a review and meta-analysis. *Am.J.Prev.Med., 23,* 51-61.

Ruidavets, J. B., Paterniti, S., Bongard, V., Giroux, M., Cassadou, S., & Ferrieres, J. (2006). Triggering of acute coronary syndromes after a chemical plant explosion. *Heart, 92,* 257-258.

Rumsfeld, J. S., MaWhinney, S., McCarthy, M., Jr., Shroyer, A. L., VillaNueva, C. B., O'Brien, M. et al. (1999). Health-related quality of life as a predictor of mortality following coronary artery bypass graft surgery. Participants of the Department of Veterans Affairs Cooperative Study Group on Processes, Structures, and Outcomes of Care in Cardiac Surgery. *JAMA, 281,* 1298-1303.

Ryan, T. J., Antman, E. M., Brooks, N. H., Califf, R. M., Hillis, L. D., Hiratzka, L. F. et al. (1999). 1999 update: ACC/AHA Guidelines for the Management of Patients With Acute Myocardial Infarction: Executive Summary and Recommendations: A report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee on Management of Acute Myocardial Infarction). *Circulation, 100,* 1016-1030.

Ryff, C. D. (1989). In the eye of the beholder: views of psychological well-being among middle-aged and older adults. *Psychol.Aging, 4,* 195-201.

Ryff, C. D., Singer, B. H., & Dienberg, L. G. (2004). Positive health: connecting well-being with biology. *Philos.Trans.R.Soc.Lond B Biol.Sci., 359,* 1383-1394.

Sandrone, G., Mortara, A., Torzillo, D., La Rovere, M. T., Malliani, A., & Lombardi, F. (1994). Effects of beta blockers (atenolol or metoprolol) on heart rate variability after acute myocardial infarction. *Am.J.Cardiol., 74,* 340-345.

Sapolsky, R., Rivier, C., Yamamoto, G., Plotsky, P., & Vale, W. (1987). Interleukin-1 stimulates the secretion of hypothalamic corticotropin-releasing factor. *Science, 238,* 522-524.

Sawayama, Y., Ariyama, I., Hamada, M., Otaguro, S., Machi, T., Taira, Y. et al. (2005). Association between chronic Helicobacter pylori infection and acute ischemic stroke: Fukuoka Harasanshin Atherosclerosis Trial (FHAT). *Atherosclerosis, 178,* 303-309.

Scheier, M. F., Matthews, K. A., Owens, J. F., Magovern, G. J., Sr., Lefebvre, R. C., Abbott, R. A. et al. (1989). Dispositional optimism and recovery from coronary artery bypass surgery: the beneficial effects on physical and psychological well-being. *J.Pers.Soc.Psychol., 57,* 1024-1040.

Scheier, M. F. & Carver, C. S. (1992). Effects of Optimism on Psychological and Physical Well-Being - Theoretical Overview and Empirical Update. *Cognitive Therapy and Research, 16,* 201-228.

Scheier, M. F., Carver, C. S., & Bridges, M. W. (1994). Distinguishing optimism from neuroticism (and trait anxiety, self-mastery, and self-esteem): a reevaluation of the Life Orientation Test. *J.Pers.Soc.Psychol., 67,* 1063-1078.

Schins, A., Tulner, D., Lousberg, R., Kenis, G., Delanghe, J., Crijns, H. J. et al. (2005). Inflammatory markers in depressed post-myocardial infarction patients. *J.Psychiatr.Res., 39,* 137-144.

Schmidt-Reinwald, A., Pruessner, J. C., Hellhammer, D. H., Federenko, I., Rohleder, N., Schurmeyer, T. H. et al. (1999). The cortisol response to awakening in relation to different challenge tests and a 12-hour cortisol rhythm. *Life Sci., 64,* 1653-1660.

Schnall, P. L., Landsbergis, P. A., & Baker, D. (1994). Job strain and cardiovascular disease. *Annu.Rev.Public Health, 15,* 381-411.

Schnall, P. L., Schwartz, J. E., Landsbergis, P. A., Warren, K., & Pickering, T. G. (1998). A longitudinal study of job strain and ambulatory blood pressure: results from a three-year follow-up. *Psychosom.Med., 60,* 697-706.

Schulz, R., O'Brien, A. T., Bookwala, J., & Fleissner, K. (1995). Psychiatric and physical morbidity effects of dementia caregiving: prevalence, correlates, and causes. *Gerontologist, 35,* 771-791.

Schwartz, G. E., Weinberger, D. A., & Singer, J. A. (1981). Cardiovascular differentiation of happiness, sadness, anger, and fear following imagery and exercise. *Psychosom.Med., 43,* 343-364.

Seeman, T. E. (1996). Social ties and health: the benefits of social integration. *Ann.Epidemiol., 6,* 442-451.

Seligman, M. E. & Csikszentmihalyi, M. (2000). Positive psychology. An introduction. *Am.Psychol., 55,* 5-14.

Servoss, S. J., Januzzi, J. L., & Muller, J. E. (2002). Triggers of acute coronary syndromes. *Prog.Cardiovasc.Dis., 44,* 369-380.

Sesso, H. D., Kawachi, I., Vokonas, P. S., & Sparrow, D. (1998). Depression and the risk of coronary heart disease in the Normative Aging Study. *Am.J.Cardiol., 82,* 851-856.

Shapiro, D., Jamner, L. D., & Goldstein, I. B. (1997). Daily mood states and ambulatory blood pressure. *Psychophysiology, 34,* 399-405.

Shedd, O. L., Sears, S. F., Jr., Harvill, J. L., Arshad, A., Conti, J. B., Steinberg, J. S. et al. (2004). The World Trade Center attack: increased frequency of defibrillator shocks for ventricular arrhythmias in patients living remotely from New York City. *J.Am.Coll.Cardiol., 44,* 1265-1267.

Shen, B. J., Avivi, Y. E., Todaro, J. F., Spiro, A., III, Laurenceau, J. P., Ward, K. D. et al. (2008). Anxiety characteristics independently and prospectively predict myocardial infarction in men the unique contribution of anxiety among psychologic factors. *J.Am.Coll.Cardiol., 51,* 113-119.

Sheps, D. S., McMahon, R. P., Pepine, C. J., Stone, P. H., Goldberg, A. D., Taylor, H. et al. (1998). Heterogeneity among cardiac ischemic and anginal responses to exercise, mental stress, and daily life. *Am.J.Cardiol., 82,* 1-6.

Sheps, D. S., McMahon, R. P., Becker, L., Carney, R. M., Freedland, K. E., Cohen, J. D. et al. (2002). Mental stress-induced ischemia and all-cause mortality in patients with coronary artery disease: Results from the Psychophysiological Investigations of Myocardial Ischemia study. *Circulation, 105,* 1780-1784.

Shetler, K., Marcus, R., Froelicher, V. F., Vora, S., Kalisetti, D., Prakash, M. et al. (2001). Heart rate recovery: validation and methodologic issues. *J.Am.Coll.Cardiol., 38,* 1980-1987.

Shumaker, S. A. & Hill, D. R. (1991). Gender differences in social support and physical health. *Health Psychol., 10,* 102-111.

Siegrist, J. (1996). Adverse health effects of high-effort/low-reward conditions. *J.Occup.Health Psychol., 1,* 27-41.

Siegrist, J. (2004). Psychosocial work environment and health: new evidence. *J.Epidemiol.Community Health, 58,* 888.

Singh, J. P., Larson, M. G., Tsuji, H., Evans, J. C., O'Donnell, C. J., & Levy, D. (1998). Reduced heart rate variability and new-onset hypertension: insights into pathogenesis of hypertension: the Framingham Heart Study. *Hypertension, 32,* 293-297.

Singh, J. P., Larson, M. G., O'Donnell, C. J., Wilson, P. F., Tsuji, H., Lloyd-Jones, D. M. et al. (2000). Association of hyperglycemia with reduced heart rate variability (The Framingham Heart Study). *Am.J.Cardiol., 86,* 309-312.

Sinha, R., Lovallo, W. R., & Parsons, O. A. (1992). Cardiovascular differentiation of emotions. *Psychosom.Med., 54,* 422-435.

Sirois, B. C. & Burg, M. M. (2003). Negative emotion and coronary heart disease. A review. *Behav.Modif., 27,* 83-102.

Sloan, R. P., Shapiro, P. A., Bagiella, E., Boni, S. M., Paik, M., Bigger, J. T., Jr. et al. (1994). Effect of mental stress throughout the day on cardiac autonomic control. *Biol.Psychol., 37,* 89-99.

Sloan, R. P., Shapiro, P. A., Bigger, J. T., Jr., Bagiella, E., Steinman, R. C., & Gorman, J. M. (1994). Cardiac autonomic control and hostility in healthy subjects. *Am.J.Cardiol., 74,* 298-300.

Smeeth, L., Thomas, S. L., Hall, A. J., Hubbard, R., Farrington, P., & Vallance, P. (2004). Risk of myocardial infarction and stroke after acute infection or vaccination. *N.Engl.J.Med., 351,* 2611-2618.

Smith, G. (2002). Scared to death? *BMJ, 325,* 1442-1443.

Smith, G. D., Ben Shlomo, Y., Beswick, A., Yarnell, J., Lightman, S., & Elwood, P. (2005). Cortisol, testosterone, and coronary heart disease: prospective evidence from the Caerphilly study. *Circulation, 112,* 332-340.

Smith, T. W. & Frohm, K. D. (1985). What's so unhealthy about hostility? Construct validity and psychosocial correlates of the Cook and Medley Ho scale. *Health Psychol., 4,* 503-520.

Smith, T. W. (1992). Hostility and health: current status of a psychosomatic hypothesis. *Health Psychol., 11,* 139-150.

Smith, T. W., Gallo, L. C., Goble, L., Ngu, L. Q., & Stark, K. A. (1998). Agency, communion, and cardiovascular reactivity during marital interaction. *Health Psychol., 17,* 537-545.

Smyth, J., Ockenfels, M. C., Porter, L., Kirschbaum, C., Hellhammer, D. H., & Stone, A. A. (1998). Stressors and mood measured on a momentary basis are associated with salivary cortisol secretion. *Psychoneuroendocrinology, 23,* 353-370.

Soderman, E., Lisspers, J., & Sundin, O. (2003). Depression as a predictor of return to work in patients with coronary artery disease. *Soc.Sci.Med., 56,* 193-202.

Soejima, K., Akaishi, M., Oyamada, K., Meguro, T., Mitamura, H., & Ogawa, S. (1999). Influence of age on ambulatory electrocardiogram-derived heart rate variability. *Can.J.Cardiol., 15,* 181-184.

Soejima, Y., Steptoe, A., Nozoe, S., & Tei, C. (1999). Psychosocial and clinical factors predicting resumption of work following acute myocardial infarction in Japanese men. *Int.J.Cardiol., 72,* 39-47.

Souverein, P. C., Berard, A., Van Staa, T. P., Cooper, C., Egberts, A. C., Leufkens, H. G. et al. (2004). Use of oral glucocorticoids and risk of cardiovascular and cerebrovascular disease in a population based case-control study. *Heart, 90,* 859-865.

Spijkerman, T. A., van den Brink, R. H., May, J. F., Winter, J. B., van Melle, J. P., de Jonge, P. et al. (2006). Decreased impact of post-myocardial infarction depression on cardiac prognosis? *J.Psychosom.Res., 61,* 493-499.

Sprafka, J. M., Burke, G. L., Folsom, A. R., McGovern, P. G., & Hahn, L. P. (1991). Trends in prevalence of diabetes mellitus in patients with myocardial infarction and effect of diabetes on survival. The Minnesota Heart Survey. *Diabetes Care, 14,* 537-543.

Stansfeld S, Fuhrer R. (2002). Social relations and coronary heart disease. In: Stansfeld SA, Marmot MG (Eds.). *Stress and the Heart: Psychosocial Pathways to Coronary Heart Disease.* London: BMJ Books, 72–85.

Stansfeld, S. A., Fuhrer, R., Shipley, M. J., & Marmot, M. G. (2002). Psychological distress as a risk factor for coronary heart disease in the Whitehall II Study. *International Journal of Epidemiology, 31,* 248-255.

Stein, P. K., Fauchier, L., & Babuty, D. (1999). Sudden death, arrhythmic events and measurements of heart rate variability. *J.Am.Coll.Cardiol., 34,* 2148-2149.

Stein, P. K., Carney, R. M., Freedland, K. E., Skala, J. A., Jaffe, A. S., Kleiger, R. E. et al. (2000). Severe depression is associated with markedly reduced heart rate variability in patients with stable coronary heart disease. *J.Psychosom.Res., 48,* 493-500.

Steinberg, J. S., Arshad, A., Kowalski, M., Kukar, A., Suma, V., Vloka, M. et al. (2004). Increased incidence of life-threatening ventricular arrhythmias in implantable defibrillator patients after the World Trade Center attack. *J.Am.Coll.Cardiol., 44,* 1261-1264.

Steptoe, A. & Ayers, S. (2005). Stress, health and illness. In: S. Sutton, A. Baum and M. Johnston (Eds.) Sage Handbook of Health Psychology. London: Sage.

Steptoe & Brydon, L. (2006). Psychological Factors and Coronary Heart Disease: The Role of Psychoneuroimmunological Processes. In: R. Ader (Eds.) *Psychoneuroimmunology. 4th edn.* Academic Press: San Diego.

Steptoe, A. (2007). Depression and Physical Illness. In: A. Steptoe (Ed). Cambridge University Press, 53-108.

Steptoe A. (2007). Cortisol awakening response. In: G Fink (Ed), *Encyclopedia of Stress, 2nd Edition.* Oxford: Academic Press, 649-653

Steptoe, A., Cropley, M., Griffith, J., & Kirschbaum, C. (2000). Job strain and anger expression predict early morning elevations in salivary cortisol. *Psychosom.Med., 62,* 286-292.

