Depression, Anxiety and Morbidity Outcomes After Cardiac Surgery

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SUMMARY

Depression and heart disease are among the top ten causes of an estimated 56 million deaths throughout the world (Lopez, Mathers, Ezzati, Jamison, & Murray, 2006). Projections by the World Health Organisation indicate that depression and cardiac disorders will indeed remain among the top ten leading causes of disease burden by the year 2020 (Lopez et al., 2006; Murray & Lopez, 1997). The extant literature describes a prognostic association between depressive symptoms and adverse coronary artery disease (CAD) outcomes (Barth, Schumacher, & Herrmann-Lingen, 2004; Rugulies, 2002; Suls & Bunde, 2005; Van der Kooy et al., 2007). These findings extend to persons having undergone cardiac revascularisation surgery (Connerney, Shapiro, McLaughlin, Bagiella, & Sloan, 2001) and have prompted various consensus panels to call for routine depression assessment among heart disease patients (Ballenger et al., 2001; Davidson et al., 2006; Lichtman et al., 2008).

By comparison to depression, anxiety has attracted a smaller share of empirical investigation and consensus panel support with respect to heart disease morbidity outcomes. This is particularly the case with regard to heart disease patients who have undergone cardiac surgery. In fact, one unanswered question to date is whether or not anxiety is related to morbidity after cardiac surgery to the same degree as has been described for depression. Notwithstanding substantial interrelation, comorbidity, and diagnostic symptom overlap between affective states and diagnostic disorders (Clark & Watson, 1991), depression and anxiety have rarely been examined concurrently among heart disease patients (Kubzansky & Kawachi, 2000; Smith & Cundiff, in press; Suls & Bunde, 2005). Thus a second unanswered question to date is whether the associations between cardiac morbidity and anxiety and depression remain after controlling for symptom interrelation and shared variance. To sufficiently address these limitations cardiac research requires timely consideration of empirically validated and contemporary understandings of affect. Adoption of such theoretical frameworks would ensure examination of the unique and therefore discriminating symptomatology of depression (e.g. anhedonia/low positive affect) and anxiety (e.g. somatic tension/physiological hyperarousal) *per se* (for reviews see Clark & Watson, 1991; Craske et al., 2009). Likewise, investigation of general distress symptoms, those empirically demonstrated to underlie and account for shared variance between depression and anxiety, is essential.

The cardiac samples described herein were exclusively comprised of persons scheduled for cardiac surgery, most commonly, coronary artery bypass graft (CABG) surgery. The current body of work was designed to investigate the individual effects of

depression, anxiety and general distress on CABG patients' morbidity outcomes after cardiac surgery. Explicitly, throughout the research program attempts were made to measure general and non-specific distress along with unique depression and anxiety symptoms, that is, anhedonia/low positive affect and somatic tension/physiological hyperarousal respectively. Therefore, this dissertation describes perhaps the first attempt to concurrently examine core discriminating depressive and anxious symptoms, under an empirically validated framework, with respect to heart disease patients and also cardiac surgery outcomes. Eight separate but related studies are presented here; seven are published and one is submitted for publication.

Study One reports the association between preoperative depression, anxiety and general distress in relation to all-cause mortality after CABG surgery. The nearly twofold increased mortality risk attributable to anxiety, but not depression or distress, emphasises the requirement to expand psychosocial risk factor investigation beyond depression. Study Two investigates psychosocial risk factors for cardiac surgery related hospital readmission within six months of CABG surgery. A significant increased risk for readmission was found for preoperative anxiety and postoperative depression, even after adjustment for general distress. The findings highlight a differential pattern of association dependent on the timing of psychosocial risk factor assessment. Study Three followed up patients six months after CABG surgery and documents the association between perioperative depression and reduced quality of life, while no significant association was evident for anxiety and general distress at perioperative assessment. Study Four describes a serial assessment of neuropsychological function six months and five years after CABG surgery by comparison to a non-surgical community control group. The study shows no support for a consistent association between depression, anxiety and distress and the neuropsychological test scores that were, on average, significantly lower than those in a non surgical control group. Study Five describes a significant association between anxiety and increased odds for in hospital atrial fibrillation arrhythmias after CABG surgery.

Study Six, Study Seven and Study Eight describe the results of a prospective cohort of N = 158 CABG patients. Firstly, Study Six reports increased odds for developing delirium attributable to preoperative major depressive disorder, but not generalised anxiety/worry disorder or panic disorder. In Study Seven, the combined morbidity and mortality outcome described by the Society of Thoracic Surgeons (Shahian et al., 2009a) was investigated with respect to affective disorders, their characteristic symptoms, and personality traits. Findings suggested that increased odds for morbidity were associated with generalised anxiety disorder and trait NA.

To further explore depression and anxiety dimensions among cardiac patients, the final study investigated the receiver operating characteristics (ROC) of self-report measures of low positive affect, somatic tension/anxious arousal, and Type D personality in relation to diagnostically ascertained affective disorders. It was found that the affect dimension ROCs performed best in the prediction of affect concordant disorders (e.g. anxious arousal and panic disorder) supporting theoretical models of affect.

The present dissertation suggests that depression, anxiety and general distress exhibit discrete associations with cardiac surgery outcomes. The distinct pattern of results may in part be due to the theoretical conceptualisation of anhedonic depression, anxious arousal and general distress (i.e. NA); the latter is theorised to explain the interrelation between depression and anxiety emotions and disorders. Other factors that have potentially impacted upon the associations with cardiac outcomes include whether self-report measures capture trait or state distress, whether such measures were dichotomised or examined as continuous variables, and whether a diagnostic interview was performed. Also, the distress assessment timing would have influenced the pattern of results (e.g. preoperative, postoperative, six-months, five years). The findings presented herein have important implications for how researchers and clinicians conceptualise, investigate and measure distress among cardiac patients with respect to morbidity outcomes. One important methodological contribution of this body of work is that a series of studies were performed employing empirically validated theoretical models of depression and anxiety. In addition, various statistical methods were described in which the effects of depression and anxiety on cardiac outcome were analysed taking into consideration the shared variance of general distress.

DECLARATION

This work contains no material which has been accepted for the award of any other degree or diploma in any university or other tertiary institution to Phillip J. Tully and, to the best of my knowledge and belief, contains no material previously published or written by another person, except where due reference has been made in the text. I give consent to this copy of my thesis when deposited in the University Library, being made available for loan and photocopying, subject to the provisions of the Copyright Act 1968. The author acknowledges that copyright of published works contained within this thesis (as listed below) resides with the copyright holders of those works. I also give permission for the digital version of my thesis to be made available on the web, via the University's digital research repository, the Library catalogue, the Australasian Digital Theses Program (ADTP) and also through web search engines, unless permission has been granted by the University to restrict access for a period of time.

Chapter III: Study One
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Chapter V: Study Three
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Chapter VII: Study Five
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Chapter X: Study Eight
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Appendix A
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Appendix B
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Appendix C
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Phillip J. Tully

Signed: _____   4/01/2011

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DEDICATIONS

For Nanna and Poppy.

LIST OF ABBREVIATIONS

AF, atrial fibrillation

AUC, area under the curve

CABG, coronary artery bypass graft

CAD, coronary artery disease

CHD, coronary heart disease

CI, confidence interval

DASS, depression anxiety and stress scales

DS14, Type D distress scale

Hb, haemoglobin

HR, hazard ratio

LVEF, left ventricular ejection fraction

MASQ, Mood and Anxiety Symptom Questionnaire

MINI, MINI International Neuropsychiatric Interview

NA, negative affect

OR, odds ratio

PVD, peripheral vascular disease

RCT, randomised control trial

ROC, receiver operating characteristic

SF-36, Medical Outcomes Study Short Form-36

OVERVIEW

Outline Of Candidature

The current dissertation was undertaken to fulfil the requirements of a combined Master of Clinical Psychology with Doctor of Philosophy at The University of Adelaide, South Australia, Australia. The program combines a Clinical Masters coursework load and 1,000 hours of clinical internship (equivalent two years fulltime) and a full research program for a Doctor of Philosophy (equivalent three years fulltime) within four years of candidature. The program rules stipulate that the research undertaken has to adopt a clinical psychology focus. All coursework and internship requirements of the Masters component of the program were completed successfully. The following thesis is submitted to fulfil the requirements of a Doctor of Philosophy.

Outline Of Thesis

This thesis investigates the hypothesis that examination of interrelated negative emotions (i.e. anxiety, depression and a shared component of NA) will facilitate understanding of the individual differences that exist in health and morbidity outcomes after cardiac surgery. The present series of studies was designed to identify whether depression, anxiety or relatively non-specific distress (e.g. NA) were associated with cardiac surgery related morbidity that requires readmission to hospital, or cause neuropsychological deterioration, delirium, arrhythmia, poorer health related quality of life, or mortality. Eight separate but related studies are presented herein as chapters. Chapter I provides an overview of the literature concerning cardiac surgery and the psychogenic correlates of cardiac surgery morbidity. This chapter also argues, from a psychosomatic perspective, that cardiac outcome research must overcome the limitations of previous studies by adopting empirically validated dimensional or phenotypic measures of depression and anxiety through a theoretical framework. Chapter II provides a summary (exegesis) of the seven studies that comprise this thesis and describes each in context. Chapters III to X consist of the eight studies in manuscript format and a statement outlining each of the authors' contributions. Chapter XI provides a summary of the results and a concluding discussion based upon the entire research program.

CHAPTER I

Preamble

Overview of Chapter

A brief literature review is provided here and each individual paper includes a separate introduction. In the present literature review firstly the epidemiology of CAD and cardiac surgery procedures are described. Then an overview of the common mortality and morbidity outcomes experienced after cardiac surgery is provided, describing the association with emotional distress. The current section concludes with a critique of previous research and justifies the simultaneous examination of depressive and anxious symptomatology to assist our understanding of morbidity following cardiac surgery. The second theme of the literature review focuses on theoretical models of depression and anxiety that inform psychiatric nomenclature and contemporary understandings of affective distress. This overview will culminate with a detailed description of the preferred theoretical model for the current thesis, David Watson and colleagues' account of anxiety and depression (Clark & Watson, 1991; Mineka, Watson & Clark, 1998; Watson et al., 1995a, 1995b), and describe thereafter the aims of the current investigation.

Literature Review

Coronary Artery Disease

Coronary artery disease refers to the accumulation of atherosclerotic plaque affecting the coronary arteries that restricts blood supply to the heart itself (Bellg, 1998; Julian, Cowan, & McLenachan, 1998). Non-modifiable risk factors for CAD include increasing age, male gender, family history and genetic disposition, while modifiable risk factors include hypertension, dietary fat intake, cholesterol levels, tobacco smoking, diabetes mellitus, physical inactivity, obesity and response to emotional or mental stress (American Heart Association, 2002). In Australia, approximately 75% of cardiac surgery patients have hypertension, 25% are diabetic and 14% are tobacco users (Dinh et al., 2009).

Clinical manifestations of CAD include angina pectoris from ischemia to the myocardium during periods of increased circulatory demands such as exercise or mental and emotional stress. While in contrast, unstable angina is a similar chest pain or discomfort caused by myocardial ischemia typically occurring at rest or without physical exertion;

sometimes a consequence of temporary coronary spasm. A myocardial infarction may also be precipitated by the sudden onset of angina like chest pain (American Heart Association, 2002). A second common CAD symptom is dyspnoea or shortness of breath upon exertion or when at rest. Disturbances in heart rhythm (arrhythmia) are less common manifestations of CAD among open-heart surgery patients, though certain arrhythmias such as ventricular tachycardia are a medical emergency and may warrant insertion of an implantable cardioverter defibrillator.

Clinical Indications for Cardiac Surgery

Apart from reducing risk of CAD related mortality, CABG surgery is indicated for patients to alleviate symptoms of angina and dyspnoea over and above medical therapy and also to reduce non-fatal endpoints such as myocardial infarction, congestive heart failure and hospitalisation. Symptom benefit (e.g. angina) is greatest among those with severe angina and lowest left ventricular function (Eagle et al., 2004). By comparison to persons treated for CAD with percutaneous coronary intervention (i.e. stenting, angioplasty), patients indicated for CABG surgery are typically older and have greater proportion of left main stem stenosis, triple vessel disease, renal dysfunction and lowered ejection fractions (Malenka et al., 2005). Despite these patients greater comorbidity, a Cochrane Collaboration systematic review by Bakhai and colleagues (2005), comparing CABG surgery to percutaneous coronary intervention in single or multiple vessel disease, reported favourable outcomes for CABG surgery with respect to major adverse cardiac events, repeat revascularisation and restenosis rates. Also, longitudinal evidence in Australia corroborates significantly decreasing mortality rates during a time when CABG surgery patients are older and present with a greater proportion of comorbidity than ever before (McCaul, Hobbs, Knuiman, Rankin, & Gilfillan, 2004).

CABG Surgical Procedure

Coronary artery bypass graft surgery is the most commonly performed open-heart procedure in Australia accounting for approximately 60% of all cardiac operations (Dinh et al., 2009). Approximately 20% of CABG surgery patients undergo a concomitant heart valve repair or replacement procedure for stenosis, regurgitation and/ or infection (Shahian et al., 2009) though this dissertation primarily concerns CABG surgery patients as described herein.

Coronary artery bypass graft surgery is the surgical process used to treat critical obstructions in coronary arteries caused by CAD. The most common technique, under general anaesthesia and mechanical ventilation, involves a thoracic sternotomy and the use of cardiopulmonary bypass. Sternotomy allows access to the thoracic cavity and the heart. Cardiopulmonary bypass technology takes over the pumping function of the heart and the respiratory function of the lungs, providing a still and bloodless field for the cardiothoracic surgeon. Prior to initiating cardiopulmonary bypass cannulae are placed usually a single venous cannula in the right atrium, and an arterial cannula into the ascending aorta. Bypass is initiated with blood draining from the right side of the heart into the cardiopulmonary bypass circuit and is returned via the arterial line into the ascending aorta. Patient temperature allowed is either allowed to passively drift or may be actively cooled on initiation of bypass to temperatures often in the range of 30 – 34 °C. To protect the myocardium during surgery and provide the surgeon with a still heart, the aorta is clamped (x-clamp) such that the heart is isolated from the circulation and intermittently infused with a cardioplegia solution to induce cardiac arrest, stopping the heart from beating. The cardiopulmonary bypass circuit comprises a reservoir, an oxygenator to add oxygen and remove carbon dioxide from the blood, a heater cooler unit to allow temperature to be controlled, filters to prevent gaseous or particulate materials from entering the patient, and a pump to propel the oxygenated blood back into the patient.

The CABG surgery procedure requires a graft (a section of artery or vein) to to supply blood distal to the narrowed and potentially occluding atherosclerotic regions within the coronary arteries. The new conduits are fashioned during the surgical process and are most commonly arterial conduits such as the internal mammary artery, reversed saphenous veins harvested from the legs, or portions of the radial artery harvested from the arm. The American Heart Association and the American College of Cardiology advocate the use of the left internal mammary artery for grafts to the left anterior descending coronary artery (Eagle et al., 2004). Supplemental grafting of other occluded vessels commonly utilises the saphenous vein predominantly for grafts to the right and circumflex coronary arteries and their branches. The occluded coronary artery is cut a short distance distally from the blockage, the healthy artery or vein is anastomosed to the side of the coronary artery. The other end, if an internal mammary graft is utilised maintains its normal connection to the circulation, whilst for a free (not connected graft) the new conduit is sewn onto the aorta. Following successful grafting to the previously stenosed coronary artery, CABG surgery patients are slowly re-warmed to normal body temperatures and weaned from cardiopulmonary bypass. Patients are typically transferred to intensive care for on average 24 hours remaining on mechanical ventilation (for about 10 hours) and spend about seven days in hospital after surgery until discharge (Dinh et al, 2009).

Emotional Distress Among Cardiac Patients

The current literature review particularly concerns psychosocial evaluations of depression and anxiety and adverse cardiac surgery outcomes as relevant to the thesis aims. Mental and environmental stress, anger, hostility, vital exhaustion, low social support, social isolation, alexithymia and Type D personality are to name but a few of the psychosocial factors that have been implicated in adverse outcomes among CAD populations. Comprehensive reviews can be found elsewhere (Chida & Steptoe, 2009; Denollet, 2005; Dreher, 2004; Krantz & MCCeney, 2002; Kubzansky & Kawachi, 2000; Suls & Bunde, 2005).

Depression Among CABG Patients

Diagnostically ascertained unipolar depression is prevalent in between 15% to 20% of CABG surgery patients (Connerney, Shapiro, McLaughlin, Bagiella, & Sloan, 2001; Dao, Chu, Springer, Hiatt, & Nguyen, 2010; Fraguas Jnr, Ramadan, Pereira, & Wajngarten, 2000). This reflects the 13% to 21% prevalence of depression among general cardiac inpatients as reported in a systematic review by Thombs and colleagues (2008). Comparatively, the point prevalence among the general population is 5% to 9% for females and 2% to 3% among males (American Psychiatric Association, 2000) suggesting cardiac patients have higher prevalence of depression than community samples.

Many people who do not meet structured diagnostic criteria for mood disturbance still report subsyndromal depressive symptoms at more severe levels than non-CAD populations (Langeluddecke, Fulcher, Baird, Hughes, & Tennant, 1989). Some patients may develop new symptoms over the course of recovery (Peterson et al, 2002). Research has suggested that 13% of CABG patients report clinically relevant depressive symptoms not evident at the time of surgery at 12 month follow up (McKhann, Borowicz, Goldsborough, Enger, & Selnes, 1999). Peterson and colleagues (2002) explain that newly developed depressive symptoms result from the stressors of surgery that can produce an adjustment reaction or reactive type depression. In contrast, remitted depression may be a reflection of the upturn in mood associated with improvements in physical condition (McKhann et al., 1999).