Steptoe, A., Wardle, J., & Marmot, M. (2005). Positive affect and health-related neuroendocrine, cardiovascular, and inflammatory processes. *Proc.Natl.Acad.Sci.U.S.A, 102,* 6508-6512.

Steptoe, A. & Wardle, J. (2005). Positive affect and biological function in everyday life. *Neurobiol.Aging, 26 Suppl 1,* 108-112.

Steptoe, A., Brydon, L., & Kunz-Ebrecht, S. (2005). Changes in financial strain over three years, ambulatory blood pressure, and cortisol responses to awakening. *Psychosom.Med., 67,* 281-287.

Steptoe, A., Strike, P. C., Perkins-Porras, L., McEwan, J. R., & Whitehead, D. L. (2006). Acute depressed mood as a trigger of acute coronary syndromes. *Biol.Psychiatry, 60,* 837-842.

Steptoe, A., Marmo, M., & Wardle, J. (2007). Positive affect and psychosocial processes related to health. *Br.J.Psychol.*.

Steptoe, A., Hamer, M., & Chida, Y. (2007). The effects of acute psychological stress on circulating inflammatory factors in humans: a review and meta-analysis. *Brain Behav.Immun., 21,* 901-912.

Steptoe, A., Gibson, E. L., Hamer, M., & Wardle, J. (2007). Neuroendocrine and cardiovascular correlates of positive affect measured by ecological momentary assessment and by questionnaire. *Psychoneuroendocrinology, 32,* 56-64.

Sterling P and Eyer J (1988). Allostasis: A new paradigm to explain arousal pathology. In: S. Fisher and J. Reason, Editors, *Handbook of Life Stress, Cognition, and Health*, New York, Wiley.

Stern, M. J., Pascale, L., & Ackerman, A. (1977). Life adjustment postmyocardial infarction: determining predictive variables. *Arch.Intern.Med., 137,* 1680-1685.

Stevens, R. J., Kothari, V., Adler, A. I., & Stratton, I. M. (2001). The UKPDS risk engine: a model for the risk of coronary heart disease in Type II diabetes (UKPDS 56). *Clin.Sci.(Lond), 101,* 671-679.

Stone, A. A., Neale, J. M., Cox, D. S., Napoli, A., Valdimarsdottir, H., & Kennedy-Moore, E. (1994). Daily events are associated with a secretory immune response to an oral antigen in men. *Health Psychol., 13,* 440-446.

Stone, AA, & Shiffman, S. (1994). Ecological momentary assessment (EMA) in behavioural medicine. *Annals of Behavioural Medicine., 16,* 199-202.

Stone, A. A., Shiffman, S., Schwartz, J. E., Broderick, J. E., & Hufford, M. R. (2003). Patient compliance with paper and electronic diaries. *Controlled Clinical Trials, 24,* 182-199.

Stone, A. A., Schwartz, J. E., Schkade, D., Schwarz, N., Krueger, A., & Kahneman, D. (2006). A population approach to the study of emotion: diurnal rhythms of a working day examined with the Day Reconstruction Method. *Emotion., 6,* 139-149.

Stone, P. H., Gibson, R. S., Glasser, S. P., DeWood, M. A., Parker, J. D., Kawanishi, D. T. et al. (1990). Comparison of propranolol, diltiazem, and nifedipine in the treatment of ambulatory ischemia in patients with stable angina. Differential effects on ambulatory ischemia, exercise performance, and anginal symptoms. The ASIS Study Group. *Circulation, 82,* 1962-1972.

Stone, P. H., Krantz, D. S., McMahon, R. P., Goldberg, A. D., Becker, L. C., Chaitman, B. R. et al. (1999). Relationship among mental stress-induced ischemia and ischemia during daily life and during exercise: the Psychophysiologic Investigations of Myocardial Ischemia (PIMI) study. *J.Am.Coll.Cardiol., 33,* 1476-1484.

Strauss, W. E., Fortin, T., Hartigan, P., Folland, E. D., & Parisi, A. F. (1995). A comparison of quality of life scores in patients with angina pectoris after angioplasty compared with after medical therapy. Outcomes of a randomized clinical trial. Veterans Affairs Study of Angioplasty Compared to Medical Therapy Investigators. *Circulation, 92,* 1710-1719.

Strik, J. J., van Praag, H. M., & Honig, A. (2003). [Depression after first myocardial infarction. A prospective study on incidence, prognosis, risk factors and treatment]. *Tijdschr.Gerontol.Geriatr., 34,* 104-112.

Strik, J. J., Denollet, J., Lousberg, R., & Honig, A. (2003). Comparing symptoms of depression and anxiety as predictors of cardiac events and increased health care consumption after myocardial infarction. *J.Am.Coll.Cardiol., 42,* 1801-1807.

Strike, P. C. & Steptoe, A. (2002). Depression, stress, and the heart. *Heart, 88,* 441-443.

Strike, P. C. & Steptoe, A. (2003). New insights into the mechanisms of temporal variation in the incidence of acute coronary syndromes. *Clin.Cardiol., 26,* 495-499.

Strike, P. C. & Steptoe, A. (2003). Systematic review of mental stress-induced myocardial ischaemia. *Eur.Heart J., 24,* 690-703.

Strike, P. C., Wardle, J., & Steptoe, A. (2004). Mild acute inflammatory stimulation induces transient negative mood. *J.Psychosom.Res., 57,* 189-194.

Strike, P. C. & Steptoe, A. (2005). Behavioral and emotional triggers of acute coronary syndromes: a systematic review and critique. *Psychosom.Med., 67,* 179-186.

Strike, P. C., Perkins-Porras, L., Whitehead, D. L., McEwan, J., & Steptoe, A. (2006). Triggering of acute coronary syndromes by physical exertion and anger: clinical and socio-demographic characteristics. *Heart, 92,* 1035-1040.

Strike, P. C., Magid, K., Whitehead, D. L., Brydon, L., Bhattacharyya, M. R., & Steptoe, A. (2006). Pathophysiological processes underlying emotional triggering of acute cardiac events. *Proc.Natl.Acad.Sci.U.S.A, 103,* 4322-4327.

Sullivan, M. D., LaCroix, A. Z., Spertus, J. A., & Hecht, J. (2000). Five-year prospective study of the effects of anxiety and depression in patients with coronary artery disease. *Am.J.Cardiol., 86,* 1135-8, A6, A9.

Sullivan, M. D., LaCroix, A. Z., Russo, J. E., & Walker, E. A. (2001). Depression and self-reported physical health in patients with coronary disease: mediating and moderating factors. *Psychosom.Med., 63,* 248-256.

Suzuki, S., Sakamoto, S., Miki, T., & Matsuo, T. (1995). Hanshin-Awaji earthquake and acute myocardial infarction. *Lancet, 345,* 981.

Taylor, C. B., Conrad, A., Wilhelm, F. H., Neri, E., DeLorenzo, A., Kramer, M. A. et al. (2006). Psychophysiological and cortisol responses to psychological stress in depressed and nondepressed older men and women with elevated cardiovascular disease risk. *Psychosom.Med., 68,* 538-546.

Tenerz, A., Nilsson, G., Forberg, R., Ohrvik, J., Malmberg, K., Berne, C. et al. (2003). Basal glucometabolic status has an impact on long term prognosis following an acute myocardial infarction in non-diabetic patients. *J.Intern.Med., 254,* 494-503.

Thayer, J. F., Friedman, B. H., & Borkovec, T. D. (1996). Autonomic characteristics of generalised anxiety disorder and worry. *Biol.Psychiatry, 39,* 255-266.

Theorell, T., Tsutsumi, A., Hallquist, J., Reuterwall, C., Hogstedt, C., Fredlund, P. et al. (1998). Decision latitude, job strain, and myocardial infarction: a study of working men in Stockholm. The SHEEP Study Group. Stockholm Heart epidemiology Program. *Am.J.Public Health, 88,* 382-388.

Thompson, D. R. & Lewin, R. J. (2000). Coronary disease. Management of the post-myocardial infarction patient: rehabilitation and cardiac neurosis. *Heart, 84,* 101-105.

Tiemeier, H., van Dijck, W., Hofman, A., Witteman, J. C., Stijnen, T., & Breteler, M. M. (2004). Relationship between atherosclerosis and late-life depression: the Rotterdam Study. *Arch.Gen.Psychiatry, 61,* 369-376.

Tofler, G. H., Stone, P. H., Maclure, M., Edelman, E., Davis, V. G., Robertson, T. et al. (1990). Analysis of possible triggers of acute myocardial infarction (the MILIS study). *Am.J.Cardiol., 66,* 22-27.

Tofler, G. H. & Muller, J. E. (2006). Triggering of acute cardiovascular disease and potential preventive strategies. *Circulation, 114,* 1863-1872.

Toubiana, L., Hanslik, T., & Letrilliart, L. (2001). French cardiovascular mortality did not increase during 1996 European football championship. *BMJ, 322,* 1306.

Townsend, P. (1990). Individual or social responsibility for premature death? Current controversies in the British debate about health. *Int.J.Health Serv., 20,* 373-392.

Trichopoulos, D., Katsouyanni, K., Zavitsanos, X., Tzonou, A., & Dalla-Vorgia, P. (1983). Psychological stress and fatal heart attack: the Athens (1981) earthquake natural experiment. *Lancet, 1,* 441-444.

Troxler, R. G., Sprague, E. A., Albanese, R. A., Fuchs, R., & Thompson, A. J. (1977). The association of elevated plasma cortisol and early atherosclerosis as demonstrated by coronary angiography. *Atherosclerosis, 26,* 151-162.

Trzcieniecka-Green, A. & Steptoe, A. (1996). The effects of stress management on the quality of life of patients following acute myocardial infarction or coronary bypass surgery. *Eur.Heart J., 17,* 1663-1670.

Tsigos, C. & Chrousos, G. P. (2002). Hypothalamic-pituitary-adrenal axis, neuroendocrine factors and stress. *Journal of Psychosomatic Research, 53,* 865-871.

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

Tsuji, H., Larson, M. G., Venditti, F. J., Jr., Manders, E. S., Evans, J. C., Feldman, C. L. et al. (1996). Impact of reduced heart rate variability on risk for cardiac events. The Framingham Heart Study. *Circulation, 94,* 2850-2855.

Uchino, B. N., Cacioppo, J. T., & Kiecolt-Glaser, J. K. (1996). The relationship between social support and physiological processes: a review with emphasis on underlying mechanisms and implications for health. *Psychol.Bull., 119,* 488-531.

Vaccarino, V., Johnson, B. D., Sheps, D. S., Reis, S. E., Kelsey, S. F., Bittner, V. et al. (2007). Depression, inflammation, and incident cardiovascular disease in women with suspected coronary ischemia: the National Heart, Lung, and Blood Institute-sponsored WISE study. *J.Am.Coll.Cardiol., 50,* 2044-2050.

Vaile, J. C., Fletcher, J., Al Ani, M., Ross, H. F., Littler, W. A., Coote, J. H. et al. (1999). Use of opposing reflex stimuli and heart rate variability to examine the effects of lipophilic and hydrophilic beta-blockers on human cardiac vagal control. *Clin.Sci.(Lond), 97,* 585-593.

Van Eck, M., Berkhof, H., Nicolson, N., & Sulon, J. (1996). The effects of perceived stress, traits, mood states, and stressful daily events on salivary cortisol. *Psychosom.Med., 58,* 447-458.

Van Eck, M., Nicolson, N. A., & Berkhof, J. (1998). Effects of stressful daily events on mood states: relationship to global perceived stress. *J.Pers.Soc.Psychol., 75,* 1572-1585.

van Eck, M. M., Nicolson, N. A., Berkhof, H., & Sulon, J. (1996). Individual differences in cortisol responses to a laboratory speech task and their relationship to responses to stressful daily events. *Biol.Psychol., 43,* 69-84.

van Jaarsveld, C. H., Sanderman, R., Miedema, I., Ranchor, A. V., & Kempen, G. I. (2001). Changes in health-related quality of life in older patients with acute myocardial infarction or congestive heart failure: a prospective study. *J.Am.Geriatr.Soc., 49,* 1052-1058.

van Jaarsveld, C. H., Sanderman, R., Ranchor, A. V., Ormel, J., van Veldhuisen, D. J., & Kempen, G. I. (2002). Gender-specific changes in quality of life following cardiovascular disease: a prospective study. *J.Clin.Epidemiol., 55,* 1105-1112.

van Melle, J. P., de Jonge, P., Spijkerman, T. A., Tijssen, J. G., Ormel, J., van Veldhuisen, D. J. et al. (2004). Prognostic association of depression following myocardial infarction with mortality and cardiovascular events: a meta-analysis. *Psychosom.Med., 66,* 814-822.

Vitaliano, P. P., Scanlan, J. M., Zhang, J., Savage, M. V., Brummett, B., Barefoot, J. et al. (2001). Are the salutogenic effects of social supports modified by income? A test of an "added value hypothesis". *Health Psychol., 20,* 155-165.

Vitaliano, P. P., Scanlan, J. M., Zhang, J., Savage, M. V., Hirsch, I. B., & Siegler, I. C. (2002). A path model of chronic stress, the metabolic syndrome, and coronary heart disease. *Psychosom.Med., 64,* 418-435.

Vitaliano, P. P., Zhang, J., & Scanlan, J. M. (2003). Is caregiving hazardous to one's physical health? A meta-analysis. *Psychol.Bull., 129,* 946-972.

Vogt, T. M., Mullooly, J. P., Ernst, D., Pope, C. R., & Hollis, J. F. (1992). Social networks as predictors of ischemic heart disease, cancer, stroke and hypertension: incidence, survival and mortality. *J.Clin.Epidemiol., 45,* 659-666.

Vogt, T., Pope, C., Mullooly, J., & Hollis, J. (1994). Mental health status as a predictor of morbidity and mortality: a 15-year follow-up of members of a health maintenance organization. *Am.J.Public Health, 84,* 227-231.

Von Arnim, T. (1996). Prognostic significance of transient ischemic episodes: response to treatment shows improved prognosis. Results of the Total Ischemic Burden Bisoprolol Study (TIBBs) follow-up. *J.Am.Coll.Cardiol., 28,* 20-24.

von Kanel, R., Mills, P. J., Fainman, C., & Dimsdale, J. E. (2001). Effects of psychological stress and psychiatric disorders on blood coagulation and fibrinolysis: a biobehavioral pathway to coronary artery disease? *Psychosom.Med., 63,* 531-544.

von Kanel, R., Mausbach, B. T., Kudielka, B. M., & Orth-Gomer, K. (2007). Relation of morning serum cortisol to prothrombotic activity in women with stable coronary artery disease. *J.Thromb.Thrombolysis.*.

Waldstein, S. R., Kop, W. J., Schmidt, L. A., Haufler, A. J., Krantz, D. S., & Fox, N. A. (2000). Frontal electrocortical and cardiovascular reactivity during happiness and anger. *Biol.Psychol., 55,* 3-23.

Wallston, B. D. & Wallston, K. A. (1978). Locus of control and health: a review of the literature. *Health Educ.Monogr, 6,* 107-117.

Wallston, B. S., Wallston, K. A., Kaplan, G. D., & Maides, S. A. (1976). Development and validation of the health locus of control (HLC) scale. *J.Consult Clin.Psychol., 44,* 580-585.

Wallston, K. A., Wallston, B. S., & DeVellis, R. (1978). Development of the Multidimensional Health Locus of Control (MHLC) Scales. *Health Educ.Monogr, 6,* 160-170.

Wang, X., Thayer, J. F., Treiber, F., & Snieder, H. (2005). Ethnic Differences and Heritability of Heart Rate Variability in African- and European American Youth. *The American Journal of Cardiology, 96,* 1166-1172.

Wannamethee, G. & Shaper, A. G. (1994). The association between heart rate and blood pressure, blood lipids and other cardiovascular risk factors. *J.Cardiovasc.Risk, 1,* 223-230.

Ware, J. E., Jr. & Sherbourne, C. D. (1992). The MOS 36-item short-form health survey (SF-36). I. Conceptual framework and item selection. *Med.Care, 30,* 473-483.

Ware, J. E., Jr. (1994). Hypertension--when is the clinical problem solved? When quality of life is secured. *Cardiology, 85 Suppl 1,* 65-70.

Ware, J. E., Jr. & Gandek, B. (1998). Methods for testing data quality, scaling assumptions, and reliability: the IQOLA Project approach. International Quality of Life Assessment. *J.Clin.Epidemiol., 51,* 945-952.

Watkins, L. L., Grossman, P., Krishnan, R., & Blumenthal, J. A. (1999). Anxiety reduces baroreflex cardiac control in older adults with major depression. *Psychosom.Med., 61,* 334-340.

Watson, D., Clark, L. A., & Tellegen, A. (1988). Development and validation of brief measures of positive and negative affect: the PANAS scales. *J.Pers.Soc.Psychol., 54,* 1063-1070.

Weber, B., Lewicka, S., Deuschle, M., Colla, M., Vecsei, P., & Heuser, I. (2000). Increased diurnal plasma concentrations of cortisone in depressed patients. *J.Clin.Endocrinol.Metab, 85,* 1133-1136.

Weinman, J., Petrie, K. J., Moss-morris, R., & Horne, R. (1996). The illness perception questionnaire: A new method for assessing the cognitive representation of illness. *Psychology & Health, 11,* 431-445.

Welin, C., Lappas, G., & Wilhelmsen, L. (2000). Independent importance of psychosocial factors for prognosis after myocardial infarction. *J.Intern.Med., 247,* 629-639.

Whang, W., Albert, C. M., Sears, S. F., Lampert, R., Conti, J. B., Wang, P. J. et al. (2005). Depression as a predictor for appropriate shocks among patients with Implantable cardioverter-defibrillators - Results from the Triggers of Ventricular Arrhythmias (TOVA) study. *Journal of the American College of Cardiology, 45,* 1090-1095.

Whitehead, D. L., Strike, P., Perkins-Porras, L., & Steptoe, A. (2005). Frequency of distress and fear of dying during acute coronary syndromes and consequences for adaptation. *Am.J.Cardiol., 96,* 1512-1516.

Whitehead, D. L., Perkins-Porras, L., Strike, P. C., & Steptoe, A. (2006). Post-traumatic stress disorder in patients with cardiac disease: predicting vulnerability from emotional responses during admission for acute coronary syndromes. *Heart, 92,* 1225-1229.

Whitehead, D. L., Perkins-Porras, L., Strike, P. C., Magid, K., & Steptoe, A. (2007). Cortisol awakening response is elevated in acute coronary syndrome patients with type-D personality. *J.Psychosom.Res., 62,* 419-425.

Whitmarsh, A., Koutantji, M., & Sidell, K. (2003). Illness perceptions, mood and coping in predicting attendance at cardiac rehabilitation. *Br.J.Health Psychol., 8,* 209-221.

Wiklund, I., Sanne, H., Elmfeldt, D., Vedin, A., & Wilhelmsson, C. (1984). Emotional reaction, health preoccupation and sexual activity two months after a myocardial infarction. *Scand.J.Rehabil.Med., 16,* 47-56.

Wiklund, I., Sanne, H., Vedin, A., & Wilhelmsson, C. (1984). Psychosocial outcome one year after a first myocardial infarction. *J.Psychosom.Res., 28,* 309-321.

Wiklund, I., Sanne, H., Vedin, A., & Wilhelmsson, C. (1984). Sick-role and attitude towards disease and working life two months after a myocardial infarction. *Scand.J.Rehabil.Med., 16,* 57-64.

Wiklund, I., Oden, A., Sanne, H., Ulvenstam, G., Wilhelmsson, C., & Wilhelmsen, L. (1988). Prognostic importance of somatic and psychosocial variables after a first myocardial infarction. *Am.J.Epidemiol., 128,* 786-795.

Wiklund, I., Herlitz, J., & Hjalmarson, A. (1989). Quality of life five years after myocardial infarction. *Eur.Heart J., 10,* 464-472.

Wiklund, I., I (1993). Subjective symptoms and well-being differ in women and men after myocardial infarction. *European Heart Journal, 14,* 1315-1319.

Williams, M. J., Poulton, R., & Williams, S. (2002). Relationship of serum ferritin with cardiovascular risk factors and inflammation in young men and women. *Atherosclerosis, 165,* 179-184.

Williams, R. B., Jr., Haney, T. L., Lee, K. L., Kong, Y. H., Blumenthal, J. A., & Whalen, R. E. (1980). Type A behavior, hostility, and coronary atherosclerosis. *Psychosom.Med., 42,* 539-549.

Willich, S. N., Levy, D., Rocco, M. B., Tofler, G. H., Stone, P. H., & Muller, J. E. (1987). Circadian variation in the incidence of sudden cardiac death in the Framingham Heart Study population. *Am.J.Cardiol., 60,* 801-806.

Willich, S. N., Lowel, H., Lewis, M., Arntz, R., Baur, R., Winther, K. et al. (1991). Association of wake time and the onset of myocardial infarction. Triggers and mechanisms of myocardial infarction (TRIMM) pilot study. TRIMM Study Group. *Circulation, 84,* VI62-VI67.

Willich, S. N., Lewis, M., Lowel, H., Arntz, H. R., Schubert, F., & Schroder, R. (1993). Physical exertion as a trigger of acute myocardial infarction. Triggers and Mechanisms of Myocardial Infarction Study Group. *N.Engl.J.Med., 329,* 1684-1690.

Willich, S. N., Maclure, M., Mittleman, M., Arntz, H. R., & Muller, J. E. (1993). Sudden cardiac death. Support for a role of triggering in causation. *Circulation, 87,* 1442-1450.

Willich, S. N. (1999). European survey on circadian variation of angina pectoris (ESCVA): design and preliminary results. *J.Cardiovasc.Pharmacol., 34 Suppl 2,* S9-13.

Wills, T. A. & Cleary, S. D. (1996). How are social support effects mediated? A test with parental support and adolescent substance use. *J.Pers.Soc.Psychol., 71,* 937-952.

Witte, D. R., Bots, M. L., Hoes, A. W., & Grobbee, D. E. (2000). Cardiovascular mortality in Dutch men during 1996 European football championship: longitudinal population study. *BMJ, 321,* 1552-1554.

Wolff, B., Grabe, H. J., Volzke, H., Ludemann, J., Kessler, C., Dahm, J. B. et al. (2005). Relation between psychological strain and carotid atherosclerosis in a general population. *Heart, 91,* 460-464.

Wong, M. L., Kling, M. A., Munson, P. J., Listwak, S., Licinio, J., Prolo, P. et al. (2000). Pronounced and sustained central hypernoradrenergic function in major depression with melancholic features: relation to hypercortisolism and corticotropin-releasing hormone. *Proc.Natl.Acad.Sci.U.S.A, 97,* 325-330.

Wood, C. & Magnello, M. E. (1992). Diurnal changes in perceptions of energy and mood. *J.R.Soc.Med., 85,* 191-194.

Wright, C. E. & Steptoe, A. (2005). Subjective socio-economic position, gender and cortisol responses to waking in an elderly population. *Psychoneuroendocrinology, 30,* 582-590.

Wulsin, L. R. & Singal, B. M. (2003). Do depressive symptoms increase the risk for the onset of coronary disease? A systematic quantitative review. *Psychosom.Med., 65,* 201-210.

Wust, S., Wolf, J., Hellhammer, D. H., Federenko, I., Schommer, N., & Kirschbaum, C. (2000). The cortisol awakening response - normal values and confounds. *Noise.Health, 2,* 79-88.

Wust, S., Federenko, I., Hellhammer, D. H., & Kirschbaum, C. (2000). Genetic factors, perceived chronic stress, and the free cortisol response to awakening. *Psychoneuroendocrinology, 25,* 707-720.

Yamabe, H., Hanaoka, J., Funakoshi, T., Iwahashi, M., Takeuchi, M., Saito, K. et al. (1996). Deep negative T waves and abnormal cardiac sympathetic image (123I-MIBG) after the Great Hanshin Earthquake of 1995. *Am.J.Med.Sci., 311,* 221-224.

Yamasaki, Y., Kodama, M., Matsuhisa, M., Kishimoto, M., Ozaki, H., Tani, A. et al. (1996). Diurnal heart rate variability in healthy subjects: effects of aging and sex difference. *Am.J.Physiol, 271,* H303-H310.

Yehuda, R., Teicher, M. H., Trestman, R. L., Levengood, R. A., & Siever, L. J. (1996). Cortisol regulation in posttraumatic stress disorder and major depression: A chronobiological analysis. *Biological Psychiatry, 40,* 79-88.

Yeragani, V. K., Pohl, R., Balon, R., Ramesh, C., Glitz, D., Jung, I. et al. (1991). Heart rate variability in patients with major depression. *Psychiatry Res., 37,* 35-46.

Yeragani, V. K., Pohl, R., Berger, R., Balon, R., Ramesh, C., Glitz, D. et al. (1993). Decreased heart rate variability in panic disorder patients: a study of power-spectral analysis of heart rate. *Psychiatry Res., 46,* 89-103.

Yeragani, V. K., Balon, R., Pohl, R., & Ramesh, C. (1995). Depression and heart rate variability. *Biol.Psychiatry, 38,* 768-770.

Yogo, Y., Hama, H., Yogo, M., & Matsuyama, Y. (1995). A study of physiological response during emotional imaging. *Percept.Mot.Skills, 81,* 43-49.

Young, E. A., Haskett, R. F., Grunhaus, L., Pande, A., Weinberg, V. M., Watson, S. J. et al. (1994). Increased evening activation of the hypothalamic-pituitary-adrenal axis in depressed patients. *Arch.Gen.Psychiatry, 51,* 701-707.

Young, L. D., Barboriak, J. J., Anderson, A. A., & Hoffman, R. G. (1980). Attitudinal and behavioral correlates of coronary heart disease. *J.Psychosom.Res., 24,* 311-318.

Ziegelstein, R. C., Fauerbach, J. A., Stevens, S. S., Romanelli, J., Richter, D. P., & Bush, D. E. (2000). Patients with depression are less likely to follow recommendations to reduce cardiac risk during recovery from a myocardial infarction. *Arch.Intern.Med., 160,* 1818-1823.

Ziegler, D., Laude, D., Akila, F., & Elghozi, J. L. (2001). Time- and frequency-domain estimation of early diabetic cardiovascular autonomic neuropathy. *Clin.Auton.Res., 11,* 369-376.

Zigmond, A. S. & Snaith, R. P. (1983). The hospital anxiety and depression scale. *Acta Psychiatr.Scand., 67,* 361-370.

Appendix 1: Patient information sheet

Royal Free and University College Medical School

UNIVERSITY COLLEGE LONDON

DEPARTMENT OF CARDIOLOGY, ROYAL FREE HOSPITAL

DEPARTMENT OF EPIDEMIOLOGY AND PUBLIC HEALTH, UCL

Study of Emotion and Heart Disease

PATIENT INFORMATION SHEET (Confidential)

You are being invited to take part in a research study. Before you decide it is important for you to understand why the research is being done and what it will involve. Please take time to read the following information carefully and discuss it with others if you wish. Ask us if there is anything that is not clear or if you would like more information. Take time to decide whether or not you wish to take part.

Thank you for reading this.

What is the purpose of the study?