Research suggests that depressive symptoms among CABG patients are associated with numerous risk factors including female gender, younger age, living alone, lower school education, dyspnoea at rest and exertion, previous myocardial infarction, lower left ventricular ejection fraction (LVEF) and use of tranquilliser medication (Dunkel et al., 2009). Cardiac patients are more likely to attribute somatic symptoms of depression to their medical

illness (Lespérance & Frasure-Smith, 2000) and potential depressive symptoms such as fatigue, loss of appetite, psychomotor retardation, insomnia, and difficulty concentrating can be the direct physiological response to a medical illness and hospitalisation (Koenig, George, Peterson, & Pieper, 1997). Research among CABG patients corroborates that somatic symptoms significantly increase in the first month after surgery (Contrada, Boulifard, Idler, Krause, & Labouvie, 2006; Vingerhoets, 1998) that may reflect a normative recovery from the physical demands of surgery. Regardless of the subtle nuances in depression measurement and relation to somatic symptoms, depression is highly prevalent among CABG patients, and as reviewed further below, appears to impact deleteriously on morbidity outcomes.

Anxiety among CABG Patients

Anxiety surprisingly features less prominently in the CABG surgery literature considering that all surgeries are stressful and some anxious apprehension and worry can be expected as part of a person's coping strategy and cognitive processing. Anxiety is highest for some persons while on the waiting list with an unknown CABG surgery date (Fitzsimons, Parahoo, Richardson, & Stringer, 2003; Koivula, Tarkka, Tarkka, Laippala, & Paunonen-Ilmonen, 2002). Fear of dying before, rather than during, surgery has been highlighted as a pervasive anxious preoccupation (Fitzsimons et al., 2003; Koivula et al., 2002). One hypothesis is that patients' anxiety response is largely due to the impending threat of surgery and the anaesthesia process, and would subside after surgery (Newman, 1984). However, recent research with CABG patients suggests that while anxiety may decrease to below preoperative levels, the severity of anxiety does not necessarily remit to below subclinical levels (Krannich et al., 2007).

Approximately 45% of CABG patients report elevated anxious symptomatology preoperatively, persisting at clinically relevant levels in 34% of patients immediately after surgery (Rymaszewska, Kiejna, & Hadrys, 2003). The finding that anxiety symptoms do not completely remit while others may develop new symptoms supports the contention that patients may experience negative and anxious cognitions such as worry about recovery from surgery. Johnston (1987) suggests the focus of anxiety is discrepant before and after surgery. That is, preoperative anxiety is focussed on the threat of physical danger, whereas postoperative anxiety is associated with increased self-focussed attention (Johnston, 1987).

The prevalence of diagnostically ascertained anxiety disorders is variable and the small sample sizes of previous studies suggest further investigation is required among CABG surgery patients. To date the prevalence has been reported as; generalised anxiety/worry disorder 2% to 5.9% (Fraguas et al., 2000; Rothenhäusler, Grieser, Nollert, Reichart,

Schelling, & Kapfhammer, 2005), panic disorder with or without agoraphobia 5.9% to 6.4% (Rafanelli, Roncuzzi, & Milaneschi, 2006; Rothenhäusler et al., 2005), social anxiety disorder 4.3% (Rafanelli et al., 2006), and obsessive compulsive disorder 2.1% (Rafanelli et al., 2006), though less has been reported for specific phobia. An audit of 62,665 electronic medical records suggested that post traumatic stress disorder was prevalent in 14.7% of CABG patients, and a further 9% of cases had comorbid post traumatic stress disorder and major depression (Dao et al., 2010). Other studies employing self-report measures of diagnostic criteria have reported a prevalence of post traumatic stress disorder symptomatology to be 24.4% with such symptomatology associated with severity of CAD and length of treatment in intensive care unit (Stoll et al., 2000).

Like depression, somatic symptoms potentially confound studies of anxiety in CAD. Fleet and colleagues (2000) explain that distinguishing independent effects particularly for panic disorder are problematic due to symptom overlap with CAD (e.g. shortness of breath, chest discomfort, tachycardia, palpitations). Among CABG surgery patients, anxiety symptoms tapping into autonomic arousal and skeletal musculature significantly increase after surgery (Andrew, Baker, Kneebone, & Knight, 2000).

Type D Personality

The Type D or *distressed* personality is characterised by a trait disposition toward negative emotional states (i.e. NA) while at the same time insecurity and inhibition in social situations, fear of rejection and disapproval. Measured with a self-report questionnaire, social inhibition is characterized by discomfort in social interactions, reticence, and lack of social poise whereas NA taps into dysphoric mood, worry, tension and irritability. Given the NA trait it is not surprising that Type D personality is associated with other measures of negative emotions such as depression and anxiety (Denollet, 2000; van Gestel et al., 2007). Some research also suggests Type D is independent not only of major depression but also of disease severity such as left ventricular function (Denollet, de Jonge, Kuyper, Schene, van Melle, Ormel, & Honig, 2009). Yet some authors question whether the NA component of Type D personality is an independent psychosocial construct (Carney, 1998; Lespérance & Frasure-Smith, 1996; Smith & MacKenzie, 2006) and query whether social dysfunction is merely an epiphenomenon of distress syndromes (Ketterer, 2010).

With respect to cardiac surgery patients Al-Ruzzeh and colleagues (2005) first reported 34.3% prevalence of Type D personality in cross-sectional follow-up 12-months after surgery; however a perioperative assessment was not performed. The only subsequent study to date reported 26% prevalence of Type D personality before surgery (Dannemann et

al., 2010). However, only 11% of these patients maintained distress levels indicative of the distressed personality six months later without any psychological intervention. These findings question the stability of Type D personality among cardiac surgery patients where limited research has been conducted to date.

Adverse Cardiac Surgery Outcomes

Cardiothoracic surgical procedures carry a degree of risk for arrhythmia, renal failure, and to a lesser extent operative mortality and neurological impairment that place a significant burden on the healthcare system in terms of monetary costs and hospital resources (Hannan et al., 2003; Lubitz et al., 1993).

Mortality

Mortality is the most exhaustively studied outcome from cardiac surgery (Shahian et al., 2009a, 2009b; Tu, Skyora, & Naylor, 1997). An evaluation of 774,881 CABG procedures identified various clinical and demographic factors that increase risk of mortality including older age, the urgency of surgery, renal dysfunction, respiratory function, previous myocardial infarction, peripheral vascular disease (PVD) and low LVEF (Shahian et al., 2009a). Self-report and diagnostically ascertained psychogenic risk factors may also play a role in mortality after CABG, independent of known medical risk factors. The largest study to date among 62,665 CABG patients showed that a comorbid post-traumatic stress disorder and major depression diagnosis was associated with a greater risk of in hospital mortality than post-traumatic stress disorder or major depression alone (Dao et al., 2010). A study employing a self-report depression symptom measure showed that persons whose depressive symptoms remitted six months after surgery were at no greater risk than those who were never depressed (Blumenthal et al., 2003). These results suggest that persistent depressive symptoms are more cardiotoxic than brief periods of depression. More recently, Connerney and colleagues (2010) found that major depression, new onset major depression, elevated depressive symptoms and cognitive-affective depressive symptoms were associated with cardiac but not all-cause mortality after CABG surgery.

In other studies, small sample size, short follow-up and few death outcomes led to wide confidence intervals (CIs) obscuring the depression effect sizes. Burg et al (2003b) reported a 23-fold increased mortality risk attributable to depression (95% CI 1.38 – 389.08; p = .03) whereas Baker et al (2001) reported a six-fold increased risk (95% CI 1.18 – 32.98; p = .05). The only CABG-mortality study concerning anxiety suggested that Spielberger Trait

Anxiety scores were associated with all-cause mortality, independent of congestive heart failure (Szekely et al., 2007), though adjustment for other covariates was lacking.

Unplanned Hospital Readmission

An unplanned readmission to hospital is the most common morbidity event a patient will experience within 30 days of CABG surgery (Almassi et al., 1997). An audit of 16,325 CABG patients across multiple hospital centres showed that the most common causes for readmissions were cardiac causes such as heart failure, myocardial ischemia, acute myocardial infarction, arrhythmias, and also coagulation causes such as thromboembolism, deep venous thrombosis and respiratory and other chest symptoms (Hannan et al., 2003). The risk factors associated with unplanned hospital readmissions are similar to those associated with mortality and largely reflect cardiac and non-cardiac comorbid conditions and the urgency of surgery (Hannan et al., 2003; Rockx et al., 2004; Stewart et al., 2000).

There are inconsistent findings with respect to the impact of psychological variables on hospital readmission rates after CABG. The association between preoperative depressive symptoms has been documented with respect to both all-cause (Saur et al., 2001) and cardiac (Burg, Benedetto, Rosenberg, & Soufer, 2003a; Oxlad et al., Stubberfield, Stuklis, Edwards, & Wade, 2006a; Scheier et al., 1999) readmissions within six months of cardiac surgery. Among the few anxiety studies to date Oxlad and colleagues (2006a) reported that postoperative anxiety was associated with cardiac readmission. However, several factors limit these findings. Firstly, only 21 readmissions were observed. Secondly, from 25 potential covariates adjustment was made only for time spent on cardiopulmonary bypass. Thirdly, the somatic focussed anxiety scale has been demonstrated elsewhere to spuriously increase after cardiac surgery (Andrew et al., 2000). As with mortality studies, previous readmission research is confounded by the absence of appropriate adjustment for medical comorbidity (Oxlad et al., 2006a; Scheier et al., 1999), small sample sizes (Burg et al., 2003a), and infrequent number of readmissions limiting statistical power (Burg et al., 2003a; Oxlad et al., 2006a; Scheier et al., 1999) suggesting the results are preliminary.

Health Related Quality Of Life

Though a nebulous term, health related quality of life is a multidimensional construct comprised of physical, mental and social aspects of health, well being and functioning, and the ability to perform everyday activities in occupational, social and leisure settings (Bosworth et al., 2000; Boudrez & De Backer, 2001; Wilson & Cleary, 1995; World Health

Organisation, 1993). Research has documented that depression in particular portends lower gains in health related quality of life post-CABG. Even though physical impairments and activity restrictions are common in the immediate postoperative period, patients reporting depressive symptoms tend not to exhibit the same magnitude of improvement in health related quality of life in the longer term compared to non-depressed persons (Goyal et al., 2005; Mallik et al., 2005; Perski et al., 1998; Ruo et al., 2003). In fact research suggests that depression symptoms are associated not only with poor emotional recovery but also poorer physical recovery. In a study of 963 CABG patients, improvement in physical health at six month follow up was lower among patients with depressive symptoms after adjustment for cardiac severity and baseline health (Mallik et al., 2005). Some studies have also reported that anxiety may deleteriously impact upon health related quality of life after CABG surgery (Hemingway & Marmot, 1999; Höfer et al., 2005; Kubzansky et al., 2006; Rothenbacher et al., 2007). However few studies have simultaneously compared depression and anxiety in relation to improvements in health related quality of life. Moreover, another limitation of studies to date is that typically only composite scores of mental and physical health are employed (e.g. Al-Ruzzeh et al., 2005; Goyal et al., 2005). By aggregating heterogenous health related quality of life domains post-CABG, potentially discrete relationships between specific aspects of health related quality of life emotional distress are neglected.

Neuropsychiatric Outcomes of Cardiac Surgery

   Short-term outcomes: delirium.

   Delirium is a state characterised by fluctuating changes in consciousness, impaired attention and acute changes in cognition that may manifest as disorientation to time, place and persons, perceptual disturbances and hallucinations (American Psychiatric Association, 2000). Delirium is the most common psychiatric disorder observed upon admission to healthcare settings (Leentjens, Maclullich, & Meagher, 2008). The incidence of delirium after cardiac surgery is reportedly between 3.1% and 50% (Kazmierski et al., 2006; Norkiene et al., 2007; Rolfson et al., 1999; Rudolph et al., 2005; Rudolph et al., 2006; Santos, Velasco, & Fraguas, 2004; Yoon et al., 2001). Cardiovascular risk factors include previous stroke, cerebrovascular disease and particularly atherosclerosis in the carotid artery and the ascending aorta (Bucerius et al., 2004; Cameron, 2007; Norkiene et al., 2007; Rolfson et al., 1999; Rudolph et al., 2005). Among CABG surgery patients, surgical risk factors include prolonged aortic cross clamping, cardiopulmonary bypass and anaesthetic times, requirement for blood transfusions and use of the intra-aortic balloon pump (Norkiene et al., 2007; Rolfson et al., 1999, Santos, Velasco & Fraguas, 2004).

Depression and other psychiatric disorders have been reported as comorbid with delirium (Dasgupta & Dumbrell, 2006; Rothenhausler et al., 2005; Thomas & Oster, 2009). Three systematic reviews identified that depression was a predisposing factor and increased the risk for delirium in the elderly (Michaud et al., 2007), cardiac surgery populations (Sockalingam et al., 2005) and non-cardiac surgery populations (Dasgupta & Dumbrell, 2006), though conflicting evidence was reported for anxiety. McAvay and colleagues (2007) showed that dysphoric mood and hopelessness were associated with incident delirium after hospitalisation. Findings from Davydow's (2009) systematic review also identified a bi-directional relationship as persons may develop subsequent distress as a response to in-hospital delirium. This is likely explained in part by common pathophysiological pathways via the limbic-hypothalamic-pituitary-adrenal-axis, inflammatory response and sympathetic nervous system suspected to affect cognition, mood and motivation and induce fatigability, anhedonia and reduce appetite. (Maclullich, Ferguson, Miller, de Rooij, & Cunningham, 2008). Symptoms diagnostically representative of the affective disorders also overlap those of delirium including attention, memory and sleep-wake cycle disturbances. Accordingly overlapping symptoms may pose a notable caveat in establishing a prognostic association between preoperative depression and anxiety and incident delirium.

Long-term outcomes: neuropsychological dysfunction.

Neuropsychological follow-up studies of CABG surgery patients are requisite to explicate whether cognitive dysfunction is related to operative factors, reflect normal age related change or progression of vascular disease. Long-term follow-up studies have yielded varying estimates of gross neuropsychological impairment (Selnes et al., 2001; Stygall et al., 2003). One study reported that up to 42% of all patients experienced deterioration when comparing five year follow up performance to presurgical functioning (Newman et al., 2001b). In contrast other studies have suggested that late neuropsychological decline affects fewer patients (Mullges, Babin-Ebell, Reents, & Toyka, 2002; Nathan et al., 2007) and is comparable to persons not undergoing CABG with similar cardiovascular risk factors (Selnes et al., 2008; van Dijk et al., 2008).

It is widely recognised in clinical settings that psychological distress can affect neuropsychological performance, motivation, test anxiety, information processing and attention (Lezak, Howieson, & Loring, 2004). The role of depression and anxiety in post-CABG neuropsychological function has typically been examined with correlation (McKhann et al., 1997, Newman et al., 2001a; Selnes et al., 2001; Stroobant & Vingerhoets, 2008) and without adjustment for covariates. Other authors have examined a single composite index of heterogeneous cognitive domains (Newman et al., 2001b; Stygall et al., 2003). Newman and

colleagues (2001a) showed that a preoperative measure of trait anxiety was only weakly associated with a composite index of neuropsychological performance at five years (Spearman r = -.179) in regression analysis adjusted for age, sex, diabetes and education. In contrast, Stroobant and Vingerhoets' (2008) follow-up of 43 CABG surgery patients three to five years after surgery suggested no correlation between neuropsychological performance and trait anxiety. Studies of short term neuropsychological performance have also shown little support for an association between neuropsychological performance and anxiety with correlation analyses (Andrew et al., 2000; Tsushima et al., 2005).

Atrial Fibrillation Arrhythmia

Atrial fibrillation (AF) arrhythmias occur in between 20% and 60% of CABG surgery patients (Echahidi, Pibarot, O'Hara, & Mathieu, 2008; Hogue, Creswell, Gutterman, & Fleisher, 2005) making it one of the most commonly experienced postoperative morbidity outcomes (Almassi et al., 1997). Atrial fibrillation developing in the postoperative period is associated with increased mortality rates (Jung, Meyerfeldt, & Birkemeyer, 2006), higher incidence of stroke (Mariscalco et al., 2007), renal failure and gastrointestinal complication (Kalavrouziotis, Buth, & Ali, 2007) and increased length of stay and hospital costs (Aranki et al., 1997).

Medical risk factors that increase the risk of AF include left ventricular dysfunction, hypertension, diabetes and obesity (Echahidi et al., 2008). Studies among non-surgical populations have shown that anxiety and other psychosocial factors may precede or be a symptom of arrhythmias (Sears et al., 2005; Suzuki & Kasanuki, 2004). Panic disorder and agoraphobic symptomatology are common in persons with paroxysmal AF (Suzuki & Kasanuki, 2004; Yavuzkir et al., 2007) and more than half of patients report anxiety during an arrhythmia attack (Hansson et al., 2004). Research has also suggested that cognitive-affective depressive symptoms are associated with a two-fold increased risk of recurrence of AF among successful electrical cardioversion patients (Lange & Herrmann-Lingen, 2007). Research among CABG surgery patients has not firmly established an association between AF and depression or anxiety with past research being conducted in 1980's (Freeman, Fleece, Folks, Waldo, & Cohen-Cole, 1984; Krantz, Arabian, Davia, & Parker, 1982). Recently Contrada et al (2008) reported a trend association between post-CABG AF and hostility without adjustment.

Behavioural and Biological Explanations of Distress and Cardiopathogenesis

Behavioural mechanisms of cardiopathogenesis.

An increased risk in CAD morbidity attributable to emotional distress is likely explained by both behavioural and biological mechanisms. With respect to the former, epidemiological surveys suggest that affective disorders are associated with larger body mass index, hypertension, hypercholesterolemia, diabetes (Barger & Sydeman, 2005), physical inactivity (Goodwin, 2003) and regular smoking and nicotine dependence (Isensee, Wittchen, Stein, Hofler, & Lieb, 2003; Lawrence, Considine, Mitrou, & Zubrick, 2010). Emotionally distressed persons may also over use illicit drugs and alcohol. Despite a greater proportion of comorbidity and clinical risk factors, patients with emotional distress and comorbid CAD are also less likely to comply with prescribed medications such as aspirin (Carney, Freedland, Eisen, Rich, & Jaffe, 1995). Concordance to exercise regimens and smoking cessation four months after myocardial infarction has also been associated with higher distress (Kuhl, Fauerbach, Bush, & Ziegelstein, 2009).

Biological mechanisms of cardiopathogenesis.

The biological mechanisms of cardiopathogenesis attributable to depression, anxiety and general distress are poorly understood. Evidence suggests the pathways are multifactorial and include the dysregulation of the hypothalamic-pituitary-adrenal axis (Krantz, Sheps, Carney, & Natelson, 2000; Lett et al., 2004; Musselman & Nemeoff, 2000), reduced heart-rate-variability (Gorman & Sloan, 2000; Musselman, Evans, & Nemeroff, 1998; Stein et al., 2000), altered serotonergic pathways, inflammatory response (Frasure-Smith et al., 2007) and altered platelet aggregability (Soufer, Arrighi, & Burg, 2002). A systematic review suggested that 20% of variability in CAD and depressive symptoms was attributable to common genetic factors and the authors speculated these could be related to inflammation and serotonin (McCaffery et al., 2006). Consequently, selective serotonin reuptake inhibitors may potentially reduce pro-inflammatory and pro-thrombotic states (Leo et al., 2006) though a survival benefit after myocardial infarction has not been consistently documented (Berkman et al., 2003).

Summary Of Depression And Anxiety In CAD

The literature reviewed above indicates that both depression and anxiety are associated with various outcomes in CABG surgery populations, parallel to what is reported among CAD patients generally. In addition, depression and anxiety share many biobehavioral mechanisms that may potentiate cardiopathogenesis. The abovementioned research however suffers from notable methodological limitations that are briefly overviewed below.

Methodological Limitations of Previous Research

Piecemeal approach to analysis of psychogenic constructs.

As described above it is clearly evident that depression and anxiety have rarely been examined concurrently in the context of cardiac surgery patients, or CAD patients generally. Denollet's (2008) findings led him observe "*In recent years, several reports have indicated that anxiety, anger, depression, worry, and mental stress are associated with CHD [coronary heart disease], cardiac death, and myocardial ischemia. The similarity of results of these reports suggests that negative emotions in general are related to CHD, but there remains a tendency to focus on only one of these emotions at a time in this context*" (pg. 949).

Reluctance to analyse multiple psychogenic cardiac risk factors simultaneously may reflect the difficulties overcoming what Ketterer et al (2002) aptly described as the "big mush." Suls and Bunde (2005) alternatively explained that competitive pressures of funding make *piecemeal* reporting of risk factors an attractive strategy despite its conceptual failings, even when a data set contains multiple emotion or trait measures. As a consequence of reporting only one psychogenic CAD risk factor Frasure-Smith and Lespérance (2003) noted that it is impossible to examine the degree to which the variables represent one or more common dimensions, obscuring the effects of more comprehensive emotional constructs.

Absence of hypotheses.

A consequence of focussing on singular psychogenic constructs is that a multitude of risk factors are purported to portend greater cardiac risk. While this may be the case, at the same time however, inconsistent findings for anger, hostility, vital exhaustion, alexithymia, social isolation, Type A behaviour pattern, in addition to depression and anxiety, are flummoxing and difficult to resolve (Chida & Steptoe, 2009; Denollet, 2005; Dreher, 2004;

Krantz & McCeney, 2002; Kubzansky & Kawachi, 2000; Suls & Bunde, 2005).

Consequently, the literature suggests a conspicuous dearth of *a priori* determined hypotheses concerning any of the abovementioned individual psychogenic constructs in relation to cardiac outcomes. As such, no previous studies have rationalised and articulated why certain negative emotions would confer cardiopathogenesis compared to other negative emotions, particularly when analysed concurrently (see Appendix A).

Measurement and conceptual interrelation of psychogenic constructs.

Smith and Cundiff (in press) suggest that studying affective risk factors individually implied an unjustified level of specificity, owing to the large degree of statistical and conceptual overlap. Theoretical overlap and measurement error question the independence of individual psychosocial risk factors for CAD outcome reported in piecemeal studies. Kubzansky and Kawachi (2000) explain in their review of depression, anxiety and anger in heart disease; "…*Anxiety and depression often occur together, but few studies measuring anger, anxiety, and depression have simultaneously accounted for the overlap between anxiety and depression in either self-report rating scales or diagnoses of clinical disorders. Further difficulty arises because measurement approaches often fail to discriminate clearly between the two emotions. As a result clear evidence that "pure" anxiety (as independent of depression), or the reverse, plays a role in CHD [coronary heart disease] has yet to be demonstrated,*" (pg. 332).

On a related point Laurent and Ettelson (2001) commented that if depression and anxiety are not differentiated, it is difficult to determine whether the variable(s) under consideration is (are) influenced by anxiety, depression, or the common aspects of both such as NA. These observations may have dramatic impacts on the outcomes of randomised controlled trials (RCTs) as delivery of effective psychological therapy is contingent on accurate diagnosis (Laurent & Ettelson, 2001). This applies to RCTs targeting depression after CABG surgery where nearly half of patients have comorbid anxiety disorders (e.g. Rollman et al., 2009; for commentary see Appendix B). Single-psychological construct CAD studies therefore directly contrast to the routine clinical and epidemiological observation that depression and anxiety share diagnostic symptoms, are interrelated and frequently co-existent within individuals. Indeed, CAD research has seemingly not drawn upon parallel psychiatric and psychological literature and diagnostic nomenclature that describes interrelated affective states and disorders.

Comorbidity between depression and anxiety.

Depression and anxiety can be classified as diagnostically separate according to diagnostic and statistical manual of mental disorders (DSM-IV) and International Classification of Diseases-10, though they can be diagnosed concurrently within an individual. Taxonomic nosologies that yield high affective disorder comorbidity rates can be explained by shared diathesis, or phenotypic features of one disorder serving to increase risk of another (Brown, Chorpita & Barlow, 1998). Across the lifespan, anxiety disorders have been shown to precede a subsequent depressive episode (Belzer & Schneier, 2004; Wittchen, Beesdo, Bittner, & Goodwin, 2003), while 90% of persons with an anxiety disorder will experience another psychiatric disorder in their lifetime (Andrews et al., 2010; Goodwin & Gotlib, 2004).

A national epidemiological study estimated that 22% of Australian persons meeting any psychiatric diagnostic criteria also met criteria for a second comorbid disorder (Slade et al., 2009). Concurrent comorbidity rates between depression and anxiety disorders are around 60% (Ninan & Berger, 2001) though highly dependent on the specific comorbid disorder pairs, with some more related than others. Weighted mean tetrachoric correlations among four national epidemiological surveys in Australia, The Netherlands and the U.S.A. (total N = 29,014) suggest that generalised anxiety disorder shares more variance with depression than with the other anxiety disorders (*r* = .65) (Watson, 2009a). The results also showed that the anxiety disorders post-traumatic stress disorder, obsessive-compulsive disorder, panic disorder and social anxiety disorder are associated more strongly to unipolar depression (overall mean *r* = 0.52) than are agoraphobia and simple/specific phobia (overall mean *r* = .65).

Indeed, an alternative perspective is that depression-anxiety comorbidity is merely an artefact of diagnostic splitting of a broader syndrome, and perhaps redundant criteria overlap (Brown, Chorpita & Barlow, 1998). Also individual differences in subtle conceptual nuances may explain inherent interrelation between affective disorders and self-report measures. For example, worry typically reserved for anxiety measures and generalised anxiety disorder can be considered as a cognitive ruminative process as observed in depressive disorders (Ninan & Berger, 2001). Also, avoidance typically observed among various phobic disorders parallels behavioural withdrawal observed in unipolar depression (Craske, Rauch, Ursano, Prenoveau, Pine, & Zinbarg, 2009). In the clinical setting a diagnostic differentiation can hinge on appropriate clinician investigation and client insight as to their primary concerns. Complicating the distinction Ninan and Berger (2001) noted criteria specifying cognitive deficits (memory difficulty, poor concentration), endocrine manifestations (change in sleep), vegetative expressions (fatigability) and behavioural manifestations (psychomotor agitation,

restlessness) were not exclusive to either mood or anxiety disorders. These observations follow revisions of the DSM-IV that excluded autonomic arousal symptoms as criteria for generalised anxiety disorder as noted by Brown and colleagues (1998), compounding the diagnostic overlap between major depression and generalised anxiety disorder. However DSM-V proposals have subsequently reneged this modification (American Psychiatric Association, 2010).

Watson (2009a) suggests that even considering changing diagnostic criteria over time, the affective disorders will inevitably have some degree of comorbidity owing to a pervasive trait-like disposition toward negative emotions. The disposition towards aversive emotional states reflects the broader affective syndrome. Other explanations evoke similarity in treatments and shared biological pathways as evidence in support of a broader distress construct. For example the similarities in response to selective serotonin re-uptake inhibitors (Levine et al., 2001) implicate common neurological and structural cognition pathways (Etkin & Wagin, 2007; Mula, Pini, Cassano, 2007). Research also suggests that in cases where depression is comorbid and secondary to panic disorder and generalised anxiety disorder, psychological treatment is met with remission of depression disorder (Borkovec, Abel, & Newman, 1995; Brown, Antony, & Barlow, 1995).

Evidence for a common negative affectivity trait.

Notwithstanding the interrelation between depression and anxiety, comparable findings with respect to cardiac outcome have led some authors to suggest that future research should consider the shared and the unique aspects of negative emotions to clarify their apparent relationship to cardiac risk (Kubzansky, Cole, Kawachi, Vokonas, & Sparrow, 2006; Suls & Bunde, 2005). These suggestions are supported by the common finding that depressive and anxious self-report items load diffusely across conceptually distinct depression and anxiety factors and contain a large non-specific NA factor particularly among cardiac populations (Barefoot et al., 2000; Bleil, Gianaros, Jennings, Flory, & Manuck, 2008; Frasure-Smith & Lespérance, 2003; Kubzansky et al., 2006; Pedersen et al., 2009; Pelle, Denollet, Zwisler, & Pedersen, 2009). In fact Frasure-Smith and Lespérance's (2003) findings, that a NA factor was associated with cardiac mortality five years after myocardial infarction, led the authors to suggest that a broad "*distress disorder*" category that comprises both anxiety and depression may increase the risk of cardiac events. In a review of the role of depression, anxiety and anger in CAD, Suls and Bunde (2005) noted that a high degree of symptomatic overlap and inconsistent results was suggestive of a common NA factor, rather than any specific mood state, being responsible for CAD morbidity.

Absence of empirically validated theory.

A long-standing criticism levelled toward cardiac psychogenic CAD research is the atheoretical approach by which it is reported (Ell & Dunkel-Schetter, 1994; Kubzansky & Kawachi, 2000). Yet review articles on the effects of depression in CAD are published as frequently as etiological and prognostic studies (Frasure-Smith & Lespérance, 2005) limiting the opportunity to accumulate and integrate empirical data into theoretical models (Dreher, 2004). Kubzansky and Kawachi (2000), in their review of negative emotions in CAD suggested that researchers should consider psychological theories of emotion to overcome limitations of previous research. The fact that similar suggestions continue to be made (Linke et al., 2009; Smith & Cundiff, in press; Suls & Bunde, 2005), suggests a critical absence of theory and testable hypotheses as abovementioned (see Appendix A).

Accumulating review evidence and expert opinion is highly suggestive that investigation of depression and CAD should concurrently consider related constructs, in particular anxiety. The suggestion to incorporate emotion theories into such research is supported by additional findings that broader non-specific emotional factors, common to depression and anxiety, may play a role in cardiac outcomes. Therefore to reconcile the limitations of previous research, whilst incorporating the abovementioned suggestions of previous reviews, the focus of the current investigation is to take into consideration anxiety and general distress alongside depression, under an empirically validated theoretical framework of emotion. Theoretical perspectives that differentiate between depression and anxiety are described and critiqued herein to determine whether they can address the abovementioned limitations and provide a framework for optimal examination of specific and non-specific components of depression and anxiety.

Theoretical Explanations Of The Relatedness Of Depression And Anxiety

Cognitive Content Specificity Hypothesis

Beck's (1976) cognitive-content specificity hypothesis is based on the premise that a unique set of cognitive processes may lead to certain emotions, and thus identification of these processes would best distinguish depression from anxiety. Beck (1976) conceptualised the depression cognitive triad relating to themes of hopelessness concerning the future, negative and pessimistic view of one's self and the world. Some authors have additionally described depressive cognitions as absolute, loss-oriented and concerning past events (e.g. failure) (Jolly, Dyck, Kramer, & Wherry, 1994). In contrast, anxious cognitions concern

themes of harm, uncontrollability, danger and an inability to manage physical and psychological threat, described as future-oriented, and relative (Jolly et al., 1994). The orientation toward future threat versus past loss and failure remains influential among DSM-V proposals to discriminate between anxiety and depression (Craske et al., 2009).

A meta-analysis of 13 studies however showed little support for the distinction of anxiety and depression based purely on cognitive content (Beck, Benedict, & Winkler, 2003). Not only were anxious and depressive cognitions highly correlated but also the affective construct specific cognitions were highly correlated with the symptoms of the other affective construct. That is, anxious cognitions were associated with depressive symptoms and vice versa, (mean r of effect sizes .48 and .43 respectively). The authors concluded that refinement of the cognitive phenomenology should consider the shared and unique affective aspects of depression and anxiety (Beck, Benedict, & Winkler, 2003). Prior to these recommendations Beck and colleagues had demonstrated maximal discrimination of depression and anxiety based on a combination of cognitions, affect and symptoms (Clark, Steer, & Beck, 1994).

Tripartite Theory of Depression and Anxiety

In contrast to Beck's (1976) hypothesis, the tripartite model (Clark & Watson, 1991) proposed that certain clusters of symptoms differentiated anxiety and depression, while accounting for a common set of non-specific symptoms, to assist with diagnostic taxonomy. Derived from a review of over 400 published articles and books pertaining to the interrelation and co-occurrence of depression and anxiety the authors hypothesised that anxiety and depression shared a large and relatively non-specific temperamental component of trait NA, synonymous with neuroticism as described in personality theory (McCrae & John, 1993). Also, depression can be characterised by anhedonia (i.e. diminished interest or pleasure) and the absence of positive affect. The anhedonic/low positive affect cluster of symptoms includes hopelessness, extreme fatigue, lethargy, apathy, behavioural withdrawal and psychomotor retardation. By contrast, anxiety is uniquely characterised by physical hyperarousal and somatic tension thus incorporating cardiovascular, autonomic, and respiratory signs that are indicative of anxiety. The physiological manifestations of arousal and somatic tension include shortness of breath, feeling dizzy, dry mouth, trembling and shaking (Clark & Watson, 1991). Figure 1 provides a graphical representation of Clark and Watsons' (1991) tripartite model.

NOTE:
This figure is included on page 20 of the print copy of
the thesis held in the University of Adelaide Library.

Figure 1. Clark and Watsons' (1991) Tripartite Conceptualisation of Depression, Anxiety and Negative Affect

Factor analysis of self-report measures has been central to validating the tripartite structure of depression and anxiety among various samples (Watson et al., 1995b) including geriatric (Cook, Orvaschel, Simco, Hersen, & Joiner, 2004; Teachman, Siedlecki, & Magee, 2007), youth (Tully, Zajac, & Venning, 2009), hypertensive (Marshall, Sherbourne, Meredeth, Camp, & Hays, 2003) and ethnically diverse samples (Kiernan et al., 2001; Yang et al., 2006). Investigations of existing self-report measures such as the Hospital Anxiety and Depression Scale consistently support a tripartite structure among cardiac patients (Barth & Martin, 2005; Dunbar, Ford, Hunt, & Der, 2000; Martin, Lewin, & Thompson, 2003; Martin, Thompson, & Chan, 2004; Wang, Lopez, & Martin, 2006). Evidence suggests that the Depression, Anxiety and Stress Scales (DASS; Brown et al., 1997a; Clara, Cox, & Enns, 2001; Crawford & Henry, 2003; Tully, Zajac, & Venning, 2009; Willemsen, Markey, Declercq, & Vanheule, 2010), a commonly employed measure in Australian clinical and research settings, is best represented in factor analysis by a tripartite structure.

In contrast to existing measures, the Mood and Anxiety Questionnaire (MASQ) was developed to maximally differentiate between depression and anxiety (Watson et al., 1995a, 1995b). Discriminant validity of this measure was demonstrated by Watson and colleagues whereby only 6% to 24% *(M* = 12%) shared variance was reported between anxious arousal and anhedonic depression/low positive affect among five psychiatric and student samples (Watson et al., 1995a). Indeed, the discriminating affect measures are likely to provide a closer approximation as to the cardiopathogenic effects of depression and anxious symptoms in prognostic studies by comparison to measures with a large portion of non-specific NA variance. However, given the theoretical basis for the MASQ, then paradoxically, it is likely that such affect dimensions alone would be associated with poor predictive values (e.g. ROCs) of anxiety and depression disorders. Nevertheless, despite being published nearly two decades ago, the tripartite model remains a pivotal conceptualisation of affective symptoms and has been developed to incorporate diagnostic categories of depression and anxiety.