Disease in the coronary blood vessels develops over many years, but exactly what triggers symptoms and heart attacks is not well understood. We are trying to find out whether lifestyle and emotional state make a contribution in some patients. We are studying the relationship between emotion and the heart in everyday life, and how our responses to emotional events in the day may relate to physical symptoms, adaptation to heart disease and quality of life. We are particularly interested in linking the psychological factors with the underlying biology of heart disease, to see whether there are differences in the various chemicals in the body that are involved in heart attacks and angina.

Who is organising and funding the research?

This research study is funded by the British Heart Foundation, and its purpose is to learn more about how our emotions and behaviour influence the cardiovascular system in health and disease. The results will help advance our knowledge of the links between the mind and the body, and develop new methods of improving patient care. The study is being carried out by Dr , a Consultant Cardiologist at the Royal Free Hospital, in collaboration with Professor Andrew Steptoe from the Department of Epidemiology and Public Health at University College London. The researchers, who are contracted by the British Heart Foundation and will carry out the work, are Dr Mimi Bhattacharyya and Dr *******.

Why have I been chosen?

We are looking to see how emotional state affects the heart. To increase the likelihood of finding any significant relationship between emotion and heart disease, we need to study patients who are having symptoms of possible heart disease.

You have been chosen as you have been having symptoms of chest pain requiring your attendance to hospital and your exercise test shows some changes on the ECG that could indicate a possibility of heart disease.

Do I have to take part?

It is up to you to decide whether or not to take part. If you do decide to take part you will be given this information sheet to keep and be asked to sign a consent form to keep. If you decide to take part you are still free to withdraw at any time and without giving a reason. A decision to withdraw at any time, or a decision not to take part, will not affect the standard of care you will receive.

What will happen to me if I take part? How You Can Help?

We would like to record the electrical activity in your heart (the ECG) by asking you to wear a monitor for 24 hours. This is like wearing a walkman. It is comfortable, discreet to wear and should not interfere in your daily activities. We also need to know about the effect that physical activity has on your heart, so we would like you to wear a special watch on your wrist which measures physical activity. After the 24 hour period, we will interview you about what has been happening in your life during the period of monitoring. This will take about one hour, and will take place in the Cardiac Department at the Royal Free or at University College London. We will also ask you to fill in some questionnaires in your own time. These concern how you are feeling about life, and how you cope with stress. This should take no longer than 30 minutes to complete. Analysis of the 24 hour ECG tape from the monitor will clarify the link between emotional events in the day and what is happening to your heart at the same time.

The second part of the study involves measurement of chemicals in your saliva (spit). There are several hormones that affect the way the body works, and fortunately these can be measured in saliva. Several times over a day of ECG monitoring, we will ask you to put a cotton dental swab in your mouth for a couple of minutes, then return it to a storage tube. We would like to do this both on the day of ECG monitoring, and then again after 6 months and 12 months. The samples you collect at home can be posted back to us (we will provide the postage and packing).

What else do I have to do?

There are no lifestyle restrictions. As we are studying emotion and heart disease in everyday life you should do everything as usual including, if applicable, taking your regular medication.

What are the possible disadvantages of taking part?

If analysis of your ECG brings up a condition that requires management, for example a significant arrhythmia, we will inform both you and staff at the clinic.

What are the possible benefits of taking part?

There are no direct immediate clinical benefits from taking part in the study. We can provide you with personal information regarding your ECG and heart rate. The information we get from this study may help us to treat future patients with coronary heart disease better. Your participation to help further this research would be appreciated.

Will my taking part in this study be kept confidential?

We want to emphasise that all results obtained will be strictly confidential and will only be used for medical research purposes. All information about you which leaves the hospital will have your name and address removed so that you cannot be recognised from it. We will inform your GP by letter about the study and your agreed participation in it with your consent.

What if something goes wrong?

We do not expect you to suffer any adverse effects from this study since we are not testing any medicines or procedures and it will not affect your clinical outcome. There are no special compensation arrangements. If you are harmed due to someone's negligence, then you may have grounds for legal action but you may have to pay for it. Regardless of this, if you wish to complain, or have any concerns about any aspect of the way you have been approached or treated during the course

of this study, the normal National Health Service complaints mechanisms should be available to you. You will be able to contact the research team in the first instance.

What will happen to the results of the research study?

The study will recruit 100 participants over a 2 year period. The results will be statistically analysed and findings subsequently published in peer reviewed journals. You will not be identified in any publication.

Who has reviewed the study?

The local research ethics committee at the Royal Free Hospital and Medical School have reviewed the study and given a favourable ethical opinion.

Contact for further Information

Many thanks for reading this. We hope you feel able to take part in our study, which will help us understand more about the causes of heart disease and how to manage it better.

If you have any questions, please contact Dr.Mimi Bhattacharyya, Department of Epidemiology and Public Health, University College London,
Telephone or email

Appendix 2: SIS study patient consent form

Royal Free and University College Medical School

DEPARTMENT OF CARDIOLOGY, ROYAL FREE HOSPITAL

DEPARTMENT OF EPIDEMIOLOGY AND PUBLIC HEALTH, UCL

Study Number:

Patient Identification Number

CONSENT FORM (Confidential)
Title of project: **A Study of Emotion and Heart Disease**

Name of Researchers: Dr , Professor Andrew Steptoe, Dr M Bhattacharyya, Dr

Any questions to Dr.M Bhattacharyya, Department of Epidemiology and Public Health, University College London,

Please initial

1. I confirm that I have read and understood the information sheet for the above study and have had the opportunity to ask questions.

2. I understand that my participation is voluntary and that I am free to withdraw at any time, without giving any reason, without my medical care or legal rights being affected.

3. I understand that sections of any of my medical notes may be looked at by regulatory authorities where it is relevant to my taking part in research. I give permission for these individuals to have access to my records. I also give permission for my GP to be informed of my participation in the study.

4. I agree to take part in the above study.

_____	_____	_____
Name of patient	Date	Signature
_____	_____	
Name of Person taking consent (if different from researcher)	Date	Signature
_____	_____	
Researcher	Date	Signature

1 for Patient; 1 for Researcher; 1 to be kept with hospital notes

Appendix 3: Day Reconstruction Method interview

DIARY OF EVENTS YESTERDAY

We would like to learn what you did and how you felt yesterday. Not all days are the same-some are better, some are worse and others are pretty typical. Here we are only asking you about **yesterday.** Because many people find it difficult to remember what exactly they did and experienced i.e. your mood and how you felt about those episodes we will do this in three steps.

First I shall ask when you woke up and when you went to sleep yesterday **(A)**

Then, we'd like you to reconstruct what your day was like as a continuous series of episodes in a film **(B)**. Think about *where* you were? *What* did you do and experience? How did you feel? For each episode I shall ask the approximate time at which episode began and ended(usually between 15mins and 2 hours).Indications of an end of an episode may be going to a different location, ending an activity or change of people with whom you were interacting.

The day will be divided up into morning (M) (waking till before lunch), afternoon (A) (12-6pm), Evening (E) (6pm till you went to bed).Try to remember each episode in detail and what you felt and how was your mood at the time.

Finally the third step involves that after reconstructing the episodes of the day, we will ask several questions about how you *felt* and moods experienced for every episode recorded **(C)**

We will ask you to fill out a time table of events in the day to jog your memory.

i) Interview (Answers to questions asked inputted directly into SPSS software programme)

About what time did you wake up yesterday?

And when did you go to sleep?

Morning

a) Episode: Please select the earliest episode you noted in the Morning: Describe it

b) When did the first episode begin and end. Please try to remember the times as precisely as you can.

c) This is episode number 1M which began at ---- and ended at ------

D) What were you doing?

-commuting	**-working**
-shopping	**-preparing food**
-doing housework	**-taking care of children**
-eating	**-watching TV**
-prayer	**-computer/internet/email**
-socialising	**-on phone**
-nap/rest	**-exercising**
-relaxing	**-intimate relations**
-other	**-driving**
-self care	**-walking**

e) Where were you?

-At home -at work -somewhere else

f) Were you interacting with anyone else (including phone)?

-No one-→*skip next question*

If you were interacting with someone (please check all that apply)

-Spouse/significant other -my children

-Friends -parents/relatives

-Co-workers -boss

-Clients/customers -other people not listed

-students

ii) **Timetable that patients are asked to complete to aid participation in DRM**

Time of day	What were you doing?	Where were you	If with someone, who?	Beginning time(B)/end time episode (E)(number)
0600-0700				
0700-0800				
0800-0900				
0900-1000				
1000-1100				
1100-1200				
1200-1300				
1300-1400				
1400-1500				
1500-1600				
1600-1700				
1700-1800				

Time of day	What were you doing?	Where were you	If with someone, who?	Beginning time(B)/end time episode (E)(number)
1800-1900				
1900-2000				
2000-2100				
2100-2200				
2200-2300				
2300-0000				

Episode number in total- **Morning**

Afternoon

Evening

iii) Ratings of emotion for each episode

How did you feel during this episode?

Please rate *each feeling* on the scale given.

***A rating of 0 means that you did not experience that feeling at all.**

***A rating of 6 means that this feeling was a very important part of the experience.**

***Please circle the number between 0 and 6 that best describes how you felt.**

	Not at all						Very Much
Impatient for it to end?.....	**0**	**1**	**2**	**3**	**4**	**5**	**6**
Happy?.....	**0**	**1**	**2**	**3**	**4**	**5**	**6**
Frustrated/annoyed?.....	**0**	**1**	**2**	**3**	**4**	**5**	**6**
Depressed/blue?.....	**0**	**1**	**2**	**3**	**4**	**5**	**6**
Warm/friendly?.....	**0**	**1**	**2**	**3**	**4**	**5**	**6**
Angry/hostile?.....	**0**	**1**	**2**	**3**	**4**	**5**	**6**
Worried/anxious?.....	**0**	**1**	**2**	**3**	**4**	**5**	**6**
Tired?.....	**0**	**1**	**2**	**3**	**4**	**5**	**6**

Appendix 4: SIS study pre interview questionnaire pack

Name:	Date:	Pt No:

Medical Research Study

Emotion and Heart Disease

Thank you very much for participating in our study of emotions and heart disease. In addition to the saliva samples we have asked you to collect, we would like you to complete this questionnaire about your lifestyle, your attitudes and opinions, the way you feel about yourself and the way you feel about your heart problem. You may feel that some of the questions do not apply to you, but please answer each question with the answer that most closely fits the way you feel.

The answers you provide in this questionnaire will be kept **strictly confidential**. The information will go into the statistics for the study, and it will not be possible to identify you personally in any reports. Under no circumstances will any of the information you give us be made available to anyone else.

Most of the questions can be answered by circling the appropriate answer.

For example:

"I can sit at ease and feel relaxed"

Definitely	Usually	Not often	Not at all

Please be sure to read the instructions to each section carefully.

What do you think caused your medical problem?

Serious illnesses like heart disease may be caused by many different factors. We would like to find out what factors you think were involved with your own illness. Listed below are a series of factors that patients in the past have thought helped to cause their heart disease symptoms. Please think about each item, then circle the answer that indicates how much you agree or disagree with each statement.

Factors that might have helped cause my illness			
My illness is hereditary – it runs in my family	**No**	**Maybe**	**Yes**
Smoking played a major role in causing my illness	**No**	**Maybe**	**Yes**
My illness was brought on by other medical problems	**No**	**Maybe**	**Yes**
Stress was a major factor in my illness	**No**	**Maybe**	**Yes**
Being overweight caused my illness	**No**	**Maybe**	**Yes**
High blood pressure was an important factor in my illness	**No**	**Maybe**	**Yes**
Diet played a major role in causing my illness	**No**	**Maybe**	**Yes**
I became ill because I over-exerted myself	**No**	**Maybe**	**Yes**
It was just by chance and bad luck that I became ill	**No**	**Maybe**	**Yes**

My illness was caused by poor medical care in the past	**No**	**Maybe**	**Yes**
Lack of exercise was a cause of my illness	**No**	**Maybe**	**Yes**
My illness was brought on by tiredness and exhaustion	**No**	**Maybe**	**Yes**
Genetic factors (genes) caused my illness	**No**	**Maybe**	**Yes**
My state of mind played a major part in causing my illness	**No**	**Maybe**	**Yes**
Working too hard caused my illness	**No**	**Maybe**	**Yes**
A germ or virus caused my illness	**No**	**Maybe**	**Yes**

This part of the questionnaire is about your emotions and how you are feeling. Read each item and circle the reply which comes closest to how you have been feeling **in the past week**.

1. I feel tense or 'wound up':

Most of the time	A lot of the time	From time to time, occasionally	Not at all

2. I get a sort of frightened feeling as if something awful is about to happen:

Very definitely and quite badly	Yes, but not too badly	A little, but it doesn't worry me	Not at all

3. Worrying thoughts go through my mind:

A great deal of the time	A lot of the time	From time to time	Only occasionally but not too often

4. I can sit at ease and feel relaxed:

Definitely	Usually	Not often	Not at all

5. I get a sort of frightened feeling like 'butterflies ' in the stomach:

Not at all	Occasionally	Quite often	Very often

6. I feel restless as if I have to be on the move:

Very much indeed	Quite a lot	Not very much	Not at all

7. I get sudden feelings of panic:

Very often indeed	Quite often	Not very often	Not at all

The following questions are about your health and daily activities. Read each item and circle one answer for each question.

1. In general would you say your health is:

Excellent	Very Good	Good	Fair	Poor

2. Compared to one year ago, how would you rate your health in general now?

Much better now than one year ago	Somewhat better now than one year ago	About the same as one year ago	Somewhat worse now than one year ago	Much worse now than one year ago

3. The following questions are about the activities you might do during a typical day.

Does **your health now limit you** in these activities? If so how much?