Hierarchical Model

Barlow, Zinbarg and colleagues (Barlow, 1991; Brown & Barlow, 1992; Zinbarg & Barlow, 1996) extended the tripartite model principles and proposed a hierarchical model to capture heterogeneity among the anxiety disorders. The authors argued that rather than a single physiological hyperarousal construct each anxiety disorder contains a unique component making differentiation from other anxiety disorders possible (Zinbarg & Barlow, 1996). Yet consistent with the tripartite model supposition, each anxiety disorder contains a shared component that represents the higher-order NA construct in what they labelled a two-level hierarchical scheme. Accordingly, the higher-order factor not only is common across the anxiety disorders, but also is shared with depression; it therefore is largely responsible for the observed overlap both (*a*) among the individual anxiety disorders and (*b*) between depression and anxiety. One limitation of applying such a model however is the requirement for multidimensional self-report scales that differentiate between multiple anxiety disorders, and distinguish these from depression, while capturing a higher order NA construct.

Integrative-Hierarchical Model

Like previous models, the integrative hierarchical model was based on the premise that each affective syndrome contained unique within disorder variance, and shared variance with NA. However, accumulating evidence reviewed by Mineka and colleagues (1998) suggested that some anxiety disorders were more laden with NA than others. For example,

epidemiological data supported a greater degree of association of NA with major depression, generalised anxiety disorder and post-traumatic stress disorder than was the case for simple phobia, obsessive compulsive disorder and social anxiety disorder (Mineka, Watson, & Clark, 1998). Thus examination of particular disorders would not only have to take into consideration their unique within-disorder symptoms, but also a differential degree of association to NA. Like the hierarchical model however, it becomes increasingly difficult to capture the symptoms of NA and unique affective disorder variance without multiple self-report measures. Moreover, there are few descriptions from the hierarchical models of core affective phenotypes as they relate more to diagnostic classification of disorders (Brown & Barlow, 1992; Mineka, Watson, & Clark, 1998; Zinbarg & Barlow, 1996).

Emotion Based Perspectives

Some authors describe depression, anxiety and fear as central to the human experience of negative emotions though nomenclature appears to be used differently by such theorists. Fear, distinct from anxiety, is a visceral response to imminent danger (real or perceived) and largely experienced as somatic symptoms (Barlow, Chorpita, & Turovsky, 1996; Craske et al., 2009). Comparatively however, fear is defined in a similar manner as how authors of the tripartite and integrative-hierarchical models depicted anxiety (Clark & Watson, 1991; Mineka, Watson & Clark, 1998). By contrast, in emotion-based theory where NA is conceptualised as a pure manifestation of anxiety (Chorpita, Albano, & Barlow, 1998), the latter construct is inclusive of avoidant behaviour, somatic experience of muscle tension and subjective worry and thus captured by measures of general distress (Craske et al., 2009). The fear, anxiety and depression structure first described by Barlow and colleagues (1996) has empirically supported correlates to the behavioural inhibition system, behavioural activation system and fight-flight neurobiological emotion systems (Gray, 1987).

Factor analysis of various self-report measures supported a best fitting model consistent with a three factor fear, anxiety and depression structure among adolescents with anxiety or comorbid anxiety and depression disorder (Chorpita, Albano, & Barlow, 1998). In discussing their findings Chorpita and colleagues (1998) noted the anxiety factor was consistent with the general distress factor described by Clark and Watson (1991), while Chorpita et al's (1998) fear factor was also analogous to the anxiety factor in Clark and Watson's (1991) model. The correlations in Chorpita and colleagues' (1998) factor analysis model suggested that visceral fear was more strongly associated ($r = .71$) with anxiety (responsible for NA) than was the case for depression and anxiety ($r = .54$). By contrast, more recent evidence incorporating structural factor analysis of epidemiological data suggests that visceral fear disorders marked by avoidance (e.g. panic disorder, agoraphobia,

social anxiety disorder, simple phobia) display comparatively less association with NA than do dysthymia, major depression, generalised anxiety disorder and post-traumatic stress disorder (Watson, 2009a), questioning whether the results of Chorpita et al (1998) would translate to diagnostic disorder categories.

Quadripartite Model

Watson's (2009a) quadripartite model is the most recent development that expands understandings of unique within disorder variance and varying strength of association to NA. However, the patterns of comorbidity evident from structural analyses of epidemiological data suggested that disorders clustered together could be theoretically differentiated based on their characteristic symptoms. Specifically, major depression, generalised anxiety disorder, post-traumatic stress disorder and dysthymic disorders loaded highly on an anxious-misery factor and were strongly associated with NA. A second class of disorders could be identified as fear based and included panic disorder, agoraphobia, social anxiety disorder and specific phobia, though it was identified that agoraphobia and specific phobia contain limited component of NA.

In support of these suggestions a confirmatory factor analysis among high school students provided structural invariance over time for a hierarchical model specifying a broad general distress factor and two intermediate breadth factors (anxious-misery and fear) (Prenoveau et al., 2010). In addition, the five narrow factors labelled anxious arousal/somatic tension, depression, social fears, fears of specific stimuli, and interoceptive/agoraphobic fears were representative of panic disorder, major depression, social anxiety disorder, specific phobia and agoraphobia. It was however observed that social fears were related to both the anxious-misery factor and that of fear.

Summary of Models of Depression and Anxiety

Such influential theorists provide impetus to shape diagnostic taxonomic systems and additionally inform practitioners, therapists and researchers (Brown & Barlow, 2005; Brown & Barlow, 2009). A summary of depression and anxiety theories is tabulated below (Table 1). In relation to the recommendations for CAD research theoretical models delineating a general distress component seem most appropriate to disentangle the effects of depression and anxiety on cardiac outcome (Suls & Bunde, 2005).

The exclusive focus on cognitions in Beck's model (1976) omits a general distress construct and excludes other symptomatic phenomena of depression and anxiety. Though contributing enormously to cognitive behavioural therapies, the utility in the present investigation of cardiac outcomes is insufficient. Three depression-anxiety-NA factors are a simplistic representation of the full phenomenology of affective symptoms, yet a distinct advantage of the tripartite model by comparison to later published models (e.g. integrative-hierarchical) is that it is symptom and not disorder based. Therefore, the tripartite model can be applied with self-report measures whilst rationalising the high degree of interrelation and symptomatic overlap by specifying a common cluster of NA symptoms whilst maximally discriminating between depression and anxiety.

It is questionable whether behavioural cardiology would benefit from the sophisticated disorder based models that encompass the full spectrum of anxiety disorders and their within disorder variance. Most research to date has been symptom based, and scant research exists as to the prognostic association between CAD outcomes and anxiety disorders other than panic disorder, post-traumatic stress disorder and generalised anxiety disorder, with little known about obsessive compulsive disorder, social anxiety disorder and specific phobias. Practically, examination of any of disorder-based discriminant model may also require an exhaustive battery of self-report measures too cumbersome for cardiology clinics and chronically ill patients. The benefit of investigating symptom based models first is that the findings may inform selection of disorder based models at a later time.

Theoretical conceptualisations that describe a depression-anxiety-NA symptom structure (or visceral fear, anxiety, depression) have the additional advantage of potential convergence with extant literature in cardiac literature. For example, taking the tripartite model into consideration, it is possible to examine the extent to which anhedonia, physical hyperarousal and NA can be amalgamated with Type D personality traits. Indeed, given the conceptual delineation of NA factor, it is thus plausible that NA inherent to Type D personality and tripartite theory converge with respect to association with adverse cardiac outcomes.

Table 1. Summary of Reviewed Depression and Anxiety Theories

			Characteristic symptoms, cognitions and behaviours of constructs		
Theory	Author	Content	Depression	Anxiety	Other
Cognitive-Content Specificity †	Beck, 1976	Cognitions	Cognitive; future oriented hopeless, negative and pessimistic view of self and world, past oriented failure and loss	Cognitive; future oriented, concerning danger, harm, uncontrollability, inability to manage threat	Not specified
Emotion ‡	Barlow, 1991	Emotions, symptoms, behaviours	Dysthymia, low positive affect	Avoidant behaviour, muscle tension, subjective worry	Fear; visceral somatic symptoms
Tripartite	Clark & Watson, 1991	Traits, symptoms	Anhedonia, low positive affect	Physiological hyperarousal and somatic tension	NA; non-specific symptoms related to both depression and anxiety
Hierarchical	Zinbarg & Barlow, 1996	Traits, symptoms	Dysthymia, low positive affect	Unique symptoms differentiate between anxiety disorders	NA; non-specific symptoms related to both depression and anxiety
Integrative-Hierarchical	Mineka et al., 1998	Disorders, symptoms, traits	Anhedonia, low positive affect	Unique symptoms differentiate between anxiety disorders, symptoms relative and not absolute	NA; differentially associated to anxiety disorders, related to unipolar depressive disorders
Quadripartite §	Watson, 2009a	Disorders	Anxious-Misery; MDD, Dysthymia, GAD, PTSD	Fear; PD, Agoraphobia, SAD, Specific Phobia	General Distress; Related to unipolar depressive disorders and differentially associated to anxiety disorders

† Depressive cognitions also described in the cognitive triad.

‡ For simplicity the author's definition of anxiety is included in the anxiety column whereas fear is listed in the 'other' column, though fear is inextricably linked to the tripartite conceptualisation of anxiety.

§ Watson's model was generally disorder based from tetrachoric correlations. Prenoveau et al (2010) recently established good confirmatory factor analysis fit indices specifying an intermediate breadth anxious-misery factor related to narrow factors tapping into positive affectivity, social fears and depression method. The fear factor was related to separate factors of social fear, fear of specific stimuli, and interoceptive/agoraphobic fear. The anxious arousal/somatic tension factor was related only to a general distress factor.

GAD, generalised anxiety/worry disorder; MDD, major depressive disorder; PD, panic disorder; PTSD, post-traumatic stress disorder; SAD, social anxiety disorder

Rationale For The Present Study

In summary of the literature presented in this chapter, depression has more commonly been implicated in morbidity and mortality studies among cardiac patients than has anxiety. Yet despite the conceptual and symptom overlap and poor discrimination of self-report measures, limited research, particularly with cardiac surgery patients, has investigated both emotions simultaneously. Moreover, to the best of the author's knowledge, no study to date has incorporated a theoretical model of emotion with respect to heart disease patient outcomes. By employing various symptom (i.e. tripartite), disorder (i.e. quadripartite) and trait (i.e. Type D) theoretical frameworks it is anticipated that the present study will foster new understandings of the ways in which depression, anxiety and NA are associated to morbidity outcomes among cardiac populations, particularly those undergoing CABG surgery. Enhanced recognition of the unique depression and anxiety symptoms, disorders and traits that contribute to CABG surgery morbidity postoperatively can improve patient care, thereby enhancing patient's quality of life. However, foreseeing the potential application for affective disorder screening, it is necessary to jointly investigate whether unique affective dimension measures can aid practitioners to easily identify distressed cardiac patients. These results may further prove beneficial to informing the design of psychological interventions for CABG surgery patients. The current study may also guide future researchers to investigate multiple psychological variables alongside depression in cardiac populations.

General Research Aims

Based on previous research and Watson and colleagues (Clark & Watson, 1991; Mineka, Watson, & Clark, 1998; Watson, 2009a) empirically validated theory, the current dissertation is based on the *a priori* hypothesis that general NA, rather than depression and anxiety, would be associated with adverse morbidity outcomes among CABG surgery patients. Secondly, it was hypothesised that only after investigation of shared variance, attributable to NA, would the morbidity risk attributable to depression and anxiety become sufficiently evident. Thirdly, in evaluation of the screening properties of measures of anhedonia and somatic tension, it was hypothesised that ROCs would be optimal when the symptom dimension was affect congruent with the criterion disorder.

The aims of this thesis are therefore:

1. To examine cardiac surgery outcomes in relation to pre-existing anxiety, depression and general negative affect

2. To determine whether unique associations exist between emotional distress and mortality, morbidity, health related quality of life, arrhythmia, neuropsychological function and delirium

3. To examine the interrelation between different theoretical models of negative affect in cardiac patients

4. To concurrently examine affective disorders, their characteristic symptoms and personality traits in relation to cardiac morbidity

5. To determine the receiver operating characteristics of self-report measures of anhedonia/low positive affect and somatic tension/physical hyperarousal with respect to affective disorders among cardiac patients

A summary of the research is now presented to provide additional information not described in the manuscripts and describe the linkage between studies.

Chapter II: Exegesis

Linkage Between Studies

The current Chapter provides a sequential summary of the individual studies that comprise the thesis by highlighting the development of the entire research project. The present Chapter outlines differences in the methodology, endpoints (dependent variables), and development of the theoretical framework across the research program, providing a brief summary of the results. The general methodological design for the thesis was to investigate anxiety and NA alongside depression in relation to morbidity and health related quality of life outcomes relevant to cardiac surgery patients. The first study was a novel examination of emotional constructs and exploratory in nature. From there, the dissertation worked on the overarching principal that only after statistical adjustment for NA would the effects of depression and anxiety constructs on cardiac morbidity become evident. Secondly, it was hypothesised *a priori* that NA would portend greater cardiac morbidity than either depression or anxiety alone.

Review of the empirical evidence of depression and anxiety on CABG outcomes justified investigation of various outcomes within the studies that comprise the thesis. These included an evaluation of mortality (Chapter III), unplanned hospital readmission (Chapter IV), health related quality of life (Chapter V) and long-term neuropsychological performance (Chapter VI). The findings collectively showed that anhedonic depression and anxious physical arousal were differentially associated to outcomes after CABG surgery. There was however little support for the hypothesis that NA may better account for cardiac morbidity beyond depression and anxiety. Thus Study Five (Chapter VII) diverges from the main hypothesis by questioning whether anxiety might display a particular association with AF arrhythmias. In Study Six diagnostically ascertained depression and anxiety disorders, along with Type D personality, were evaluated with respect to delirium. Study Seven evaluated disorder, state and trait measures of depression and anxiety with respect to a 30-day combined morbidity endpoint. Study Eight considered the affective dimensions in relation to specific disorders to determine whether they could serve as suitable screening measures among cardiac patients.

Choice of Self-Report Distress Measures

The retrospective datasets employed in this thesis evaluated self-report distress measured with the Depression, Anxiety and Stress Scales (DASS) (Lovibond & Lovibond, 1995a, 1995b). As described further in Chapters III to VII this questionnaire taps into anhedonic depression, physiological hyperarousal and general distress. Indeed, though not designed to measure the tripartite constructs, several confirmatory factor analysis studies have shown that the DASS is best represented by a tripartite factor structure (Crawford & Henry, 2003; Tully, Zajac & Venning, 2009; Willemsen, Markey, Declercq & Vanheule, 2010). In addition, the measure is widely reported to have excellent psychometric properties, most notably the stable, internally consistent and coherent factor structure (Antony, Bieling, Vox, Enns, & Swonson, 1998; Crawford & Henry, 2003; Gloster et al., 2008; Norton, 2007; Page et al., 2007). Hence the DASS served as an appropriate measure of anhedonic depression, anxious arousal and general distress in Chapters III to VII.

Prospective recruitment provided a welcome opportunity to revise the self-report inventories and adopt the MASQ originally devised to capture tripartite constructs (Watson et al., 1995a, 1995b). Prospective recruitment also permitted a disorder based diagnostic interview before surgery to ascertain the prevalence of affective disorders and screen patients for potentially confounding psychiatric disorders (e.g. active psychosis, personality disorders and dementia).

Preliminary Notes on Published Papers

A general point concerning the data reported herein is that Studies One to Five would not have been possible without the generous provision of unpublished data sets from the Cardiac Surgery Research and Perfusion Group at Flinders Medical Centre. Indeed, the Department of Cardiac and Thoracic Surgery, Flinders Medical Centre, is a small centre compared to international institutions. The study hospital performed around 300 non-emergent CABG procedures per annum during the prospective study recruitment period. The number of CABG surgery patients operated upon, each study's exclusion criteria, competing research trials and other factors limit the number of patients available for prospective recruitment during the course of a four year PhD candidature whilst completing coursework and clinical internships. The benefit of employing previously collected data was that five year longitudinal follow-up was possible to report mortality and neuropsychological outcome. Finally, the published papers presented herein contain varying terminology, particularly so for depression and anxiety. The studies also employed varying methodology to answer a specific research question with disparate endpoints. The papers were inevitably influenced

by the respective journals' space requirements, specificity of data reporting required and the comments and suggestions of the blinded reviewers and editors. Such discrepancies might also reflect a shift in understanding of the literature during the course of the research program. These data concerning theoretical formulations of depression and anxiety are also provided in historical context as psychiatry looks to reframe diagnostic criteria for depression and anxiety disorders (Craske et al., 2009; Watson, 2009a).

Individual Study Notes

Study One (Chapter III).

The aim of Study One was to examine a broader range of preoperative self-reported distress symptoms in relation to post-CABG mortality than had previous studies. This study overcomes the limitations of previous research by examining anxiety and general stress in relation to mortality, and also examining preoperative depression. Previous studies had typically measured depression symptoms a month after discharge from hospital, and not assessed anxiety or stress. The study also aimed to produce externally valid results given that previous depression studies had analysed fewer than ten deaths and reported wide confidence intervals (Baker et al., 2001; Burg, Benedetto, & Soufer, 2003b) suggesting that external validity was poor. In the current study there were few cardiac related deaths to examine in a manner that could be considered externally valid without overfitting multivariable hazard models. Methodologically it was also ideal to adjust for known mortality risk factors and thus medical covariates were selected based on previous research such as the Working Group Panel on the Collaborative CABG Database Project (Jones et al., 1996).

Study One showed that preoperative anxiety was associated with all-cause mortality after the index CABG procedure, independent of covariates. Depression showed a trend level association while stress was not associated with mortality as hypothesised. The findings appeared externally valid and robust as most medical covariates also increased the risk of mortality in multivariable hazard models. However, one limitation of this study was that though anxiety, depression and stress were examined, the analysis was in isolation and neglected their joint or simultaneous effects, and also the shared distress variance attributable to NA. A second limitation was that no measure of postoperative distress was available for analyses, so it was plausible that postoperative depression might be associated with mortality as previous studies had demonstrated.

Study Two (Chapter IV).

Study Two examined morbidity events that necessitated readmission after CABG in relation to self-reported depression, anxiety and general distress at the time of the index revascularisation surgery. The study addressed several limitations of previous research, including those of Study One, in that the simultaneous effects of anxiety and depression were examined after accounting for the variance and potential confound of NA, for preoperative and postoperative distress.

The readmission endpoint was defined as a principal diagnosis that necessitated hospital admission (excluding emergency department visits), and was related to cardiovascular or vascular disease, or the surgical procedure itself, after the index procedure. The criterion list of readmission causes was established in consultation with a cardiothoracic surgeon, Associate Professor John L. Knight and perfusionist and thesis supervisor, Associate Professor Robert A. Baker who were blinded to the psychological distress scores of patients and the total readmission rate.

The results showed that no matter how the stress variable was entered into the regression models, and regardless of whether continuous or dichotomised distress data was analysed, preoperative anxiety was associated with hospital readmission. These results thus supported the role of preoperative anxiety in post CABG outcome as reported in Study I. The results of Study II also suggested that postoperative depression (continuous scores) was associated with increased readmission risk, though the dichotomised finding was at trend level (p = .06). Intriguingly, stress was associated with a reduced readmission risk that was perhaps explained by patients effectively employing problem focussed or emotion coping strategies. An alternative explanation is that multicollinearity produced the paradoxical result for general distress. In summary of Study II, there was no support for the hypothesis that general stress/NA would be associated with an increased risk of hospital readmission.

The limitation of Study Two was that examining the simultaneous entry of DASS scores might lead to multicollinearity. Furthermore statistical adjustment for stress would inevitably lead to examination of partialled and residual variance of depression and anxiety. Thus to overcome such a limitation it would be necessary to examine depression, anxiety and stress in isolation, in addition to a combined multivariable model, when analysing a particular endpoint. This would enable inspection of whether results for each particular distress construct were consistent in univariable and multivariable analyses and whether partialling of residualized variance from NA impacted on the results.

Study Three (Chapter V).

Study Three had a similar aim and statistical methodology to that of Study Two, whereby depression and anxiety, independent of the effects of stress/NA were examined though the outcome variable was self-reported health related quality of life six months after surgery. Study Three further examined each psychological predictor in isolation to determine the unique associations, that is, without partialled variance. The sample for Study Three was the same as that recruited for Study Two.

One limitation identified with past health related quality of life CABG surgery research was that typically composite indices of heterogeneous health related quality of life domains were examined. It was plausible in light of the findings in Study Two that depression and anxiety may have discrete associations to health related quality of life that would not be detected by cumbersome aggregate scores of different domains. Thus in Study Three individual health related quality of life domains were analysed from the Rand Corporation's Medical Outcomes Study Short Form 36 (SF-36), rather than the composite physical and mental health indices.

The results generally suggested, regardless of whether preoperative or postoperative distress scores were examined, that elevated depression scores were associated with worse health related quality of life for normally distributed data tapping into vitality and social role functioning and physical and general health. When non-normally distributed health related quality of life domains were examined, preoperative depression was associated with poorer emotional and physical role functioning. There was little support for an association between health related quality of life and either stress or anxiety. Though not supporting the study hypothesis, the results did however suggest that depression symptoms, but not those of anxiety or stress were uniquely associated with specific health related quality of life domains.

One limitation of Study Three was that only in-hospital distress was analysed in relation to six month subjective assessment of health related quality of life. That is, it was possible that subjective experience of psychological distress at six months follow-up might also impact on concurrent assessments of health related quality of life at six months. In order to overcome this limitation it would be beneficial to also measure distress when a subjective outcome such as health related quality of life or neuropsychological function is assessed, as was the case in Study Four.

Study Four (Chapter VI).

In Study Four the detrimental effects of depression and anxiety independent of stress/NA were evaluated with respect to neuropsychological function after cardiac surgery. Discrepant from the methodology of Studies One to Three, distress was also measured at follow-up and analysed concurrently with neuropsychological assessment.

Study Four also attempted to address several limitations of previous research on post CABG cognitive functioning by examining anxiety and stress in addition to depression, as few reports had considered anxiety. Moreover, previous studies elsewhere had employed correlation analyses thus neglecting the impact of covariates, or examined a composite index of heterogenous neuropsychological domains (e.g. Stygall et al., 2003) that are poor reflections of domain specific cognitive function. Numerous studies had also employed biased and arbitrary statistical methodology to define neuropsychological deterioration without adequately controlling for practice effects, measurement error and regression toward the mean phenomena. To overcome these limitations neuropsychological deterioration was determined with standardised regression based (SRB) methodology as favoured by review evidence (Raymond, Hinton-Bayre, Radel, Ray, & Marsh, 2006; Temkin, Heaton, Grant, & Dikmen, 1999) and reported previously in the cardiac surgery field (Kneebone, Luszcz, Baker, & Knight, 2005; Tully, Baker, Kneebone, & Knight, 2008b). The neuropsychological test battery, in consultation with a clinical neuropsychologist, was designed principally to assess heterogenous cognitive domains as endorsed by the Statement of Consensus of Neurobehavioral Outcomes after Cardiac Surgery (Murkin et al., 1995).

The results of Study Four were surprising as psychological distress was generally unrelated to the cognitive domains that were significantly lower among a surgery group in comparison to a control group. Thus, the results did not show a consistent pattern of association between psychological distress and neuropsychological impairment. In contrast to previous studies, Study Four suggested that neuropsychological decline after CABG has been largely overestimated, and that psychological distress has no consistent impact on cognitive function after CABG.

Study Five (Chapter VII).

Study Five examined postoperative AF after the index CABG procedure with respect to anxiety, depression and stress. However, Study Five deviated from the straightforward hypothesis that NA would account for post CABG outcomes owing to the generally null findings for Studies I to IV. Thus here it was considered plausible that individual morbidity

outcomes might be uniquely associated with a psychogenic risk factor (e.g. anxiety but not depression). Previous research had consistently demonstrated evidence that anxiety was associated with AF and ventricular tachycardia, though there was also some evidence that depression was associated with sudden cardiac death and ventricular tachycardia. However, Watson and colleagues' (1991) tripartite framework conceptualises somatic tension and physiological arousal symptoms as characteristic of anxiety with many symptoms overlapping those experienced as part of AF (e.g. palpitations, shortness of breath). Thus Study Five sought to determine whether physiological arousal anxiety was related to new onset AF after cardiac surgery, above and beyond the effects of depression and NA. A second aim of the study was to determine which, if any, subsets of anxiety symptoms were related to AF paying particular attention to cognitive and somatic symptoms.

All electrocardiograms of patients with documented postoperative AF were evaluated by Dr. Jayme Bennetts who was blinded to patients' psychological distress scores, and the blinded coding yielded an excellent Kappa agreement with electrocardiogram technician reports (κ = .91). The results suggested that an increase in autonomic arousal was associated with an increase in odds for AF, whereas and in contrast, an increase in subjective experience of anxious affect was associated with a reduced risk of AF. It was suggested from these findings that a cognitive rather than somatic focus of anxiety symptoms is beneficial for CABG patients at risk of, or already experiencing, AF. The study findings were largely inconclusive as to whether anxiety was predictive of AF, as patients may have responded to the self-report distress measure when already experiencing AF symptoms. Thus a limitation was that postoperative assessment of distress was confounded by arrhythmia symptom burden and morbidity.

Study Six (Chapter VIII):

The sixth study for this thesis examined the risk of incident delirium attributable to preoperative depression, anxiety and personality traits. This study sought to overcome the main limitations of the abovementioned work that indicated no support for an association between NA and cardiac morbidity outcome by incorporating a diagnostic assessment of psychiatric affective disorders major depression, panic disorder, and generalised anxiety disorder and a measure of Type D personality to capture trait NA. The shift toward diagnostic disorders was also informed by Watson's (2009a) re-examination of the affective disorders, superseding the tripartite conceptualisation. The general hypothesis concerning NA was reinstated for Study VI.

Patients were assessed for delirium postoperatively by structured interview and classified according to DSM-IV-TR criteria. However, particular to the current study, perceptual disturbances and/ or gross language disturbances were requisite for a delirium classification as other symptoms such as memory impairment, disorientation, psychomotor agitation, and disturbed sleep-wake cycles overlap some affective disorders. In other words, it was important to stringently classify patients according to delirium criteria without confounds of pre-morbid depression and/ or anxiety symptoms. Also, a structured psychiatric interview was employed to screen for psychotic disorders and lifetime history of alcohol and substance abuse that formed part of the study exclusion criteria. The rationale was that psychotic disorders and alcohol/substance abuse and withdrawal were often comorbid with depression and anxiety, and secondly were risk factors themselves for delirium.

The results suggested that major depression was associated with incident delirium, and given the methodological approach, was perhaps not merely a reflection of common diagnostic features. Inconsistent support was found for the hypothesis implicating NA in delirium as two highly NA laden constructs, generalised anxiety disorder and Type D personality, showed a differential association with delirium. It is worth emphasising that self-reported measures of depression and anxiety were obtained in this prospectively recruited sample though were in fact omitted from the results based on the recommendations from the blinded journal reviews. In doing so, this study represents an overly simplified application of Watson's (2009a) conceptualisation of affective disorders in relation to adverse cardiac surgery outcome.

Study Seven (Chapter IX).

The seventh study sought to overcome the limitations of the abovementioned studies that showed limited association between general distress/NA and various individually examined post-CABG outcomes. The first limitation addressed in Study Seven was employing a questionnaire designed specifically to measure anhedonic depression and physiological hyperarousal, and trait NA. Also, structured diagnostic interview for affective disorders and a measure of Type D personality traits was included, together providing disorder, symptom and trait measures of depression, anxiety and NA. Owing to Watson's (2009a) updated quadripartite theoretical model, published during candidature for this dissertation, Study Seven conceptualised physiological hyperarousal as reflective of panic disorder and not all anxiety disorders.

Study Seven continued the investigation of cardiac morbidity outcomes. Time constraints of the research program necessitated that a morbidity outcome could be

ascertained with short duration of follow up. Morbidity risk was adopted from the Society of Thoracic Surgeons morbidity risk model (Shahian et al., 2009) though in addition within hospital arrhythmia was analysed inclusive of atrial and ventricular arrhythmias. The author undertook Study Seven data analyses during a three week laboratory visit to The Universitiet van Tilburg, The Netherlands, in July 2009.

The results of Study Seven showed that GAD and Trait NA were associated with morbidity, though state NA failed to attain statistical significance. The findings point to the possibility that disorder and trait, rather than state, NA/general distress is associated with cardiac morbidity beyond clinical risk factors after CABG surgery.

Study Eight (Chapter X).

Up to this point in the research program the tripartite and hierarchical models had proved beneficial to discriminate between affective states and determine the prognostic association with cardiac outcomes. However, it was foreseeable as a practical application of such findings to screen for highly distressed and potentially at risk CABG surgery patients. Therefore a ROC study was undertaken to firstly describe the sensitivity, specificity and predictive values of the MASQ dimensions with respect to major depression, panic disorder and general anxiety. Secondly, this study aimed to further explore the extent to which the affective disorders were associated with affect dimensions along with state and trait NA. The results generally suggested that ROCs were more favourable when MASQ affect congruent dimensions were tested (e.g. anhedonia in relation to major depression), whereas, non-specific state and trait distress performed no better than chance. However, regression analysis additionally supported that significant state and trait variance were associated with the affective disorders.

Summary of Thesis Results

In summary of the above described studies a differential pattern was observed between psychogenic risk factors depending on the outcome variable, time-frame for follow-up, and also the conceptualisation, measurement and statistical control for general NA. The findings are suggestive that psychogenic risk factors may pose discrete associations with cardiac surgery outcomes, though there was generally little support for the hypothesis regarding state NA. Nevertheless the results encourage expanding the breadth of research of cardiac risk factors to encompass anxiety alongside depression. The implications of these results for psychological theory, clinical practice and comparison to work elsewhere will be

discussed more fully in Chapter XI along with the limitations and suggestions for future research.

Contribution To Knowledge

These studies represent a significant contribution to the behavioural cardiology and psychosomatic medicine field by describing the independent effects of NA, depression and anxiety on various post-CABG surgery outcomes within a developing theoretical framework and research paradigm. The thesis addresses an important gap in knowledge by using an empirically supported model of depression and anxiety, tripartite and hierarchical, to interpret the association with CABG surgery patient outcomes, while at the same time overcoming many methodological limitations of previous studies. Furthermore and perhaps for the first time, Study VII simultaneously examined Type D personality traits, affective disorders and phenotypic symptoms in relation to cardiac morbidity outcomes. This thesis has addressed numerous limitations of previous research and provides commentary on the utility of theoretical models in heart disease research. The issues addressed herein may provide a framework for investigating multiple psychogenic risk factors among other cardiac populations and psychosomatic medicine generally. As a consequence of these findings future psychosomatic research should aim to investigate depression, anxiety and NA simultaneously and disentangle their unique association with the pathophysiological mechanisms of CAD and heart disease outcomes. Moreover, considering the complexity of identifying single or broad affective states in relation to heart disease outcomes further research should be expanded to consider behavioural and social factors.

Chapter III Study One

Anxiety and Depression As Risk Factors For Mortality After Coronary Artery Bypass Surgery

Statement of contributors

Phillip Tully (*Candidate*)

Responsible for study conception, literature review, data analysis, manuscript drafting and preparation, manuscript submission, response to reviewers and revisions.

Signed: Date: 4/01/2011

Assoc Prof Robert Baker and Assoc Prof John Knight (*Co-authors*)

We provided ongoing supervision throughout the research programme that lead to this publication and there was ongoing collaboration between Mr. Tully and us in refining the direction of the research. Mr. Tully was responsible for writing this paper; our role was to comment on drafts, make suggestions on the presentation of material in the paper, and to provide editorial input. We also provided advice on responding to comments by the journal reviewers and editor. We hereby give our permission for this paper to be incorporated in Mr. Tully's submission for the degree of Doctor of Philosophy from the University of Adelaide.

Signed: Robert Baker   Date: 4/01/2011

Signed: John Knight   Date: 4/01/2011

Abstract

This retrospective study examined the association between symptoms of depression, anxiety, and mortality risk following CABG surgery. We assessed 440 CABG surgery patients' scores on the DASS and followed up mortality status for a median of 5 years, 10 months. There were 67 (15% of total) deaths overall during the follow-up period. Adjusted survival analysis showed that preoperative depressive symptoms were not associated with a significantly higher risk of mortality. Survival analysis with preoperative anxiety adjusted for covariates showed a significantly increased mortality risk [hazard ratio (HR) = 1.88; 95% CI = 1.12 − 3.17, p = .02]. Preoperative anxiety symptoms were significantly associated with increased mortality risk after adjustment for known mortality risk factors. Future research should further explore the simultaneous role of anxiety and depression on mortality following CABG surgery.

Introduction

Unipolar depression is under recognised in people with CAD (Gonzalez et al., 1996). Among patients undergoing CABG surgery, the prevalence of clinical depression is consistently reported at around 20% (Connerney, Shapiro, McLaughlin, Bagiella, & Sloan, 2001; Fraguas Junior, Ramadan, Pereira, & Wajngarten, 2000). Subthreshold depressive symptoms in the absence of diagnostic interview are reportedly high, between 32% and 43% (Borowicz, Royall Jr, Grega, Selnes, Lyketsos, & McKhann, 2002; Pirraglia, Peterson, Williams-Russo, Gorkin, & Charlson, 1999). Research further suggests that anxiety is frequently comorbid with depression among CAD outpatients (Bankier, Januzzi, & Littman, 2004), while self-reported anxiety symptoms correlate moderately with depression (Duits et al., 1999).

Unfortunately, despite treatment for the relief of CAD symptoms, CABG patients with depressive symptoms experience more cardiac morbidity and fatal cardiac events (Burg, Benedetto, & Soufer, 2003; Connerney et al., 2001). In the largest study of depression among CABG patients, Blumenthal et al. (2003) reported a significantly higher mortality risk for patients with depressive symptoms (HR = 2.4; 95% CI 1.4 – 4.0, p = .001) independent of demographic and clinical risk factors. These recent findings highlight the importance of patient's mood state to cardiac surgery outcomes. However, the role of anxiety in long-term mortality has been neglected among CABG patients, despite recognition of its role in short-term morbidity (Pignay-Demaria, Lespérance, Demaria, Frasure-Smith, & Perrault, 2003).

The limitations of previous post-CABG mortality and depression studies include small sample size and wide confidence intervals (Baker, Andrew, Schrader, & Knight, 2001; Burg Benedetto, & Soufer, 2003). The studies reporting no differences in mortality between depressive and non-depressive patients have used assessments conducted after discharge (Borowicz et al., 2002) or have used generic health instruments (Saur et al., 2001). Few studies have assessed anxiety in relation to post-CABG mortality despite apparent conceptual and diagnostic overlap with depression (Ninan & Berger, 2001). Given the high interrelation shared by anxiety and depression, it is requisite to assess the role of both negative affective states on mortality using a measure with adequate discrimination between their respective symptomatology.

We report findings from a retrospective cross-sectional study on the survival of patients undergoing open-heart surgery and the association with depressive and anxious symptoms using the DASS (Lovibond & Lovibond, 1995b). As the DASS underwent unique psychometric development to maximally discriminate depressive and anxious symptoms, it may avoid the possible confounds of other measures with overlapping factor structures among cardiac patients (Barth & Martin, 2005; Martin, Lewin, & Thompson, 2003; Martin, Thompson, & Barth, 2008). The aim of the present study was to assess the association between self-reported depressive mood, anxiety, and mortality outcomes of patients following CABG with or without a concomitant valve procedure.