- Vigorous activities – such as running, lifting heavy objects, participating in a strenuous sport

Yes, limited a lot	Yes, limited a little	No, not limited at all

- Moderate activities – such as moving a table, pushing a vacuum cleaner, bowling, or playing golf.

Yes, limited a lot	Yes, limited a little	No, not limited at all

- Lifting or carrying groceries.

Yes, limited a lot	Yes, limited a little	No, not limited at all

- Climbing **several** flights of stairs.

Yes, limited a lot	Yes, limited a little	No, not limited at all

- Climbing **one** flight of stairs.

Yes, limited a lot	Yes, limited a little	No, not limited at all

- Bending, kneeling, or stooping.

Yes, limited a lot	Yes, limited a little	No, not limited at all

- Walking **more than a mile**.

Yes, limited a lot	Yes, limited a little	No, not limited at all

- Walking **half a mile**.

Yes, limited a lot	Yes, limited a little	No, not limited at all

- Walking **one hundred yards**.

Yes, limited a lot	Yes, limited a little	No, not limited at all

- Bathing or dressing yourself.

Yes, limited a lot	Yes, limited a little	No, not limited at all

4. During the **past 4 weeks**, have you had any of the following problems with your work or other regular daily activities **as a result of your physical health**?

- Cut down the **amount of time** you spent on work or other activities.

Yes	No

- **Accomplished less** than you would like.

Yes	No

- Were limited in the **kind** of work or other activities.

Yes	No

- Had **difficulty** performing the work or other activities (for example, it took extra effort).

Yes	No

5. During the **past 4 weeks**, have you had any of the following problems with your work or other regular daily activities **as a result of any emotional problems** (such as feeling depressed or anxious)?

- Cut down on the **amount of time** you spent on work or other activities:

Yes	No

- **Accomplished less** than you would like:

Yes	No

- Didn't do work or other activities as **carefully** as usual:

Yes	No

6. During the **past 4 weeks**, to what extent has your physical health or emotional problems interfered with your normal social activities with family, friends, neighbours, or groups?

Not at all	Slightly	Moderately	Quite a bit	Extremely

7. How much **bodily** pain have you had during the **past 4 weeks**?

None	Very mild	Mild	Moderate	Severe	Very severe

8. During the **past 4 weeks**, how much did **pain** interfere with your normal work (including both work

outside the home and housework)?

Not at all	A little bit	Moderately	Quite a bit	Extremely

9. These questions are about how you feel and how things have been with you **during the past 4 weeks**. For each question, please give the one answer that comes closest to the way you have been feeling. How much of the time during the **past 4 weeks**:

- Did you feel full of life?

All of the time	Most of the time	A good bit of the time	Some of the time	A little bit of the time	None of the time

- Have you been a very nervous person?

All of the time	Most of the time	A good bit of the time	Some of the time	A little bit of the time	None of the time

- Have you felt so down in the dumps that nothing could cheer you up?

All of the time	Most of the time	A good bit of the time	Some of the time	A little bit of the time	None of the time

- Have you felt calm and peaceful?

All of the time	Most of the time	A good bit of the time	Some of the time	A little bit of the time	None of the time

- Did you have a lot of energy?

All of the time	Most of the time	A good bit of the time	Some of the time	A little bit of the time	None of the time

- Have you felt downhearted and low?

All of the time	Most of the time	A good bit of the time	Some of the time	A little bit of the time	None of the time

- Did you feel worn out?

All of the time	Most of the time	A good bit of the time	Some of the time	A little bit of the time	None of the time

- Have you been a happy person?

All of the time	Most of the time	A good bit of the time	Some of the time	A little bit of the time	None of the time

- Did you feel tired?

All of the time	Most of the time	A good bit of the time	Some of the time	A little bit of the time	None of the time

10. During the **past 4 weeks**, how much of the time has your **physical health or emotional problems** interfered with your social activities (like visiting friends, relatives, etc.)?

All of the time	Most of the time	A good bit of the time	Some of the time	A little bit of the time	None of the time

11. How **TRUE** or **FALSE** is **each** of the following statements for you?

- I seem to get ill more easily than other people.

Definitely True	Mostly True	Don't Know	Mostly False	Definitely False

- I am as healthy as anybody I know.

Definitely True	Mostly True	Don't Know	Mostly False	Definitely False

- I expect my health to get worse.

Definitely True	Mostly True	Don't Know	Mostly False	Definitely False

- My health is excellent.

Definitely True	Mostly True	Don't Know	Mostly False	Definitely False

The following statements concern your attitudes and opinions. Please indicate the extent you agree with each of the following statements. Please tick one answer for each statement. There are no right or wrong answers.

		Strongly Disagree	Disagree	Neutral	Agree	Strongly Agree
1	In uncertain times, I usually expect the best					
2	It's easy for me to relax					
3	If something can go wrong for me, it will					
4	I'm always optimistic about my future					
5	I enjoy my friends a lot					
6	It's important for me to keep busy					
7	I hardly ever expect things to go my way					
8	I don't get upset too easily					
9	I rarely count on good things happening to me					
10	Overall, I expect more good things to happen to me than bad					

This part of the questionnaire consists of 21 groups of statements. After reading each group of statements carefully, circle the number (0, 1, 2, or 3) next to the one statement in each group which **best** describes the way you have been feeling the **past week, including today**. If several statements within a group seem to apply equally well, circle each one. **Be sure to read all the statements in each group before making your choice.**

1. 0 I do not feel sad.
   1 I feel sad.
   2 I am sad all the time and I can't snap out of it.
   3 I am so sad or unhappy that I can't stand it.

2. 0 I am not particularly discouraged about the future.
   1 I feel discouraged about the future.
   2 I feel I have nothing to look forward to.
   3 I feel that the future is hopeless and that things cannot improve.

3. 0 I do not feel like a failure.
   1 I feel I have failed more than the average person.
   2 As I look back on my life, all I can see is a lot of failures.
   3 I feel I am a complete failure as a person.

4. 0 I get as much satisfaction out of things as I used to.
   1 I don't enjoy things the way I used to.
   2 I don't get real satisfaction out of anything anymore.
   3 I am dissatisfied or bored with everything.

5. 0 I don't feel particularly guilty.
   1 I feel guilty a good part of the time.
   2 I feel guilty most of the time.
   3 I feel guilty all of the time.

6. 0 I don't feel I am being punished.
   1 I feel I may be punished.
   2 I expect to be punished.
   3 I feel I am being punished.

7. 0 I don't feel disappointed in myself.
   1 I am disappointed in myself.

2 I am disgusted with myself.
3 I hate myself.

8. 0 I don't feel I am any worse than anybody else.

1 I am critical of myself for my weaknesses or mistakes.
2 I blame myself all the time for my faults.
3 I blame myself for everything bad that happens.

9. 0 I don't have any thoughts of killing myself.

1 I have thoughts of killing myself, but I would not carry them out.
2 I would like to kill myself.
3 I would kill myself if I had the chance.

10. 0 I don't cry any more than usual.

1 I cry more now than I used to.
2 I cry all the time now.
3 I used to be able to cry, but now I can't cry even though I want to.

11. 0 I am no more irritated now than I ever am.

1 I get annoyed or irritated more easily than I used to.
2 I feel irritated all the time now.
3 I don't get irritated at all by the things that used to irritate me.

12. 0 I have not lost interest in other people.

1 I am less interested in other people than I used to be.
2 I have lost most of my interest in other people.
3 I have lost all of my interest in other people.

13. 0 I make decisions about as well as I ever could.

1 I put off making decisions more than I used to.
2 I have greater difficulty in making decisions than before.
3 I can't make decisions at all any more.

14. 0 I don't feel I look any worse than I used to.

1 I am worried that I am looking old or unattractive.
2 I feel that there are permanent changes in my appearance that make me look unattractive.

3 I believe that I look ugly.

15. 0 I can work about as well as before.

1 It takes an extra effort to get started at doing something.
2 I have to push myself very hard to do anything.
3 I can't do any work at all.

16. 0 I can sleep as well as usual.

1 I don't sleep as well as I used to.
2 I wake up 1-2 hours earlier than usual and find it hard to get back to sleep.
3 I wake up several hours earlier than I used to and cannot get back to sleep.

17. 0 I don't get more tired than usual.

1 I get tired more easily than I used to.
2 I get tired from doing almost anything.
3 I am too tired to do anything.

18. 0 My appetite is no worse than usual.

1 My appetite is not as good as it used to be.
2 My appetite is much worse now.
3 I have no appetite at all anymore.

19. 0 I haven't lost much weight, if any, lately.

1 I have lost more than 5 pounds.
2 I have lost more than 10 pounds.
3 I have lost more than 15 pounds.

I am purposely trying to lose weight by eating less. Yes _____ No_____

20. 0 I am no more worried about my health than usual.

1 I am worried about physical problems such as aches and pains; or upset stomach; or constipation.
2 I am very worried about physical problems and it's hard to think of much else.
3 I am so worried about my physical problems that I cannot think about anything else.

21. 0 I have not noticed any recent change in my interest in sex.

1 I am less interested in sex than I used to be.
2 I am much less interested in sex now.
3 I have lost interest in sex completely

That is the end of the questionnaire. Please check that you have answered all of the questions and then post the questionnaire back to us. Thank you very much for taking the time to make this important contribution to our study of emotion and heart disease. We may be in touch with you regarding a follow up stage of the study, in which case we look forward to speaking with you soon.

Appendix 5: SIS Study – 6 month telephone follow up

Patient name	
SIS no	
Interviewer	
Date of Fitting of Monitor	
Date of Removal Monitor/Interview	
Date of telephone follow up	

Subsequent problems?	YES / NO - specify
Re – admission?	YES / NO
Coronary Angiogram?	YES/NO
Result? ▪ Normal ▪ Angioplasty ▪ Stent ▪ CABG ▪ Complications/Miscell	
Date of coronary angiogram if still awaiting?	
Other medical problems	
Recurrence of symptoms?	YES / NO

Seen GP since discharge?	YES / NO
GP checked cholesterol?	YES / NO
GP checked BP?	YES / NO
GP checked blood sugar (if appropriate)	YES / NO

Attended rehab course?(if MI)	YES / NO	Where?

No. of sessions attended e.g 6/8	
Found rehab course useful?	YES / NO

Did you receive advice about the following either in hospital or subsequently on a cardiac rehab course? YES/NO?

Subject	Advice given?	Advice implemented?	Comments?
Exercise	YES / NO	YES / NO / PARTIAL	
Weight	YES / NO	YES / NO / PARTIAL	
Stress	YES / NO	YES / NO / PARTIAL	
Alcohol	YES / NO	YES / NO / PARTIAL	
Diet	YES / NO	YES / NO / PARTIAL	(fruit/veg/oily fish/lowfat)
Were you a smoker before your heart problem? YES / NO			
Were you advised to stop YES / NO			
Advice implemented YES / NO / PARTIAL - specify			
Relapsed? - reason?			
How many a day do you smoke now?			

What medication are you currently taking? Any problem with medication?

I forget to take my medicine	ALWAYS/OFTEN/SOMETIMES/RARELY/NEVER
I alter the dose of my medications	ALWAYS/OFTEN/SOMETIMES/RARELY/NEVER
I stop taking my medicines for a while	ALWAYS/OFTEN/SOMETIMES/RARELY/NEVER

I decide to miss out a dose	ALWAYS/OFTEN/SOMETIMES/RARELY/NEVER
I take less than instructed	ALWAYS/OFTEN/SOMETIMES/RARELY/NEVER
I never forget to take my medicine	ALWAYS/OFTEN/SOMETIMES/RARELY/NEVER

Thank you. Mention questionnaire pack.

Appendix 6: SIS study 6 month follow up questionnaire

Name:	Date:	Pt No:

Medical Research Study

Emotion and Heart Disease

Thank you very much for participating in our study of emotions and heart disease. In addition to the saliva samples we have asked you to collect, we would like you to complete this questionnaire about your lifestyle, your attitudes and opinions, the way you feel about yourself and the way you feel about your heart problem. You may feel that some of the questions do not apply to you, but please answer each question with the answer that most closely fits the way you feel.

The answers you provide in this questionnaire will be kept **strictly confidential**. The information will go into the statistics for the study, and it will not be possible to identify you personally in any reports. Under no circumstances will any of the information you give us be made available to anyone else.
Most of the questions can be answered by circling the appropriate answer.

For example:

"I can sit at ease and feel relaxed"

Definitely	Usually	Not often	Not at all

Please be sure to read the instructions to each section carefully.

Serious heart disease may be caused by many different factors. We would like to find out what factors you think were involved with your own illness. Listed below are a series of factors that patients in the past have thought helped to cause their heart disease symptoms. Please think about each item, then circle the answer that indicates how much you agree or disagree with each statement.