Method

Patients

The patient sample for this retrospective study consisted of all 1,686 consecutive patients undergoing a first-time CABG with or without a concomitant valve procedure using cardiopulmonary bypass over a 10-year period between January 16, 1996, and February 17, 2006. Patients were recruited into ongoing neuropsychological trials, and inclusion criteria were age ≥ 18 years, CABG procedure with cardiopulmonary bypass, and able and willing to provide informed consent. Patients were ineligible for the following reasons (n = 1246): off-pump surgery (n = 259); emergency surgery (n = 170); residency outside South Australia (n = 167); history of head injury with loss of consciousness (n = 143); previous cardiac surgery procedure with cardiopulmonary bypass (n = 141); participating in another cardiac surgery study (n = 108); not attending preadmission or on ward for less than 24 hours (n = 100); refused (n = 65); language, reading, writing, or vision difficulty (n = 54); dementia (n = 18); met criteria for confusion with the Short Portable Mental Status Questionnaire (Eissa, Andrew, & Baker, 2003) (n = 9); health reasons (n = 9); psychotic, personality, or developmental disorder (n = 8); unable to give informed consent (n = 2); and age ≤ 18 years (n = 2). A total of 440 patients met inclusion criteria and were analysed in this study with a follow-up for a median of 5 years, 10 months.

Depression and Anxiety Assessment

Depression and anxiety symptoms were assessed using the DASS (Lovibond & Lovibond, 1995b), a self-report measure with three scales (depression, anxiety, stress). Research has supported a uniform factor structure of the DASS and favourable internal

reliability (Antony et al., 1998; Brown, Chorpita, Korotitsch, & Barlow, 1997; Crawford & Henry, 2003; Lovibond & Lovibond, 1995a; Nieuwenhuijsen, de Boer, Verbeek, Blonk, & van Dijk, 2003). The DASS depression scale correlates moderately with the Beck Depression Inventory (r = .74 – .75) (Brown et al., 1997a; Lovibond & Lovibond, 1995a) and the depression scale of the Hospital Anxiety Depression Scale (r = .66 – .75) (Crawford & Henry, 2003; Nieuwenhuijsen et al., 2003). The DASS anxiety scale correlates well with the Beck Anxiety Inventory (r = .81 – .83) (Brown et al., 1997a; Lovibond & Lovibond, 1995a) and the Hospital Anxiety and Depression Scale-anxiety subscale (r = .62 – .66) (Crawford & Henry, 2003; Nieuwenhuijsen et al., 2003).

Scores ≥10 on the DASS-depression scale are considered to reflect mild depressive symptoms (Lovibond & Lovibond, 1995b), and this criterion was also set for the present study, as has been used previously (Baker et al., 2001). The criterion for mild anxiety was set at ≥10 in accordance with normative data (Lovibond & Lovibond, 1995b) and previous research (Oxlad et al., 2006a), and mild stress was set at ≥15 based on normative data (Lovibond & Lovibond, 1995b). Internal consistency of the DASS scales was excellent in this study (α ≥ .90). The DASS was administered the day before surgery or at preadmission clinic in the week before surgery.

Surgical Technique

Patients underwent conventional CABG with or without valve replacement with cardiopulmonary bypass. Cardiopulmonary bypass was instituted after positioning of a single two-stage atrial cannula and an ascending aortic cannula, whereas for mitral valve surgery, dual vena cava cannulation was used. The cardiopulmonary bypass circuit included a hollow fibre membrane oxygenator (Maxima, Medtronic USA; Capiox SX18 or SX25, Terumo Japan), hard-shell venous reservoir, nonbiocompatible polyvinyl chloride tubing, and a 40-μm arterial line filter. Flow rates were maintained at 1.6–2.4 l/min per square meter, alpha-stat pH management was employed, with gravity venous drainage and target activated clotting time of N400. Various temperature management strategies were employed [normothermic (36–37°C), tepid (32–35°C), or moderate systemic hypothermia (30–32°C)]. After placement of the aortic cross clamp, cardioplegic arrest was induced with blood cardioplegia. Proximal anastomoses were performed after application of a partial (side-biting) aortic clamp. Cardiotomy suction was only utilized in valve procedures. Patients were rewarmed at rates not in excess of 1°C per minute and separated from cardiopulmonary bypass when nasopharyngeal temperatures exceeded 36.5°C.

Mortality Assessment

Mortality status was ascertained by the National Death Index, as provided by the Australian Institute of Health and Welfare for use in epidemiological studies and medical research. National Death Index data was provided in international classification of disease coding up until December 31, 2006, and this date was taken as the end of the study period. All participants provided informed consent, and this study received approval from the institutional research ethics committee (Approval #54/99, 4/023, 199/017, 1999/106).

Statistical Analysis

Data were analysed using SPSS 12.0.1 statistical software package (SPSS, Chicago, IL, USA). We compared deceased patients with those alive (or censored) at end of follow-up on baseline demographic, clinical, and surgical variables. We also compared baseline depressive and non-depressive groups and also anxious and non-anxious groups on the demographic and clinical variables. Quantitative data were compared with independent sample t tests or Mann–Whitney U tests (depending on variable distribution), while categorical data were analysed with the χ2 statistic, with Fisher's two-tailed exact test used if expected cell sizes were small. To determine mortality risk, we first identified potential baseline covariates derived largely from the recommendations of the Working Group Panel on the Cooperative CABG database project (Jones et al., 1996). Using survival analysis with the Mantel Cox log-rank test, we entered the following binary coded variables (0 = no, 1 = yes): female sex, myocardial infarction within 30 days, unstable angina, impaired LVEF (≤35%), concomitant valve procedure, congestive heart failure, diabetes mellitus, cerebrovascular disease, PVD, chronic obstructive pulmonary disease, renal failure, and urgent surgery (elective as reference category), while age was split into tertiles (youngest as reference category). We retained covariates with log-rank test p ≤.10 and entered these covariates into Cox proportional hazards models along with the psychological variables. The proportionality of hazards assumption was checked by examination of the baseline hazards function plot and also the log-minus-log plot of survival function. We did not identify any influential observations, and there were no highly collinear variables.

Results

The sample consisted predominantly of males (80%), with a mean age of 64 years, and 33 (8%) patients underwent a concomitant valve replacement (30 aortic, two mitral, 1 aortic and mitral) as shown in Table 2. The crude all-cause mortality was 15% (n = 67) within

the follow-up period, and 33% (n = 22) of these were from cardiac causes, with 28% (n = 19) non-cardiac causes, while a further 37% (n = 25) were unknown according to National Death Index classification. Comparison of the deceased and alive CABG patients at the study's conclusion shows an association between mortality and age, PVD, cerebrovascular disease, renal disease, concomitant valve procedure, and length of stay (Table 2). In the deceased patients, median survival was 4.7 years (range width 15 days to 10.8 years).

At baseline, 20% (n = 89) of patients were identified as having mild depressive symptoms, while mild anxiety was evident among 23% (n = 102) and 21% (n = 94) were stressed. Comparison of baseline depressed and non-depressed patients showed that both groups were equal on most demographic and clinical measures although a trend towards impaired LVEF was identified among the depressive group [χ^2 (1) = 3.05, p = .08]. There were no significant associations identified between baseline anxiety and demographic or clinical variables. Five patients were taking anxiolytics or antidepressant medication before surgery (four benzodiazepines, one tricyclic antidepressant). A trend toward significance was observed for preoperative dichotomised depression and the use of psychoactive medications [χ^2 (1) = 4.96, p = .06] but not use of psychotropic medication and dichotomised anxiety [χ^2 (1) = 2.04, p = .17].

From the potential covariates, analysed with Mantel Cox log-rank tests, we found that older age, renal disease, concomitant valve procedure, cerebrovascular disease, and PVD were associated with a higher risk of mortality (all p ≤ .10, results not shown). To determine the unique mortality risk attributable to depression, adjusted survival analysis was undertaken for baseline depression, and a separate analysis was undertaken for anxiety. The unadjusted Cox proportional hazards model with dichotomised preoperative depressive symptoms showed no association with mortality (HR = 1.36; 95% CI .78 – 2.39, p = .28). The adjusted hazard model for baseline depressive symptoms showed that all covariates apart from cerebrovascular disease remained associated with an increased risk of mortality, while baseline depression was associated with a trend towards significance (adjusted HR = 1.61; 95% CI 0.91 – 2.85, p = .10), as shown in Table 3. The unadjusted hazard model for preoperative anxiety showed a significantly increased risk of mortality (HR = 1.82; 95% CI 1.09 – 3.04, p = .02). In adjusted analysis, anxiety remained associated with all-cause mortality (adjusted HR = 1.88; 95% CI = 1.12 – 3.17, p = .02), while the covariates age, renal disease, cerebrovascular disease, and concomitant valve procedure remained associated with an increased mortality risk (Table 4).

Table 2. Demographic and Clinical Data According to Mortality Status

	Alive	Deceased	
	n = 373	n = 67	*P*
Demographic and clinical			
Age tertiles			
35 – 59	132 (35%)	9 (13%)	< .001
60 – 70	145 (39%)	26 (39%)	.99
> 71	96 (26%)	32 (48%)	< .001
Female	78 (21%)	12 (18%)	.58
LVEF (altered/impaired) ≤ 35%	13 (4%)	3 (5%)	.69
Hypertension	204 (54%)	44 (66%)	.10
Unstable angina	31 (8%)	4 (6%)	.51
Congestive heart failure	19 (5%)	2 (3%)	.46
Previous MI < 30 days	28 (8%)	3 (5%)	.37
Diabetes mellitus	69 (19%)	15 (22%)	.46
COPD	14 (4%)	3 (5%)	.78
PVD	68 (18%)	27 (40%)	< .001
Cerebrovascular disease	14 (4%)	8 (12%)	.01
Renal disease	6 (2%)	4 (6%)	.05
Urgent procedure	79 (21%)	14 (21%)	.96
Surgical			
Concomitant valve replacement	13 (3%)	20 (30%)	<. 01
Median procedure time (min)	136 (51 – 327)	128 (58 – 208)	.07
Median CPB time (min)	50 (13 – 156)	50 (19 – 153)	.77
Median cross clamp time (min)	29 (6 – 119)	28 (8 – 120)	.51
≥ 3 grafts	172 (46%)	27 (41%)	.41
Median time in ICU (days)	24 (3 – 191)	24 (8 – 220)	.12
Median length of stay (days)	6 (2 - 36)	7 (4 - 25)	.001

CPB, cardiopulmonary bypass time; COPD; chronic obstructive pulmonary disease; ICU, intensive care unit; LVEF, left ventricular ejection fraction, MI; myocardial infarction; PVD, peripheral vascular disease

Table 3. Adjusted Hazard Model for All Cause Mortality and Baseline Depressive Symptoms

	β	Hazard Ratio	95% CI	P
Baseline depressive symptoms[§]	.48	1.61	0.91 – 2.85	.10
Age tertiles				
35 – 59 (reference)	-	-	-	
60 – 70	.72	2.05	0.95 – 4.46	.07
> 71	1.14	3.12	1.44 – 6.79	<. 01
Renal disease	1.46	4.31	1.45 – 12.77	<. 01
Concomitant valve procedure	.77	2.16	1.16 – 4.03	.02
Cerebrovascular disease	.62	1.85	0.85 – 4.06	.12
PVD	.56	1.75	1.06 – 2.88	.03

[§]*Adjusted for age (tertiles), renal disease, concomitant valve procedure, cerebrovascular disease, peripheral vascular disease*

Table 4. Adjusted Hazard Model for All Cause Mortality and Baseline Anxiety Symptoms

	β	Hazard Ratio	95% CI	P
Baseline anxious symptoms[§]	.63	1.88	1.12 – 3.17	.02
Age tertiles				
35 – 59 (reference)	-	-	-	
60 – 70	.74	2.10	0.96 – 4.57	.06
> 71	1.11	3.05	1.40 – 6.12	<. 01
Renal disease	1.19	3.30	1.13 – 9.63	.03
Concomitant valve procedure	.78	2.18	1.17 – 4.08	.01
Cerebrovascular disease	.80	2.21	1.01 – 4.84	.05
PVD	.49	1.64	0.98 – 2.71	.06

[§]*Adjusted for age (tertiles), renal disease, concomitant valve procedure, cerebrovascular disease, peripheral vascular disease*

Inspection of the adjusted cumulative survival from the Cox proportional hazards model in Figure 2 shows divergent survival lines for anxious and non-anxious patients. The unadjusted hazard model for stress did not support an increased mortality risk (HR = 1.08; 95% CI .61 – 1.91, p = .80). After adjustment for covariates, baseline stress remained not significantly associated with all-cause mortality (HR = 1.51, 95% CI = 0.84 – 2.73, p = .17).
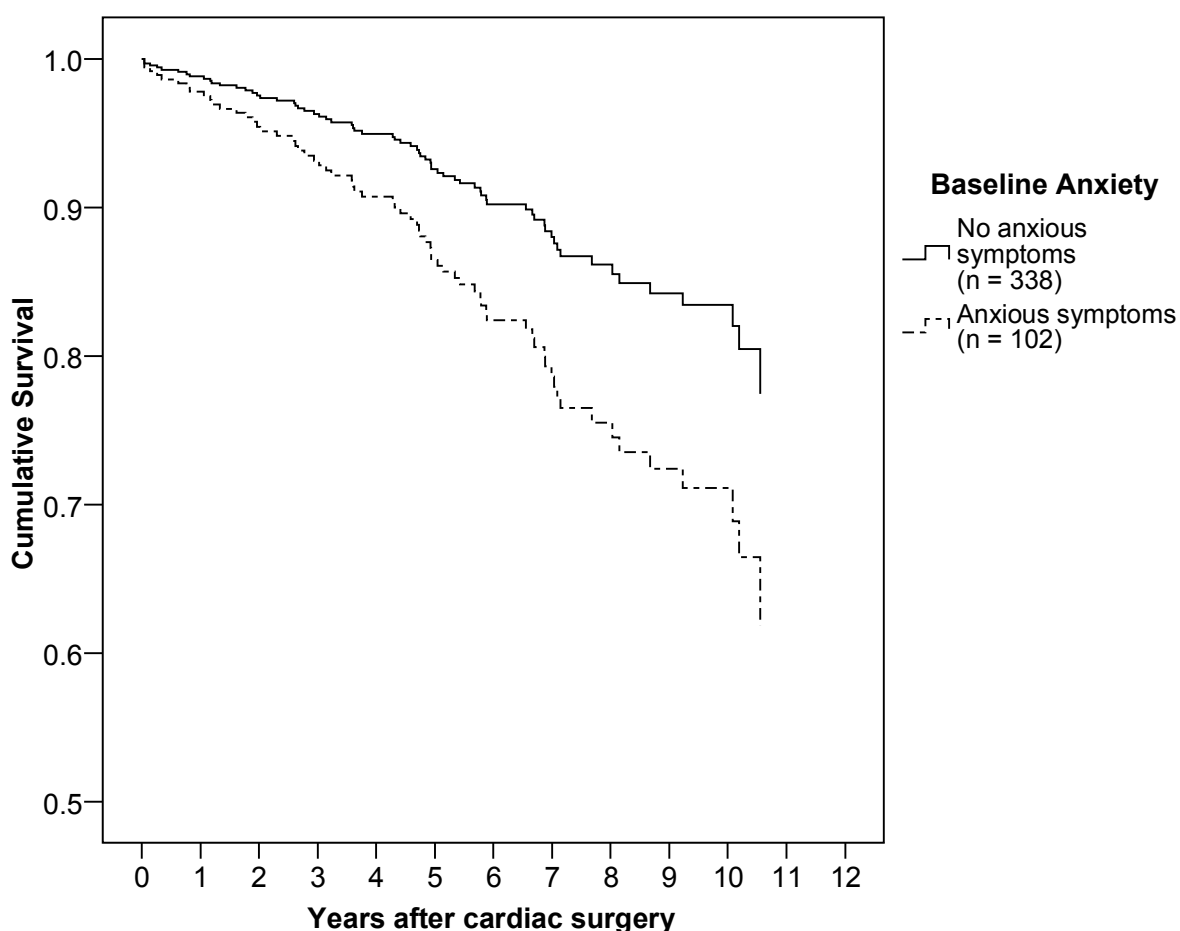
Figure 2. Adjusted Cox Proportional Survival Function for Baseline Anxiety

Figure 2. Coronary artery bypass graft patient adjusted cumulative survival in years after surgery for all-cause mortality is plotted for patients with anxiety symptoms before surgery (DASS anxiety score ≥ 10; n = 102) against patients without anxiety symptoms before surgery (DASS anxiety score ≤ 9; n = 338). Adjusted Cox-proportional hazard model for baseline anxiety for all-cause mortality, adjusted for older age, renal disease, concomitant valve procedure, cerebrovascular disease and peripheral vascular disease (HR = 1.88; 95% CI = 1.12 – 3.17, p = .02).

Discussion

This study adds to previous research by showing the postoperative mortality risk associated with depressive and anxious symptoms measured at the time of CABG surgery. In what we believe is the first study reporting both depression and anxiety measures to determine mortality risk after CABG, anxiety symptoms increased all-cause mortality risk. The results of the present study also show a trend towards significance for depression and mortality risk as previous studies have shown (Baker, Andrew, Schrader, & Knight, 2001; Blumenthal et al., 2003; Burg, Benedetto, & Soufer, 2003). The mortality risk attributable to

depression may have been attenuated by the associated trend towards use of psychotropic medications.

The findings of our study differ from previous research as the DASS-depression scale only measures depressed mood, rather than sleep disturbances and appetite changes that may tap into underlying physical illness. Vingerhoets (1998) has shown somatic depressive symptoms significantly increase following CABG and argued that such scale items should be omitted from analysis. However, it is indeed possible that depressed CABG patients experience more somatic and vegetative complaints than affective symptoms. For example, Fraguas and colleagues (2000) reported that sleep disturbances were the most common depressive symptoms among CABG patients with major depression.