1. What do you think caused your symptoms?

Factors that might have helped cause my illness			
My illness is hereditary – it runs in my family	**No**	**Maybe**	**Yes**
Smoking played a major role in causing my illness	**No**	**Maybe**	**Yes**
My illness was brought on by other medical problems	**No**	**Maybe**	**Yes**
Stress was a major factor in my illness	**No**	**Maybe**	**Yes**
Being overweight caused my illness	**No**	**Maybe**	**Yes**
High blood pressure was an important factor in my illness	**No**	**Maybe**	**Yes**
Diet played a major role in causing my illness	**No**	**Maybe**	**Yes**
I became ill because I over-exerted myself	**No**	**Maybe**	**Yes**
It was just by chance and bad luck that I became ill	**No**	**Maybe**	**Yes**
My illness was caused by poor medical care in the past	**No**	**Maybe**	**Yes**
Lack of exercise was a cause of my illness	**No**	**Maybe**	**Yes**
My illness was brought on by tiredness and exhaustion	**No**	**Maybe**	**Yes**
Genetic factors (genes) caused my illness	**No**	**Maybe**	**Yes**
My state of mind played a major part in causing my illness	**No**	**Maybe**	**Yes**
Working too hard caused my illness	**No**	**Maybe**	**Yes**
A germ or virus caused my illness	**No**	**Maybe**	**Yes**

2. This part of the questionnaire is about your emotions and how you are feeling. Read each item and circle the reply which comes closest to how you have been feeling **in the past week.**

I feel tense or 'wound up':

Most of the time	A lot of the time	From time to time, occasionally	Not at all

I get a sort of frightened feeling as if something awful is about to happen:

Very definitely and quite badly	Yes, but not too badly	A little, but it doesn't worry me	Not at all

Worrying thoughts go through my mind:

A great deal of the time	A lot of the time	From time to time	Only occasionally but not too often

I can sit at ease and feel relaxed:

Definitely	Usually	Not often	Not at all

I get a sort of frightened feeling like 'butterflies ' in the stomach:

Not at all	Occasionally	Quite often	Very often

I feel restless as if I have to be on the move:

Very much indeed	Quite a lot	Not very much	Not at all

I get sudden feelings of panic:

Very often indeed	Quite often	Not very often	Not at all

3. The following questions are about your health and daily activities. Read each item and circle one answer for each question.

1. In general would you say your health is:

Excellent	Very Good	Good	Fair	Poor

2. Compared to one year ago, how would you rate your health in general now?

Much better now than one year ago	Somewhat better now than one year ago	About the same as one year ago	Somewhat worse now than one year ago	Much worse now than one year ago

3. The following questions are about the activities you might do during a typical day.

Does **your health now limit you** in these activities? If so how much?

- Vigorous activities – such as running, lifting heavy objects, participating in a strenuous sport

Yes, limited a lot	Yes, limited a little	No, not limited at all

Moderate activities – such as moving a table, pushing a vacuum cleaner, bowling, or playing golf.

Yes, limited a lot	Yes, limited a little	No, not limited at all

- Lifting or carrying groceries.

Yes, limited a lot	Yes, limited a little	No, not limited at all

- Climbing **several** flights of stairs.

Yes, limited a lot	Yes, limited a little	No, not limited at all

-
- Climbing **one** flight of stairs.

Yes, limited a lot	Yes, limited a little	No, not limited at all

- Bending, kneeling, or stooping.

Yes, limited a lot	Yes, limited a little	No, not limited at all

- Walking **more than a mile**.

Yes, limited a lot	Yes, limited a little	No, not limited at all

- Walking **half a mile**.

Yes, limited a lot	Yes, limited a little	No, not limited at all

- Walking **one hundred yards**.

Yes, limited a lot	Yes, limited a little	No, not limited at all

- Bathing or dressing yourself.

Yes, limited a lot	Yes, limited a little	No, not limited at all

4. During the **past 4 weeks**, have you had any of the following problems with your work or other regular daily activities **as a result of your physical health**?

- Cut down the **amount of time** you spent on work or other activities.

Yes	No

- **Accomplished less** than you would like.

Yes	No

- Were limited in the **kind** of work or other activities.

Yes	No

- Had **difficulty** performing the work or other activities (for example, it took extra effort).

Yes	No

5. During the **past 4 weeks**, have you had any of the following problems with your

work or other regular daily activities **as a result of any emotional problems** (such

as feeling depressed or anxious)?

- Cut down on the **amount of time** you spent on work or other activities:

Yes	No

- **Accomplished less** than you would like:

Yes	No

- Didn't do work or other activities as **carefully** as usual:

Yes	No

6. During the **past 4 weeks**, to what extent has your physical health or emotional problems interfered with your normal social activities with family, friends, neighbours, or groups?

Not at all	Slightly	Moderately	Quite a bit	Extremely

7. How much **bodily** pain have you had during the **past 4 weeks**?

None	Very mild	Mild	Moderate	Severe	Very severe

8. During the **past 4 weeks**, how much did **pain** interfere with your normal work (including both work outside the home and housework)?

Not at all	A little bit	Moderately	Quite a bit	Extremely

9. These questions are about how you feel and how things have been with you **during the past 4 weeks**. For each question, please give the one answer that comes closest to the way you have been feeling. How much of the time during the **past 4 weeks**:

- Did you feel full of life?

All of the time	Most of the time	A good bit of the time	Some of the time	A little bit of the time	None of the time

- Have you been a very nervous person?

All of the time	Most of the time	A good bit of the time	Some of the time	A little bit of the time	None of the time

- Have you felt so down in the dumps that nothing could cheer you up?

All of the time	Most of the time	A good bit of the time	Some of the time	A little bit of the time	None of the time

- Have you felt calm and peaceful?

All of the time	Most of the time	A good bit of the time	Some of the time	A little bit of the time	None of the time

- Did you have a lot of energy?

All of the time	Most of the time	A good bit of the time	Some of the time	A little bit of the time	None of the time

- Have you felt downhearted and low?

All of the time	Most of the time	A good bit of the time	Some of the time	A little bit of the time	None of the time

- Did you feel worn out?

All of the time	Most of the time	A good bit of the time	Some of the time	A little bit of the time	None of the time

- Have you been a happy person?

All of the time	Most of the time	A good bit of the time	Some of the time	A little bit of the time	None of the time

- Did you feel tired?

All of the time	Most of the time	A good bit of the time	Some of the time	A little bit of the time	None of the time

10. During the **past 4 weeks**, how much of the time has your **physical health or emotional problems** interfered with your social activities (like visiting friends, relatives, etc.)?

All of the time	Most of the time	A good bit of the time	Some of the time	A little bit of the time	None of the time

11. How **TRUE** or **FALSE** is **each** of the following statements for you?

- I seem to get ill more easily than other people.

Definitely True	Mostly True	Don't Know	Mostly False	Definitely False

- I am as healthy as anybody I know.

Definitely True	Mostly True	Don't Know	Mostly False	Definitely False

- I expect my health to get worse.

Definitely True	Mostly True	Don't Know	Mostly False	Definitely False

- My health is excellent.

Definitely True	Mostly True	Don't Know	Mostly False	Definitely False

12. This section of the questionnaire is concerned with how many people you see or talk to **on a regular basis** including family, friends, workmates, neighbours, etc. Please circle your answer to each question.

1. Do you have children?

If Yes, how often do you see or talk on the phone to your children?

Never	Once a month	Once every two weeks	Once a week	Every day

2. Are either of your parents living?

If your mother is living, how often do you see or talk on the phone to her?

Never	Once a month	Once every two	Once a week	Every day

		weeks		

If your father is living, how often do you see or talk on the phone to him?

Never	Once a month	Once every two weeks	Once a week	Every day

3. If you are married or living with your partner, are either of your in-laws (spouse's parents) living?

If your mother-in-law is living, how often do you see or talk on the phone to her?

Never	Once a month	Once every two weeks	Once a week	Every day

If your father-in-law is living, how often do you see or talk on the phone to him?

Never	Once a month	Once every two weeks	Once a week	Every day

4. Are there other relatives who you feel close to?

If Yes, how often do you see or talk on the phone to these relatives?

Never	Once a month	Once every two weeks	Once a week	Every day

5. Do you have friends who you feel close to (i.e., people you feel at ease with, can talk to about private matters, and can call on for help)?

If Yes, how often do you see or talk on the phone to these friends?

Never	Once a month	Once every two weeks	Once a week	Every day

6. Do you belong to a church, temple, mosque or other religious group?

If Yes, how often do you talk to members of this religious group?

Never	Once a month	Once every two weeks	Once a week	Every day

7. Do you attend any classes (school, university, technical training, or adult education) on a regular basis?

If Yes, how often do you talk to fellow students or teachers?

Never	Once a month	Once every two weeks	Once a week	Every day

8. If you are currently working, how often do you talk to people (other than those you supervise) at work?

Never	Once a month	Once every two weeks	Once a week	Every day

9. How often do you visit or talk to your neighbours?

Never	Once a month	Once every two weeks	Once a week	Every day

10. Are you currently involved in any regular volunteer work?

If Yes, how often do you talk to people involved in this work?

Never	Once a month	Once every two weeks	Once a week	Every day

11. Do you belong to any non-religious groups? Examples include social clubs, recreational groups, trades unions, etc.

If Yes, how often do you talk to fellow group members?

Never	Once a month	Once every two weeks	Once a week	Every day

13. The scale below is made up of a list of statements each of which may or may not be true of you. Please read each item and decide whether the statement is TRUE or FALSE as it pertains to you personally and circle your choice. This is not a test so there are no right or wrong answers.

1.	There is at least one person I know whose advice I really trust	TRUE	FALSE
2.	There is no one I can trust to give me good advice about money matters	TRUE	FALSE
3.	There is no one I know who will tell me honestly about how I'm handling my problems	TRUE	FALSE
4.	When I need suggestions about how to deal with a personal problem I know there is someone I can turn to	TRUE	FALSE
5.	I feel that there is no one with whom I can share my most private worries and fears	TRUE	FALSE
6.	If I had to go away for a few weeks, someone I know would look after my house	TRUE	FALSE
7.	If I were sick and needed someone to drive me to the doctor, I would have trouble finding someone.	TRUE	FALSE

8.	There are several different people with whom I enjoy spending time	TRUE	FALSE
9.	I don't often get invited to do things with others	TRUE	FALSE
10.	If I were sick, there would be almost no one I could find to help me with my daily chores	TRUE	FALSE
11.	If I had to post an important letter at the post office by 5 o'clock and couldn't make it, there is someone who could do it for me	TRUE	FALSE
12.	If I needed a lift to the airport very early in the morning, I would have a hard time finding anyone to take me	TRUE	FALSE

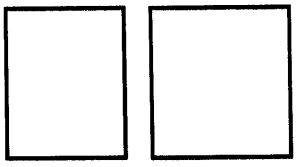
14. Below are some statements which describe people's beliefs and attitudes and the way they might react to some situations. If the statement applies to you or describes you in general, tick the True column. If the statement does not describe you, indicate False.

TRUE FALSE

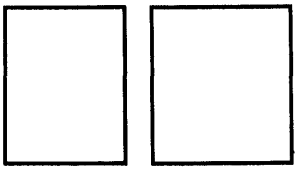
a.

I think a great many people exaggerate their misfortunes to gain the sympathy and help of others.

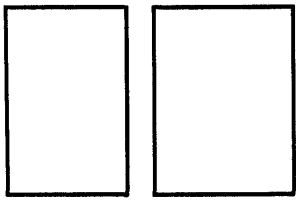
b. I think most people would lie to get ahead.



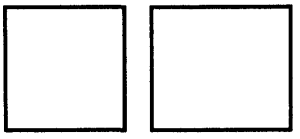
c. When someone does me wrong I feel I should pay him back if I can, just for the principle of the thing.



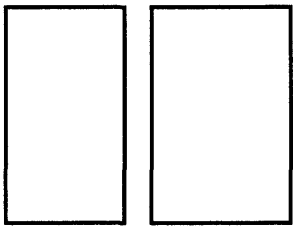
d. Most people are honest chiefly through fear of being caught.



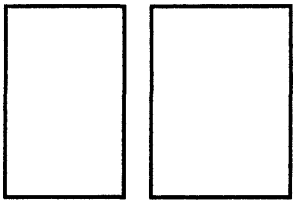
e. Most people will use somewhat unfair means to gain profit or an advantage rather than to lose it.



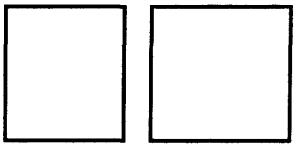
f. It takes a lot of argument to convince most people of the truth.



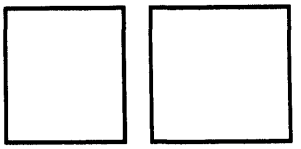
g. I don't blame anyone for trying to grab everything he/she can get in this world.



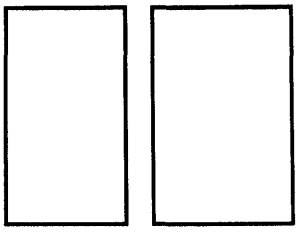
h. No one cares much what happens to you.



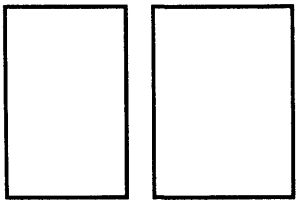
i. It is safer to trust nobody.



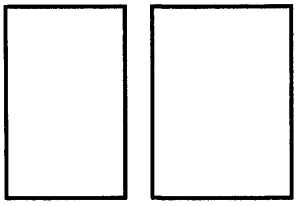
j. Most people make friends because friends are likely to be useful to them.



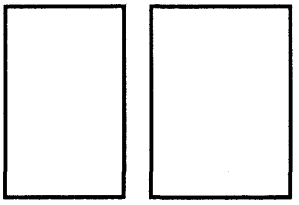
k. Most people inwardly dislike putting themselves out to help other people.



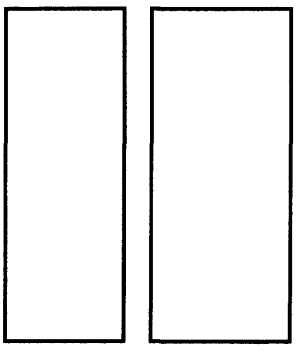
l. I am often inclined to go out of my way to win a point with someone who has opposed me.



m. I do not blame a person for taking advantage of someone who lays himself open to it.



n. People generally demand more respect for their own rights than they are willing to allow for others.



15. Listed below is a series of statements concerning the ways in which people think about their heart problem. Read each item carefully, and indicate how far you agree with it, using the scale on the right hand side. For example, if you agree with statement 3 quite strongly, you would circle number 5.