Self-reported depressive symptoms correlate moderately with other psychological variables (e.g., anxiety and hostility), suggesting a broader approach to psychological distress may be valuable for studying outcomes of CAD than depression alone (Suls & Bunde, 2005). In our adjusted analysis, mild non-specific anxiety increased the risk of all-cause mortality nearly twofold independent of other significant covariates. However, the DASS anxiety scale contains physiological and autonomic markers for anxiety that are common to patients recovering from CABG (Andrew et al., 2000). As anxiety was measured at baseline, we do not believe this limits the present findings. Nevertheless, recent research using structural equation modelling has suggested that somatic factors lead to depression and anxiety prior to CABG (Duits et al., 2002), highlighting the complex relationship between physical disease and negative affective states.

The DASS scale has been consistently found to have distinct factors with few cross-loading items (Antony et al., 1998; Brown et al., 1997a; Crawford & Henry, 2003; Lovibond & Lovibond, 1995a; Nieuwenhuijsen, de Boer, Verbeek, Blonk, & van Dijk, 2003), suggesting coherent separation of anxiety and depression items. Given the current findings with distinct anxious and depressive symptoms, it is possible that anxiety rather than depression confers an increased mortality risk. However, together, the combined effects of depression and anxiety may potentiate the physiological mechanisms that predispose psychologically distressed people to cardiopathogenesis and cardiac events. Supporting this, Watkins et al. (2006) showed that a composite of phobic anxiety and depressive symptomatology had the largest effect size for risk of arrhythmias than depression or phobic anxiety alone among people with CAD (OR = 1.6; 95% CI 1.2 - 2.1, p = .002). The biological mechanisms hypothesized to increase the risk of cardiopathogenesis among depressed people (e.g., enhanced platelet aggregability, reduced heart rate variability, dysregulation of the hypothalamic–pituitary–adrenal axis) have also been found among anxious patients (Carney, Freedland, Miller, & Jaffe, 2002; Gorman & Sloan, 2000; Zaubler & Katon, 1996). In our

study, the cause of death could not be ascertained for 37% of patients, while 28% of deaths were clearly not from cardiac causes. This suggests that the hypothesized physiological changes in response to elevated anxiety would not explain all post-CABG mortality. Yet, anxiety, along with depression, has also been associated with health behaviours that might explain higher mortality risk including nonadherence to medications and rehabilitation, sedentary lifestyle, and smoking (Barger & Sydeman, 2005; Carney et al., 2002; Goodwin, 2003).

Indeed, supporting emotionally distressed patients is consistent with quality care irrespective of the overall influence on patient survival. However, null treatment effects for psychological interventions for cardiac patients along with paradoxical findings in favour of control groups are not uncommon (Lie, Arnesen, Sandvik, Hamilton, & Bunch, 2007; Sebregts, Falger, Appels, Kester, & Bar, 2005). While previous trials post MI have generally been able to reduce depressive symptoms, only modest effects on survival and cardiac end points were obtained (Berkman et al., 2003; Glassman et al., 2002). The challenge for intervention studies is potentially to concurrently address depression and anxiety rather than either in isolation and also to do so both before and after surgery. As the majority of CABG patients will not meet diagnostic criteria for anxiety or depression, psychoeducation regarding mood and anxiety could be incorporated into cardiac rehabilitation, while reductions in negative emotions may come from individually tailored interventions (Rozanski, Blumenthal, & Kaplan, 1999).

Several limitations need to be recognized when interpreting the findings of this study including the number of deaths. Secondly, whilst all data were collected prospectively the tenet of this study was retrospective. We have included high risk patients in our sample such as those with cerebrovascular disease, renal failure, and those undergoing a concomitant procedure to establish whether findings of previous studies would generalize. Our study was underpowered to assess adjusted mortality risk attributable to both depression and anxiety simultaneously, and this may be a beneficial avenue for future studies. The use of a single-hospital recruitment site tempers the generalisability of our results. Dichotomisation for subthreshold depression and anxiety was based on normative data whereas other self-report measures such as the Beck Depression Inventory have recommended cutoffs to determine caseness for major depression, a major advantage of these scales.

In conclusion, this study has demonstrated that mild anxiety is associated with a nearly twofold independent mortality risk. Although depressive symptoms were not significantly associated with increased risk we recommend that future research should further explore the simultaneous role of anxiety and depression on mortality following CABG.

Chapter IV Study Two

The Role Of Depression And Anxiety Symptoms In Hospital Readmissions After Cardiac Surgery

Statement of contributors

Phillip Tully (*Candidate*)

Responsible for study conception, literature review, data analysis, manuscript drafting and preparation, manuscript submission, response to reviewers and revisions.

Signed: Date: 4/01/2011

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We provided ongoing supervision throughout the research programme that lead to this publication and there was ongoing collaboration between Mr. Tully and us in refining the direction of the research. Mr. Tully was responsible for writing this paper; our role was to comment on drafts, make suggestions on the presentation of material in the paper, and to provide editorial input. We also provided advice on responding to comments by the journal reviewers and editor. We hereby give our permission for this paper to be incorporated in Mr. Tully's submission for the degree of Doctor of Philosophy from the University of Adelaide.

Signed: Robert Baker   Date: 4/01/2011

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Abstract

The objective of this study was to determine the association between depression, anxiety and general stress symptoms with hospital readmissions after CABG surgery. Two hundred and twenty six CABG surgery patients completed baseline self-report measures of depression, anxiety and stress and 222 patients completed these measures after surgery on the hospital ward. The hospital readmission outcomes at six months were analysed using multivariable proportional hazard models. When analysed as continuous variables in multivariable analyses, preoperative anxiety and postoperative depression predicted readmissions independent of medical covariates. In multivariable analyses with dichotomised anxiety, depression and stress, more than two-fold increase in readmission risk was attributable to preoperative anxiety and postoperative depression, independent of covariates. These results lend further support to previous research that has shown the symptoms of depression and anxiety are associated with morbidity following CABG surgery. The findings highlight the need to develop suitable interventions for anxiety and depression among CABG surgery patients.

Introduction

Coronary artery disease is a progressive condition most commonly caused by atherosclerotic plaque disease, characterized by occlusion in the coronary arteries that supply blood to the heart (Julian, Cowan, & McLenachan, 1998). Reduced blood flow or ischemia to the myocardium results in angina pectoris and dyspnoea (Morrow, Gersh, & Braunwald, 2005). Coronary artery bypass graft surgery is a common technique to treat CAD, and new conduits are grafted around blockages using harvested sections of artery or reversed vein (Morrow, Gersh, & Braunwald, 2005.

Symptoms of anxiety and unipolar depression are common psychological disturbances among patients with CAD, including those undergoing CABG surgery (Bankier, Januzzi, & Littman, 2004; Pignay-Demaria, Lespérance, Demaria, Frasure-Smith, & Perrault, 2003). It is recognized that depression portends an independent risk for CAD morbidity (Davidson, Kupfer, & Bigger, 2006; Lett et al., 2004), yet accumulating evidence suggests that interrelated emotions such as anxiety and stress are also risk factors for mortality, myocardial infarction (MI) and unstable angina (Bunker et al., 2003; Kubzansky, Cole, Kawachi, Vokonas, & Sparrow, 2006; Kubzansky, Davidson, & Rozanski, 2005; Kubzansky et al., 1997; Rothenbacher, Hahmann, Wüsten, Koenig, & Brenner, 2007; Rozanski, Blumenthal, & Kaplan, 1999; Suls & Bunde, 2005). These findings are not surprising given that depression and anxiety have overlapping symptoms that correlate in the moderate range (Clark & Watson, 1991; Ninan & Berger, 2001), and that these two negative emotions have been reported to share a common underlying component of general NA (Clark & Watson, 1991). Specifically, NA is the general disposition towards experiencing negative emotional states characterized by distress, worry, pessimism, irritability and restlessness (Watson, 2000).

The broadening of psychological risk factors for cardiac morbidity corresponds in a timely fashion to empirical research that has examined the interrelation between anxiety and depression, emphasizing their common and unique symptoms, and the general tendency to experience NA (Clark & Watson, 1991). Specifically, Clark and Watson (1991) proposed a tripartite model in which depression and anxiety share general negative affect symptoms such as irritability and restlessness, and thus these symptoms are not unique to either anxiety or depression. Specific anxiety symptoms exclusively reflect physical hyperarousal and somatic tension (e.g. trembling, shakiness) whereas depressive symptoms are characterized by anhedonia (i.e. the loss of interest or pleasure) and typical symptoms include hopelessness, crying and suicidal ideation (Clark & Watson, 1991). This latent

tripartite structure has been supported in a broad range of clinical and medical settings (Cook, Orvaschel, Simco, Hersen, & Joiner, 2004; Geisser, Cano, & Foran, 2006; Teachman, Siedlecki, & Magee, 2007; Watson et al., 1995a, 1995b), and may prove useful for interpretation of the role of negative emotions in patients with coronary artery disease. Importantly, the addition of theoretically driven research on psychological and cardiac outcomes may foster novel understandings of disease-affect relationships as other authors have shown (Oxlad, Stubberfield, Stuklis, Edwards, & Wade, 2006b).

The main limitation of research on negative emotions on CABG patient outcomes is that typically only depression is assessed thus precluding a potential role of anxiety. Given that depression and anxiety are interrelated and do not occur in isolation, it is necessary to analyse these negative emotional states concurrently rather than separately in relation to cardiac outcomes. However, in previous CABG studies attributing an independent risk to depression, it cannot be ruled out that conceptually related affective states (i.e. anxiety) also confer CAD event risk. Moreover, it is indeed possible that cardiac morbidity previously attributed to depression or anxiety is confounded by shared variance with general negative affect symptoms that are measured within poorly constructed self-report inventories (Clark & Watson, 1991). To overcome these shortcomings of previous CABG studies we propose to study psychological variables and hospital readmission outcomes using the tripartite model as a theoretical framework. Specifically, we aim to examine the potential role of depression, anxiety and general NA on cardiac outcomes. Consistent with review evidence supporting an association of both depressive and anxious symptoms with CAD morbidity implicating a common disposition to NA (Suls & Bunde, 2005), we hypothesize that general stress symptoms (i.e. NA) will be associated with an increased risk of unplanned hospital readmissions after CABG surgery.

Methods

Patients

The sample for this study consisted of patients undergoing first-time CABG surgery between January 1999 and December 2005 at the Flinders Medical Centre, South Australia. There were 681 CABG cases evaluated for inclusion in the study. Inclusion criteria were: age >18 years, isolated CABG procedure with cardiopulmonary bypass, able and willing to provide informed consent. Patients were ineligible for the following reasons (n = 443): residency outside South Australia (n = 156), language, reading, writing or vision difficulty (n = 82), emergency surgery (n = 60), refused (n = 53), suspected or diagnosed dementia or met criteria for baseline confusion with the Short Portable Mental Status Questionnaire (Eissa et

al, 2003) (n = 27), participating in another cardiac surgery study (n = 26), other (n = 14), unable to give informed consent (n = 12), psychotic, personality or developmental disorder (n = 8), health reasons (n = 5). A total of 238 patients were recruited at baseline, with patients excluded from final analysis for the following reasons; death before surgery (n = 1), surgery postponed indefinitely (n = 3), switched to surgery without cardiopulmonary bypass intraoperatively (n = 8). The final baseline sample was 226 patients (time 1), and 4 declined participation immediately post-surgery (time 2, n = 222). All patients provided informed consent and this study has received ethics approval from the respective hospital and university institutions (approval numbers: 57/067, H-148-2006).

Measures

The components of the tripartite model were measured with the DASS (Lovibond & Lovibond, 1995a, 1995b), a 42 item self-report measure that consists of three scales (depression, anxiety, stress) (for review see Lovibond 1998). Participants were asked to rate how often they experienced each of the symptoms over the preceding week on a four point likert scale. Examples of depression scale items include ''I couldn't seem to experience any positive feeling at all'' and ''I just couldn't seem to get going.'' The anxiety scale contains such items as ''I felt scared without any good reason'' and ''I felt I was close to panic.'' The stress scale includes items such as ''I tended to over-react to situations'' and ''I found myself getting impatient when I was delayed in any way.''

Confirmatory factor analysis has supported a latent structure of anhedonia, physiological hyperarousal and general distress factors (Brown et al. 1997a; Clara et al. 2001) indicating it is an appropriate measure of the tripartite model. The DASS has a uniform factor structure, high internal consistency and test retest reliability (Clara et al. 2001; Crawford and Henry 2003) and has been used with cardiac surgery patients (Andrew et al. 2000; Oxlad et al. 2006a). In statistical analyses with dichotomised DASS scores, a mild level from normative data (Lovibond and Lovibond 1995b) was adopted on all subscales: depression ≥10, anxiety ≥8, stress ≥15, as is consistent with previous studies (Oxlad et al., 2006a). Patients completed the DASS at preadmission clinic in the week before scheduled surgery and again four days after surgery on the hospital ward, in a fashion similar to other pre and post test design studies of CABG patient mood state (Oxlad et al. 2006a; Andrew et al. 2000).

Readmission Outcome

The dependent variable in this study was time in days to the first unplanned readmission related to coronary artery bypass procedure or cardiovascular or vascular causes, within six months of surgery. Readmission data were ascertained from patient telephone interview at six months and confirmed via an electronic database that links eight of South Australia's metropolitan hospitals. Electronic readmission data were extracted by the first author using the principal diagnosis at readmission and up to fifteen additional diagnoses that were ascertained by the treating physician and coded according to International Classification of Disease criteria version 10 (World Health Organization, 2007). Hospitals were contacted for patient notes if not available on the electronic database (3 patients). A board certified cardiothoracic surgeon and a perfusionist (R.A.B.), blinded to patient psychological distress results, independently coded readmissions according to whether they were related to surgery, cardiovascular disease or vascular diseases, or other. Cardiovascular or vascular readmissions were recorded for International Classification of Disease codes I00 - I99, with the exception of deep vein thrombosis, pericardial effusion and cardiac tamponade that were classed as surgery related. Other readmissions related to coronary bypass procedures included coagulation management, wound management, pneumonia or respiratory complications, atypical chest pain, pleural effusion, revascularization procedures and gastrointestinal obstructions. Mortality was ascertained from the National Death Index, provided by the Australian Institute of Health and Welfare.

Statistical Analysis

Data were analysed using SPSS 12.0.1 ® statistical software package (SPSS Inc., Chicago, IL). Patients with hospital readmission, and patients identified with mild levels of depression, anxiety and stress, were compared on baseline demographic, clinical and surgical variables. Quantitative data were compared with independent samples t-tests or Mann–Whitney U-tests (depending on variable distribution), while categorical data were analysed with the χ^2 statistic, with Fisher's two-tailed exact test used where appropriate. Partial correlation coefficients were performed between DASS scales at the same observation period, to ascertain the interrelation between scales adjusting for shared variance.

Baseline demographic, clinical and surgical variables were selected as potential covariates for morbidity based on previous research (Hannan et al., 2003; Heijmans, Maessen, & Roekaerts, 2003; Jarvinen, Huhtala, Laurikka, & Tarkka, 2003; Jones et al., 1996; Shroyer et al., 2003; Steuer et al., 2002; Tu, Sykora, & Naylor, 1997). We analysed

age (quartiles), female sex, LVEF, urgency of surgery (elective vs. urgent), chronic lung disease, congestive heart failure, diabetes mellitus, PVD, renal disease, previous myocardial infarction within 90 days, hypertension, and Canadian Cardiovascular Society Angina grade III/IV (versus grade I/II) and psychoactive medication use (i.e. antidepressants, sedatives, anxiolytics and antihypnotics). These covariates were forced into adjusted Cox proportional hazard models, testing for time (days) to the first unplanned readmission. Multivariable hazard models were performed with DASS subscale continuous scores, and again as dichotomised variables, forcing each variable into the hazard model. The rationale for simultaneous forced entry of psychological variables was to assess the association between morbidity and each conceptually related domain of the tripartite model, as each of the tripartite factors are interrelated and occur concurrently. We performed secondary hazard model analyses in the same fashion described above, though we entered only the stress scores at the second step, and depression and anxiety scores at the third step of the regression models. Here the rationale was to determine the role of depression and anxiety on readmission outcomes controlling for the effects of general NA. During data screening we did not find any outliers that influenced hazard models, and multicollinearity statistics were acceptable as determined by squared multiple correlations <.90 (Tabachnick & Fidell, 2000) and inspection of correlations between regression coefficients. The proportionality of hazards assumption was checked initially by entering covariates as interactions with time and also ascertained graphically in final models via examination of the baseline hazards function plot and also the log-minus log plot of survival function.

Results

The sample was predominantly male (83%) with a mean age of 63 years, and the mean DASS scores are shown in Table 5. The results show that patients experiencing a subsequent readmission had higher preoperative anxiety and postoperative depression scores in comparison to non-readmitted patients. When baseline DASS sub scale scores were dichotomised at a mild level of negative affect symptoms or greater, 47 (20.1%) patients had depressive symptoms, 71 (31.4%) had anxious symptoms and 49 (21.7%) had mild stress. At postoperative assessment, 52 (23.5%) patients had scores indicative of depression, while 101 (45.5%) patients had mild anxious symptoms, and 43 (19.4%) had mild stress. Partial correlation coefficients between DASS scale scores for the same observation period were modest as shown in Table 6, suggesting moderate interrelations between scales controlling for variance shared with other dimensions of the tripartite model.