	Strongly disagree 1	*Disagree somewhat 2*	*Slightly disagree 3*	*Slightly Agree 4*	*Agree somewhat 5*	*Strongly Agree 6*
1. If my heart problem worsens it is my own behaviour which determines how soon I feel better again.	1	2	3	4	5	6
2. Most things that affect my heart problem happen to me by chance.	1	2	3	4	5	6
3. If I see my doctor regularly, I am less likely to have problems with my heart problem.	1	2	3	4	5	6
4. I am directly responsible for my heart problem getting better or worse.	1	2	3	4	5	6
5. Luck plays a big part in determining how my heart problem improves.	1	2	3	4	5	6

6. Other people play a big role in whether my heart problem improves, stays the same, or gets worse.	1	2	3	4	5	6
7. Whatever goes wrong with my heart problem is my own fault.	1	2	3	4	5	6
8. Whatever improvement occurs with my heart problem is largely a matter of good fortune.	1	2	3	4	5	6
9. Following doctor's orders to the letter is the best way to keep my heart problem from getting worse.	1	2	3	4	5	6
10. The main thing which affects my my heart problem is what I myself do.	1	2	3	4	5	6

11. If my heart problem worsens, it's a matter of fate.	1	2	3	4	5	6
12. The type of help I receive from other people determines how soon my heart problem improves.	1	2	3	4	5	6
13. If my heart problem takes a turn for the worse, it is because I have not been taking proper care of myself.	1	2	3	4	5	6
14. If I am lucky, my heart problem will get better.	1	2	3	4	5	6
15. Whenever my heart problem worsens, I should consult a medically trained professional.	1	2	3	4	5	6
16. I deserve the credit when my heart problem improves and the blame when it gets worse.	1	2	3	4	5	6
17. As to my heart problem, what will be will be.	1	2	3	4	5	6

18. In order for my heart problem 1 2 3 4 5 6
to improve, it is up to other people
to see that the right things happen.

16. This part of the questionnaire consists of 21 groups of statements. After reading each group of statements carefully, circle the number (0, 1, 2, or 3) next to the one statement in each group which **best** describes the way you have been feeling the **past week, including today**. If several statements within a group seem to apply equally well, circle each one. **Be sure to read all the statements in each group before making your choice.**

1. 0 I do not feel sad.
1 I feel sad.
2 I am sad all the time and I can't snap out of it.
3 I am so sad or unhappy that I can't stand it.

2. 0 I am not particularly discouraged about the future.
1 I feel discouraged about the future.
2 I feel I have nothing to look forward to.
3 I feel that the future is hopeless and that things cannot improve.

3. 0 I do not feel like a failure.
1 I feel I have failed more than the average person.
2 As I look back on my life, all I can see is a lot of failures.
3 I feel I am a complete failure as a person.

4. 0 I get as much satisfaction out of things as I used to.

1 I don't enjoy things the way I used to.

2 I don't get real satisfaction out of anything anymore.

3 I am dissatisfied or bored with everything.

5. 0 I don't feel particularly guilty.

1 I feel guilty a good part of the time.

2 I feel guilty most of the time.

3 I feel guilty all of the time.

6. 0 I don't feel I am being punished.

1 I feel I may be punished.

2 I expect to be punished.

3 I feel I am being punished.

7. 0 I don't feel disappointed in myself.

1 I am disappointed in myself.

2 I am disgusted with myself.

3 I hate myself.

8. 0 I don't feel I am any worse than anybody else.

1 I am critical of myself for my weaknesses or mistakes.

2 I blame myself all the time for my faults.

3 I blame myself for everything bad that happens.

9. 0 I don't have any thoughts of killing myself.

1 I have thoughts of killing myself, but I would not carry them out.

2 I would like to kill myself.

3 I would kill myself if I had the chance.

10. 0 I don't cry any more than usual.

1 I cry more now than I used to.

2 I cry all the time now.

3 I used to be able to cry, but now I can't cry even though I want to.

11. 0 I am no more irritated now than I ever am.

1 I get annoyed or irritated more easily than I used to.

2 I feel irritated all the time now.

3 I don't get irritated at all by the things that used to irritate me.

12. 0 I have not lost interest in other people.

1 I am less interested in other people than I used to be.

2 I have lost most of my interest in other people.

3 I have lost all of my interest in other people.

13. 0 I make decisions about as well as I ever could.

1 I put off making decisions more than I used to.

2 I have greater difficulty in making decisions than before.

3 I can't make decisions at all any more.

14. 0 I don't feel I look any worse than I used to.

1 I am worried that I am looking old or unattractive.

2 I feel that there are permanent changes in my appearance that make me look unattractive.

3 I believe that I look ugly.

15. 0 I can work about as well as before.

1 It takes an extra effort to get started at doing something.

2 I have to push myself very hard to do anything.

3 I can't do any work at all.

16. 0 I can sleep as well as usual.

1 I don't sleep as well as I used to.

2 I wake up 1-2 hours earlier than usual and find it hard to get back to sleep.

3 I wake up several hours earlier than I used to and cannot get back to sleep.

17. 0 I don't get more tired than usual.

1 I get tired more easily than I used to.

2 I get tired from doing almost anything.

3 I am too tired to do anything.

18. 0 My appetite is no worse than usual.

1 My appetite is not as good as it used to be.

2 My appetite is much worse now.

3 I have no appetite at all anymore.

19. 0 I haven't lost much weight, if any, lately.

1 I have lost more than 5 pounds.

2 I have lost more than 10 pounds.

3 I have lost more than 15 pounds.

20. 0 I am no more worried about my health than usual.

1 I am worried about physical problems such as aches and pains; or upset stomach; or constipation.

2 I am very worried about physical problems and it's hard to think of much else.

3 I am so worried about my physical problems that I cannot think about anything else.

21. 0 I have not noticed any recent change in my interest in sex.

1 I am less interested in sex than I used to be.

2 I am much less interested in sex now.

3 I have lost interest in sex completely.

That is the end of the questionnaire. Please check that you have answered all of the questions and then post the questionnaire back to us. Thank you very much for taking the time to make this important contribution to our study of emotion and heart disease. We may be in touch with you regarding a follow up stage of the study, in which case we look forward to speaking with you soon.

Appendix 7: ACCENT invitation letter to patient for taking part in 36 month follow up.

Royal Free and University College Medical School

UNIVERSITY COLLEGE LONDON

DEPARTMENT OF EPIDEMIOLOGY AND PUBLIC HEALTH

Gower Street Campus

Dear

I have taken over from Dr *****and Dr ****** whom you may recall when you took part in our research study, approximately 3 years ago when you were initially admitted to hospital for a heart problem. I enclose the patient information sheet on the study to jog your memory.

As discussed on the telephone, I would be so appreciative if you would consider taking part in the very final phase of our study of stress and heart disease. We would like you to complete the enclosed questionnaire pack, which contains some questions you answered in hospital, but which we need to ask you again as a means of finding out how you are feeling now.

Please use the enclosed **FREEPOST** envelope to send back the questionnaire pack.

We have a telephone number recorded for you but if this is due to be changed, I would be grateful if you could write it on the questionnaire by your name if you are agreed to this.

Thank you once again for your help, I hope all is well. Feel free to ring on the telephone extension below if you have any queries whatsoever.

Yours Sincerely,

Dr Mimi Bhattacharyya

Clinical Research Fellow

Appendix 8: ACCENT patient information sheet

Royal Free and University College Medical School

UNIVERSITY COLLEGE LONDON

DEPARTMENT OF EPIDEMIOLOGY AND PUBLIC HEALTH

Study of Emotional Factors and Quality of Life in Heart Disease

PATIENT INFORMATION SHEET (Confidential)

This research study is funded by the British Heart Foundation to try and explore how our emotions and behaviour influence the cardiovascular system in health and disease. The results of this study will help advance our knowledge of the links between the mind and the body. This exciting and important area of medical science will contribute to the understanding of heart disease, and aims to improve both the prevention and the treatment of this common illness. The study was being carried out by Professor Andrew Steptoe from the Department of Epidemiology and Public Health at University College London, in collaboration with Dr from the Department of Clinical Cardiology. The researchers who will carry out the work are Dr******, Dr ******* and Dr ******* **and Dr Mimi Bhattacharyya.**

Exactly what triggers heart attacks and unstable angina is unknown. We still don't know why people have a heart attack on one specific day and not on the day before or the day after. It is likely to represent a complex interaction of several factors. We are trying to find out whether lifestyle and emotional state make a contribution in some patients. We also want to learn more about how people respond emotionally to coming into hospital with a heart problem, and how these responses may relate to physical recovery and quality of life. We are particularly interested in linking the psychological factors with the underlying biology of heart disease, to see whether there are differences in the various chemicals in the blood that are involved in heart attacks and angina.

How You Can Help

You may remember taking part in a research study a while back in which we interviewed you about what has been happening in your life over the last six months, right up until you came into hospital. We also asked you to fill in some questionnaires in your own time. These concern how you are feeling about life, and how you cope with stress. We would like to follow this up three years after being in hospital. This would

involve a telephone interview and filling out a questionnaire similar to the one you have previously completed for us one year after being in hospital.

We want to emphasise that all results obtained will be strictly confidential and will only be used for medical research purposes. You will be free to withdraw from the study at any time without giving a reason. Taking part or deciding not to take part will not affect your medical treatment in any way.

Many thanks for reading this.

We hope you feel able to take part in our study, which will help us understand more about the causes of heart disease and how to manage it better.

Any questions to Dr.Mimi Bhattacharyya, Department of Epidemiology and Public Health, University College London

Appendix 9: ACCENT patient consent form

Royal Free and University College Medical School

UNIVERSITY COLLEGE LONDON

DEPARTMENT OF EPIDEMIOLOGY AND PUBLIC HEALTH

Study Number

CONSENT FORM (Confidential)

Title of project: **A Study of the Emotional and Behavioural Factors in Acute Coronary Syndromes**

Name of Researchers: Professor Andrew Steptoe, Dr.*****, Dr. *****Dr Mimi Bhattacharyya.**

Any questions to **Dr. Bhattacharyya**, Department of Epidemiology and Public Health, University College London

Please initial

1. I confirm that I have read and understood the information sheet for the above study and have had the opportunity to ask questions.

2. I understand that my participation is voluntary and that I am free to withdraw at any time, without giving any reason, without my medical care or legal rights being affected.

3. I understand that sections of any of my medical notes may be looked at by regulatory

authorities where it is relevant to my taking part in research. I give permission for these individuals to have access to my records.

4. I agree to take part in the above study and be involved in follow up for three years after the initial study.

Name of patient	Date	Signature

Researcher	Date	Signature

1 for Patient; 1 for Researcher; 1 to be kept with hospital notes

Appendix 10: ACCENT study 12 and 36 month telephone questionnaire

Patient name	
EMOT no	
Interviewer	
Date of admission	
Date of telephone follow up	

Subsequent heart problems?	YES / NO - specify
Severity (circle)	Mild Moderate Severe
Other major med probs?	
Re – admission?	YES / NO
Revascularisation procedure?	YES / NO
Recurrence of symptoms?	YES / NO
Limiting Angina?	YES / NO

Seen GP last 3 months?	YES / NO
GP checked cholesterol?	YES / NO
Cholesterol level	Mmol/l
GP checked BP?	YES / NO
GP checked blood sugar (if appropriate)	YES / NO

Attended rehab course?	YES / NO Where?
No. of sessions attended e.g 6/8	
Found rehab course useful?	YES / NO

Do you feel that your lifestyle has changed since your heart problem?

How?

Did you receive advice about the following either in hospital or subsequently on a cardiac rehab course?

Subject	Advice given?	Advice implemented?	Comments?
Exercise	YES / NO	YES / NO / PARTIAL	
Weight	YES / NO	YES / NO / PARTIAL	
Stress	YES / NO	YES / NO / PARTIAL	
Alcohol	YES / NO	YES / NO / PARTIAL	
Diet	YES / NO	YES / NO / PARTIAL	
Were you a smoker before your heart problem? YES / NO			
Were you advised to stop YES / NO			
Advice implemented YES / NO / PARTIAL - specify			
Relapsed? - reason?			
How many a day do you smoke now?			

What medication are you currently taking?

Any problems with meds?	YES / NO - specify
Do you take all your tablets every day?	
How often do you miss a dose?	

Working pre heart problem?	YES / NO
Back to work?	YES / NO
When returned to work	
Full / part time / light duties?	

Do you have any further thoughts about anything that may have triggered off your heart problem?

Thank you. Mention questionnaire pack.

Appendix 11: 12 and 36 month questionnaire

Name:	Date:	Pt No:

Medical Research Study

Emotion and Heart Disease

Thank you very much for participating in the third phase of our study of emotions and heart disease. We would like you to complete this questionnaire about your lifestyle, your attitudes and opinions, the way you feel about yourself and the way you feel about your heart problem. You may feel that some of the questions do not apply to you, but please answer each question with the answer that most closely fits the way you feel.

The answers you provide in this questionnaire will be kept **strictly confidential.** The information will go into the statistics for the study, and it will not be possible to identify you personally in any reports. Under no circumstances will any of the information you give us be made available to anyone else.

Most of the questions can be answered by circling the appropriate answer.

For example:

"I can sit at ease and feel relaxed"

Definitely	Usually	Not often	Not at all

Please be sure to read the instructions to each section carefully.

What do you think caused your heart problem?

Serious heart disease may be caused by many different factors. We would like to find out what factors you think were involved with your own illness. Listed below are a series of factors that patients in the past have thought helped to cause their heart disease symptoms. Please think about each item, then circle the answer that indicates how much you agree or disagree with each statement.

Factors that might have helped cause my illness:			
My illness is hereditary – it runs in my family	**No**	**Maybe**	**Yes**
Smoking played a major role in causing my illness	**No**	**Maybe**	**Yes**
My illness was brought on by other medical problems	**No**	**Maybe**	**Yes**
Stress was a major factor in my illness	**No**	**Maybe**	**Yes**
Being overweight caused my illness	**No**	**Maybe**	**Yes**
High blood pressure was an important factor in my illness	**No**	**Maybe**	**Yes**

Diet played a major role in causing my illness	**No**	**Maybe**	**Yes**
I became ill because I over-exerted myself	**No**	**Maybe**	**Yes**
It was just by chance and bad luck that I became ill	**No**	**Maybe**	**Yes**
My illness was caused by poor medical care in the past	**No**	**Maybe**	**Yes**
Lack of exercise was a cause of my illness	**No**	**Maybe**	**Yes**
My illness was brought on by tiredness and exhaustion	**No**	**Maybe**	**Yes**
Genetic factors (genes) caused my illness	**No**	**Maybe**	**Yes**
My state of mind played a major part in causing my illness	**No**	**Maybe**	**Yes**
Working too hard caused my illness	**No**	**Maybe**	**Yes**
A germ or virus caused my illness	**No**	**Maybe**	**Yes**

This part of the questionnaire is about your emotions and how you are feeling. Read each item and circle the reply which comes closest to how you have been feeling **in the past week**.

2. I feel tense or 'wound up':

Most of the time	A lot of the time	From time to time, occasionally	Not at all

8. I get a sort of frightened feeling as if something awful is about to happen:

Very definitely and quite badly	Yes, but not too badly	A little, but it doesn't worry me	Not at all

9. Worrying thoughts go through my mind:

A great deal of the time	A lot of the time	From time to time	Only occasionally but not too often

10.I can sit at ease and feel relaxed:

Definitely	Usually	Not often	Not at all

11.I get a sort of frightened feeling like 'butterflies ' in the stomach:

Not at all	Occasionally	Quite often	Very often

12.I feel restless as if I have to be on the move:

Very much indeed	Quite a lot	Not very much	Not at all

13.I get sudden feelings of panic:

Very often indeed	Quite often	Not very often	Not at all

The following questions are about your health and daily activities. Read each item and circle one answer for each question.

1. In general would you say your health is:

Excellent	Very Good	Good	Fair	Poor

2. Compared to one year ago, how would you rate your health in general now?

Much better now than one year ago	Somewhat better now than one year ago	About the same as one year ago	Somewhat worse now than one year ago	Much worse now than one year ago

3. The following questions are about the activities you might do during a typical day Does **your health now limit you** in these activities? If so how much?

- Vigorous activities – such as running, lifting heavy objects, participating in a strenuous sport

Yes, limited a lot	Yes, limited a little	No, not limited at all

- Moderate activities – such as moving a table, pushing a vacuum cleaner, bowling, or playing golf.

Yes, limited a lot	Yes, limited a little	No, not limited at all

Lifting or carrying groceries.

Yes, limited a lot	Yes, limited a little	No, not limited at all

- Climbing **several** flights of stairs.

Yes, limited a lot	Yes, limited a little	No, not limited at all

- Climbing **one** flight of stairs.

Yes, limited a lot	Yes, limited a little	No, not limited at all

- Bending, kneeling, or stooping.

Yes, limited a lot	Yes, limited a little	No, not limited at all

- Walking **more than a mile**.

Yes, limited a lot	Yes, limited a little	No, not limited at all

- Walking **half a mile**.

Yes, limited a lot	Yes, limited a little	No, not limited at all

- Walking **one hundred yards**.

Yes, limited a lot	Yes, limited a little	No, not limited at all

- Bathing or dressing yourself.

Yes, limited a lot	Yes, limited a little	No, not limited at all

4. During the **past 4 weeks**, have you had any of the following problems with your work or other regular daily activities **as a result of your physical health**?

Cut down the **amount of time** you spent on work or other activities.

Yes	No

-
- **Accomplished less** than you would like.

Yes	No

- Were limited in the **kind** of work or other activities.

Yes	No

- Had **difficulty** performing the work or other activities (for example, it took extra effort).

Yes	No

5. During the **past 4 weeks**, have you had any of the following problems with your work or other regular daily activities **as a result of any emotional problems** (such as feeling depressed or anxious)?

- Cut down on the **amount of time** you spent on work or other activities:

Yes	No

- **Accomplished less** than you would like:

Yes	No

- Didn't do work or other activities as **carefully** as usual:

Yes	No

6. During the **past 4 weeks**, to what extent has your physical health or emotional problems interfered with your normal social activities with family, friends, neighbours, or groups?

Not at all	Slightly	Moderately	Quite a bit	Extremely

7. How much **bodily** pain have you had during the **past 4 weeks**?

None	Very mild	Mild	Moderate	Severe	Very severe

8. During the **past 4 weeks**, how much did **pain** interfere with your normal work (including both work outside the home and housework)?

Not at all	A little bit	Moderately	Quite a bit	Extremely

9. These questions are about how you feel and how things have been with you **during the past 4 weeks**. For each question, please give the one answer that comes closest to the way you have been feeling. How much of the time during the **past 4 weeks**:

- Did you feel full of life?

All of the time	Most of the time	A good bit of the time	Some of the time	A little bit of the time	None of the time

- Have you been a very nervous person?

All of the time	Most of the time	A good bit of the time	Some of the time	A little bit of the time	None of the time

- Have you felt so down in the dumps that nothing could cheer you up?

All of the time	Most of the time	A good bit of the time	Some of the time	A little bit of the time	None of the time

- Have you felt calm and peaceful?

All of the time	Most of the time	A good bit of the time	Some of the time	A little bit of the time	None of the time

- Did you have a lot of energy?

All of the time	Most of the time	A good bit of the time	Some of the time	A little bit of the time	None of the time

- Have you felt downhearted and low?

All of the time	Most of the time	A good bit of the time	Some of the time	A little bit of the time	None of the time

- Did you feel worn out?

All of the time	Most of the time	A good bit of the time	Some of the time	A little bit of the time	None of the time

- Have you been a happy person?

All of the time	Most of the time	A good bit of the time	Some of the time	A little bit of the time	None of the time

- Did you feel tired?

All of the time	Most of the time	A good bit of the time	Some of the time	A little bit of the time	None of the time

10. During the **past 4 weeks**, how much of the time has your **physical health or emotional problems** interfered with your social activities (like visiting friends, relatives, etc.)?

All of the time	Most of the time	A good bit of the time	Some of the time	A little bit of the time	None of the time

11. How **TRUE** or **FALSE** is **each** of the following statements for you?

- I seem to get ill more easily than other people.

Definitely True	Mostly True	Don't Know	Mostly False	Definitely False

- I am as healthy as anybody I know.

Definitely True	Mostly True	Don't Know	Mostly False	Definitely False

- I expect my health to get worse.

Definitely True	Mostly True	Don't Know	Mostly False	Definitely False

- My health is excellent.

Definitely True	Mostly True	Don't Know	Mostly False	Definitely False

These questions relate to thoughts and/or feelings you may have experienced over the last few months since you had the acute heart symptoms which led to your hospital admission. Please circle whichever answer seems to apply closest you.

1. Have you had upsetting thoughts or images that related to your heart problem and that came into your head when you didn't want them to?

Not at all	Once per week or less	2 – 4 times per week	5 or more times per week

2. Have you been having bad dreams or nightmares about your heart problem?

Not at all	Once per week or less	2 – 4 times per week	5 or more times per week

3. Have you had the experience of reliving the time when your acute heart symptoms occurred, acting or feeling as if it were happening again?

Not at all	A little bit	Somewhat	Very much

4. Have you felt very emotionally upset when reminded of the time your acute heart symptoms came on, such as becoming very scared, angry, sad?

Not at all	Once in a while	Somewhat	Very much

5. Have you been having physical reactions if reminded of when your heart symptoms first occurred, for example heart beating fast, breaking out in a cold sweat etc?

Not at all	Once per week or less	2 – 4 times per week	5 or more times per week

6. Have you been trying not to think about or have feelings associated with your heart problem?

Not at all	Once in a while	Somewhat	Very much

7. Have you been making efforts to avoid activities, situations, or places that remind you of when the symptoms that led to your being admitted to hospital started?

Not at all	Once in a while	Somewhat	Very much

8. Have you been unable to remember any important parts of the time when your heart problem started and when you got into hospital?

Not at all	A little bit	Somewhat	Very much

9. Have you found that you have not been interested in things you used to enjoy doing?

Not at all	A little bit	Somewhat	Very much

10. Have you felt distant or cut off from others?

Not at all	Once in a while	Somewhat	Very much

11. Have you felt emotionally numb, for example, felt sad but couldn't cry, unable to have loving feelings?

Not at all	Once in a while	Somewhat	Very much

12. Have you felt that any future plans or hopes have changed because of the heart problem that led to your going into hospital?

Not at all	Once in a while	Somewhat	Very much

13.Have you been having problems falling or staying asleep?

Not at all	Once per week or less	2 – 4 times per week	5 or more times per week

14.Have you been more irritable or had outbursts of anger?

Not at all	Once per week or less	2 – 4 times per week	5 or more times per week

15.Have you been having difficulty concentrating, for example drifting in and out of conversations, losing track of the story on television, difficulty remembering what you have read?

Not at all	Once in a while	Somewhat	Very much

16.Have you been overly alert, for example checking to see who is around you?

Not at all	A little bit	Half of the time	Almost always

17.Have you been jumpier or more easily startled?

Not at all	A little bit	Half of the time	Almost always

This part of the questionnaire consists of 21 groups of statements. After reading each group of statements carefully, circle the number

(0, 1, 2, or 3) next to the one statement in each group which **best** describes the way you have been feeling the **past week, including today**. If several statements within a group seem to apply equally well, circle each one. **Be sure to read all the statements in each group before making your choice.**

1.	0	I do not feel sad.
	1	I feel sad.
	2	I am sad all the time and I can't snap out of it.
	3	I am so sad or unhappy that I can't stand it.
2.	0	I am not particularly discouraged about the future.
	1	I feel discouraged about the future.
	2	I feel I have nothing to look forward to.
	3	I feel that the future is hopeless and that things cannot improve.
3.	0	I do not feel like a failure.
	1	I feel I have failed more than the average person.
	2	As I look back on my life, all I can see is a lot of failures.
	3	I feel I am a complete failure as a person.
4.	0	I get as much satisfaction out of things as I used to.
	1	I don't enjoy things the way I used to.
	2	I don't get real satisfaction out of anything anymore.
	3	I am dissatisfied or bored with everything.
5.	0	I don't feel particularly guilty.
	1	I feel guilty a good part of the time.
	2	I feel guilty most of the time.
	3	I feel guilty all of the time.
6.	0	I don't feel I am being punished.
	1	I feel I may be punished.
	2	I expect to be punished.
	3	I feel I am being punished.
7.	0	I don't feel disappointed in myself.
	1	I am disappointed in myself.
	2	I am disgusted with myself.

	3	I hate myself.
8.	0	I don't feel I am any worse than anybody else.
	1	I am critical of myself for my weaknesses or mistakes.
	2	I blame myself all the time for my faults.
	3	I blame myself for everything bad that happens.
9.	0	I don't have any thoughts of killing myself.
	1	I have thoughts of killing myself, but I would not carry them out.
	2	I would like to kill myself.
	3	I would kill myself if I had the chance.
10.	0	I don't cry any more than usual.
	1	I cry more now than I used to.
	2	I cry all the time now.
	3	I used to be able to cry, but now I can't cry even though I want to.
11.	0	I am no more irritated now than I ever am.
	1	I get annoyed or irritated more easily than I used to.
	2	I feel irritated all the time now.
	3	I don't get irritated at all by the things that used to irritate me.
12.	0	I have not lost interest in other people.
	1	I am less interested in other people than I used to be.
	2	I have lost most of my interest in other people.
	3	I have lost all of my interest in other people.
13.	0	I make decisions about as well as I ever could.
	1	I put off making decisions more than I used to.
	2	I have greater difficulty in making decisions than before.
	3	I can't make decisions at all any more.
14.	0	I don't feel I look any worse than I used to.
	1	I am worried that I am looking old or unattractive.
	2	I feel that there are permanent changes in my appearance that make me look unattractive.
	3	I believe that I look ugly.

15. 0 I can work about as well as before.
1 It takes an extra effort to get started at doing something.
2 I have to push myself very hard to do anything.
3 I can't do any work at all.

16. 0 I can sleep as well as usual.
1 I don't sleep as well as I used to.
2 I wake up 1-2 hours earlier than usual and find it hard to get back to sleep.
3 I wake up several hours earlier than I used to and cannot get back to sleep.

17. 0 I don't get more tired than usual.
1 I get tired more easily than I used to.
2 I get tired from doing almost anything.
3 I am too tired to do anything.

18. 0 My appetite is no worse than usual.
1 My appetite is not as good as it used to be.
2 My appetite is much worse now.
3 I have no appetite at all anymore.

19. 0 I haven't lost much weight, if any, lately.
1 I have lost more than 5 pounds.
2 I have lost more than 10 pounds.
3 I have lost more than 15 pounds.

I am purposely trying to lose weight by eating less. Yes _____
No_____

20. 0 I am no more worried about my health than usual.
1 I am worried about physical problems such as aches and pains; or upset stomach; or constipation.
2 I am very worried about physical problems and it's hard to think of much else.
3 I am so worried about my physical problems that I cannot think about anything else.

21. 0 I have not noticed any recent change in my interest in sex.

1 I am less interested in sex than I used to be.

2 I am much less interested in sex now.

3 I have lost interest in sex completely.

That is the end of the questionnaire. Please check that you have answered all of the questions and then post the questionnaire back to us. This is the final questionnaire in this study. Thank you very much for taking the time to make this important contribution to our research of emotions and heart disease.