Table 5. Comparison of Baseline Demographic, Clinical and Surgical Variables Between Patients Able and Unable to Complete the Study (N = 226)

Demographic and Clinical	Readmitted n = 72	Not readmitted n = 154	P
Age M (*SD*)	62.9 (9.7)	63.2 (9.7)	.80
Age quartiles ≤56	22 (31%)	40 (26%)	
57 – 64	21 (29%)	39 (25%)	
65 – 70	37 (24%)	37 (24%)	
≥ 71	38 (25%)	38 (25%)	.67
Sex (% female)	11 (15%)	27 (18%)	.67
Angina CCS class III/IV	23 (32%)	54 (35%)	.91
Congestive heart failure	6 (8%)	10 (6%)	.62
LVEF ≥ 60	50 (69%)	116 (75%)	
45-59	13 (18%)	25 (16%)	
31-45	8 (11%)	9 (6%)	
≤ 30%	1 (1%)	4 (3%)	.48
Urgent procedure	13 (18%)	25 (16%)	.73
Hypertension	49 (68%)	90 (58%)	.17
Myocardial infarction < 90 days	20 (28%)	36 (23%)	.49
Smoking history	46 (64%)	112 (73%)	.25
Chronic lung disease	18 (25%)	26 (17%)	.16
PVD	15 (21%)	20 (13%)	.12
Diabetes mellitus	18 (25%)	29 (19%)	.28
Renal disease	3 (4%)	2 (1%)	.18
Surgical Median (range)			
Procedure time (min)	144 (59 – 221)	146 (51 – 247)	.94
Time on CPB (min)	54 (22 – 106)	53 (23 – 116)	.88
Time cross clamp (min)	32 (0 – 66)	31 (0 – 68)	.94
Time ICU (hours)	23 (3 – 191)	23.5 (3 – 191)	.40
≥ 3 grafts	35 (49%)	80 (52%)	.67
Postoperative length of stay	6.0 (4 – 36)	5.0 (2 – 18)	.19
DASS scores M (SD)			
Baseline [a]			
Depression	6.0 (6.3)	5.5 (5.7)	.59
Anxiety	7.7 (6.9)	5.9 (6.3)	.05
Stress	9.8 (8.5)	9.3 (8.4)	.71
Postoperative [b]			
Depression	8.2 (9.0)	5.9 (7.0)	.04
Anxiety	9.7 (8.7)	8.9 (7.6)	.50
Stress	8.5 (9.1)	8.1 (8.5)	.76

CCS Class, Canadian Cardiovascular Society; CPB, cardiopulmonary bypass; ICU, intensive care unit; LVEF, left ventricular ejection fraction;
a. N = 226
b. N = 222

Table 6. Partial Correlations Between Measures of Depression, Anxiety and Stress

Preoperative	1	2	3
1. Preoperative depression	-		
2. Preoperative anxiety	.43** [a]	-	
3. Preoperative stress	.39** [b]	.50** [c]	-
Postoperative	4	5	6
4. Postoperative depression	-		
5. Postoperative anxiety	.31** [d]	-	
6. Postoperative stress	.40** [e]	.60** [f]	-

*** p<.001*

Preoperative n = 226; Postoperative n = 222

a. adjusted for preoperative stress; b. adjusted for preoperative anxiety; c adjusted for preoperative depression; d adjusted for postoperative stress; e adjusted for postoperative anxiety; f adjusted for postoperative depression

There were no associations between psychological status and demographic or clinical variables suggesting patients were not reporting higher distress due to physical morbidity. The recruited sample medication list was screened for antidepressants, sedatives, anxiolytics and antihypnotics, and four patients were on Benzodiazepine's (3 Temazepam, 1 Diazepam) and one patient was taking a tricyclic antidepressant (Amitriptyline). The use of psychoactive medication was associated with a trend for dichotomised mild anxiety symptoms, $\chi^2 (1) = 4.26$, $p = .05$. There was no association between use of psychoactive medications and mild depressive symptoms, $\chi^2 (1) = 1.21$, $p = .28$, or any association with medications and stress, $\chi^2 (1) = 1.01$, $p = .30$.

Within six-months of CABG there were 72 (32%) readmissions related to the surgical procedure, cardiovascular or vascular disease. The most common readmission causes were infection, respiratory complications and pleuritic chest pain (all 13.9%), arrhythmia (12.5%), angina (11.1%) and CHF (9.7%) (Table 7). One patient that died of MI was censored from all hazard modelling analyses. There were no baseline differences in demographic, clinical, or surgical variables between patients that had a readmission and those that did not.

Table 7. Readmission Causes and Classification

Principal cause	N	% of total
Cardiovascular or vascular		
Angina	8	11.1
Arrhythmia	9	12.5
Heart failure	7	9.7
Myocardial infarction	3	4.2
Stroke	1	1.4
Vascular (aortic aneurysm and dissection)	2	2.8
Cardiovascular subtotal	30	41.7
Surgical		
Atypical chest pain (sternotomy, myofascial)	2	2.8
Deep vein thrombosis	2	2.8
Gastrointestinal complication or obstruction	2	2.8
Infection	10	13.9
Leg cellulitis	1	1.4
Other	2	2.8
Pericardial effusion	1	1.4
Pleural effusion	1	1.4
Pleuritic chest pain	10	13.9
Respiratory complication	10	13.9
Revascularization procedure	1	1.4
Surgical subtotal	42	58.5
Total	N = 72	100

Primary Multivariable Analysis Of Hospital Readmissions

Continuous DASS scores.

The multivariable hazard models with simultaneous entry of each psychological construct show the risk attributable to negative affective states for the interrelated dimensions of the tripartite model. When DASS sub-scale scores were entered simultaneously as continuous variables in a hazard model adjusted for all covariates, only a one-point increase in baseline anxiety score was found to increase readmission risk by 12% (HR = 1.12; 95% CI 1.04 − 1.20, *p* = .002), and these results are shown in Table 8. The covariates associated with a trend towards significantly increased readmission risk were hypertension (*p* = .06), PVD (*p* = .09), Canadian Cardiovascular Society class III/IV (*p* = .09), age range 65 − 70 years (*p* = .18) and left ventricular ejection fraction 31 − 45% (*p* = .17). General stress was also associated with a trend towards a significantly reduced readmission

risk (HR = .96; 95% CI .91 – 1.01, *p* = .12). The multivariable adjusted hazard model for postoperative DASS sub-scale scores showed that a one-point increase in depression scale score was associated with an increased risk of readmission (HR = 1.08; 95% CI 1.03 – 1.14, *p* = .004), as shown in Table 8. In addition, a one point increase in stress scale score was associated with a reduction in readmission risk (HR = .94; 95% CI .88 – 1.00, *p* = .04). Among the covariates, PVD was associated with a significantly increased risk of readmission (HR = 1.96; 95% CI 1.07 – 3.59, *p* = .03), and the covariates associated with a trend towards increased readmission risk included age range 65 – 70 years (*p* = .11), age ≥ 71 (*p* = .07) and hypertension (*p* = .12).

Dichotomised DASS scores.

Following analysis with DASS scores as continuous variables, the dichotomised psychological variables were entered into hazard models simultaneously to determine the combined contributions of a mild level of each negative affect construct. The multivariable hazard model showed that baseline dichotomised anxiety was associated with a three-fold increased readmission risk (HR = 3.14; 95% CI 1.66 – 5.94, *p* < .001), supporting the model with continuous data (results shown in Table 8). The adjusted survival function for patients with baseline dichotomised anxiety symptoms in Figure 3 shows divergent survival curves. The dichotomised stress variable was however associated with a reduced readmission risk (HR = .38; 95% CI .17 – .82, *p* = .02). The covariates associated with a nearly two-fold increased risk of readmission included PVD (HR = 1.92; 95% CI 1.06 – 3.50, *p* = .03), and also hypertension (HR = 1.83; 95% CI 1.05 – 3.18, *p* = .03). Covariates associated with a trend towards an increased readmission risk included age range 65–70 years (*p* = .15), age ≥ 71 (*p* = .13), Canadian Cardiovascular Society class III/IV (*p* = .19) and left ventricular ejection fraction 31% – 45% (*p* = .13).

The multivariable hazard model for postoperative dichotomised DASS scores showed that depression was associated with a trend towards increased readmission risk (HR = 2.06; 95% CI .97 – 4.40, *p* = .06). Among the covariates, PVD was associated with a two-fold increased readmission risk (HR = 2.13; 95% CI 1.15 – 3.89, *p* = .02). The covariates associated with a trend towards increased readmission risk included age ≥71 (*p* = .14), CCS class III/IV (*p* = .18) and hypertension (*p* = .11).

Table 8. Multivariable Adjusted Hazard Models of Six Month Readmission With Continuous and Dichotomised Psychological Variables

DASS scores	Hazard Ratio [a]	95% CI	P
Continuous			
Time 1			
Depression	.96	.89 - 1.03	.21
Anxiety	1.12	1.04 - 1.20	.002
Stress	.96	.91 - 1.01	.12
Time 2			
Depression	1.08	1.03 - 1.14	.004
Anxiety	1.00	.94 - 1.07	.95
Stress	.94	.88 - 1.00	.04
Dichotomised			
Time 1			
Depression	.80	.38 - 1.68	.56
Anxiety	3.14	1.66 - 5.94	<.001
Stress	.38	.17 - .82	.02
Time 2			
Depression	2.06	.97 - 4.40	.06
Anxiety	.82	.44 - 1.52	.53
Stress	.77	.34 - 1.78	.55

a. Adjusted for age quartiles, female sex, LVEF, urgency of surgery, chronic lung disease, CHF, diabetes mellitus, PVD, renal disease, previous MI, hypertension, CCS class III/IV and psychoactive medication use
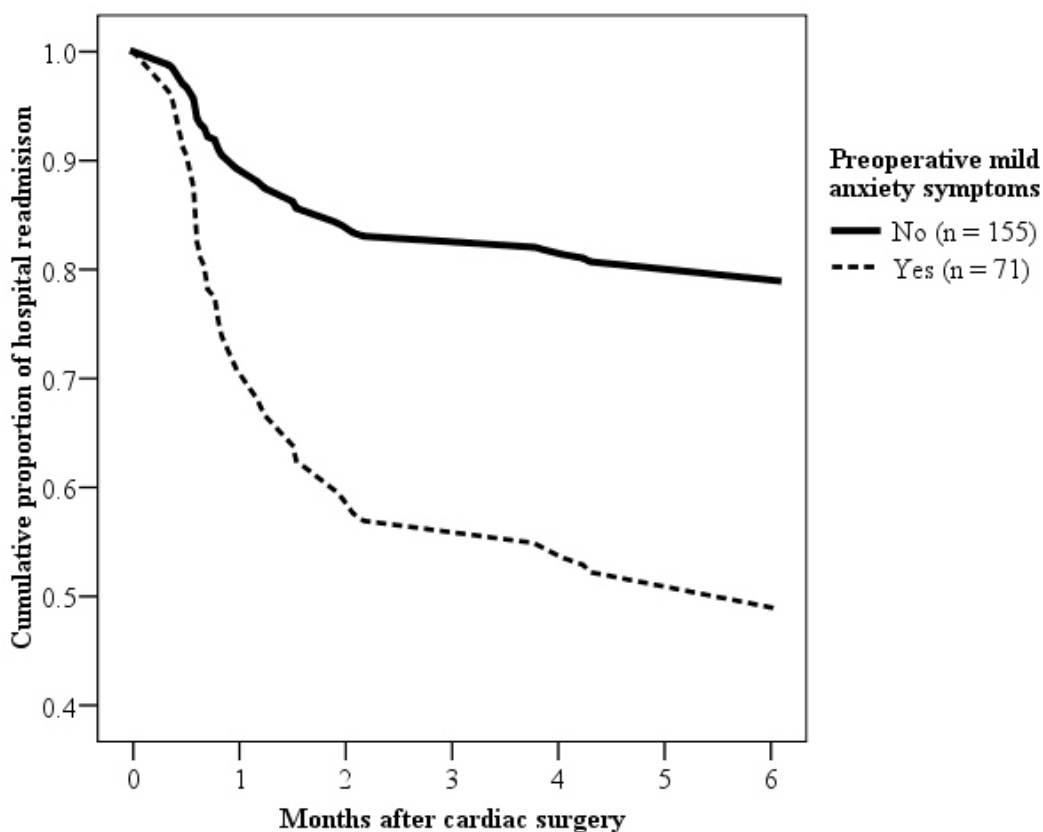
Figure 3. Adjusted Survival Function of Patient Readmission for Preoperatively Anxious and Non-anxious Cardiac Surgery Patients

Legend Figure 3: Coronary artery bypass graft patient adjusted cumulative survival in months after surgery for six-month readmission is plotted for patients with mild anxiety symptoms before surgery (DASS anxiety score ≥ 8; n = 71) against patients without anxiety symptoms before surgery (DASS depression score ≤ 7; n = 155). The Cox-proportional hazard model for preoperative anxiety symptoms is adjusted for age quartiles, female sex, LVEF, urgency of surgery, chronic lung disease, CHF, diabetes mellitus, PVD, renal disease, previous MI, hypertension, CCS class and psychoactive medication use (HR = 3.14; 95% CI 1.66 - 5.94, p <.001).

Secondary Multivariable Analysis Of Hospital Readmissions

In secondary analyses, we repeated the hazard models in the same fashion described above, though we entered stress scores at the second step, followed by depression and anxiety scores at the third step. The aim was to determine whether the risk attributable to depression and anxiety reported in Table 8 was independent of general stress. The results were unchanged and supported significant effects for preoperative anxiety and postoperative depression in both continuous and dichotomised analysis, even after adjustment for stress. Specifically, preoperative anxiety was again associated with a 12%

increased readmission risk in continuous analysis while a three-fold increased risk of readmission was also attributable to preoperative dichotomised anxiety. The results specific to depression also supported an 8% increased readmission risk attributable to a one-point increase in postoperative depression score. A trend was again supported for a two-fold increased readmission risk and postoperative depression in dichotomised analyses. Taken together, the results suggest that the readmission risk attributable to depression and anxiety was upheld after adjustment for the effects of conceptually interrelated general stress symptoms. When stress scores were entered before depression and anxiety, results showed that preoperative stress was associated with a significantly reduced readmission risk in dichotomised analyses (HR = .38; 95% CI .17 – .82, p = .01). Continuous analysis supported a reduced readmission risk attributable to increased postoperative stress and this was again by 6%.

Discussion

The relationship between negative emotions and cardiovascular diseases is one of the most studied in psychosomatic and health research. Readmission following cardiac surgery places a significant burden on the healthcare system (Lubitz, Gornick, Mentnech, & Loop, 1993) and is therefore an important area of study for health resources planning. This research adds to previous studies by using an empirically supported model of depression and anxiety to interpret the association with CABG patient outcomes where an increased risk of readmission was associated with preoperative anxiety and postoperative depression. Both depression and anxiety have been implicated in lower concordance to cardiac rehabilitation programs (Komorovsky et al., 2008) and this may partly explain our findings. However and surprisingly, increased stress lowered the readmission risk in the preoperative and postoperative period in continuous and dichotomised analyses respectively. Overall, the main hypothesis that morbidity would be associated with higher general stress was not supported.

The six-month readmission rate in the present study was 32% and the most common causes were for infections, pleuritic chest pain, respiratory complications, arrhythmia and angina as is consistent with previous readmission studies (Jarvinen et al. 2003; Hannan et al. 2003). The present results lend further support to the role of preoperative anxiety in adverse CABG patient outcomes (Tully, Baker, & Knight, 2008). Our findings suggest that elevated anxious hyperarousal symptoms reported prior to surgery portend greater morbidity risk, although there was no association between postoperative anxiety and morbidity. It is possible that physical anxiety symptoms measured after surgery tap in to general physical

discomfort or autonomic arousal rather than anxious affect (Andrew et al. 2000), suggesting our results are potentially biased towards an effect for baseline anxiety. The findings for anhedonic depression support previous research where post cardiac event depression predicted cardiac related hospital readmission with a mixed cohort of patients after CABG or MI (Levine et al., 1996). Nonetheless, the observation that the DASS variables attained significance in adjusted hazard models, yet only depression and anxiety were bivariately associated with readmission indicates the possible influence of moderator and suppressor variables. The present findings warrant replication given the interrelation between DASS measures and the differential pattern of results perioperatively. One possible explanation for our results is that depression and anxiety may exert a causal influence on each other with each negative emotion more dominant at one particular time point over the perioperative period (e.g. anxiety preoperatively), as has been reported elsewhere in a study employing structural equation modelling (Duits et al., 1999). Another explanation is that the increased risk attributable to depression and anxiety symptoms are perhaps capitalizing on chance variation and require replication in larger samples.

In the present study, an increase in stress postoperatively was paradoxically associated with a 6% reduction in readmission risk when analysed as a continuous variable. The dichotomised analyses also showed that postoperative stress was associated with a reduced readmission risk. While this was a surprising observation, it was possible that patients reporting higher stress, and therefore with lower readmission risk, used problem focused or emotion focused coping strategies (Shelley & Pakenham, 2007) and were more likely to adhere to rehabilitation guidelines and engage in more health promoting behaviours. Nevertheless, our findings may not generalize to other studies as we utilized a definition of stress as general state-NA, the symptoms of which are common to depression and anxiety. This contrasts to previous cardiovascular research where stress is inconsistently defined and measured as other reviewers have noted (Bunker et al., 2003; Holmes, Krantz, Rogers, Gottdiener, & Contrada, 2006). For example, stress may be operationalised to include muscle tension and autonomic arousal that overlaps anxious symptomatology. Thus, there are limited studies to directly compare our results with, although the underlying general NA construct as we have defined here parallels the trait NA that forms part of the Type-D personality construct. Future studies would be required to clarify the role of NA, as some research suggests that trait NA, in combination with the tendency to inhibit one's expression of negative emotions in social situations (i.e. Type-D personality), is predictive of cardiac outcomes and not merely the presence of NA in isolation (Denollet et al., 1996; for review see Denollet & Van Heck, 2001). Thus future research should consider whether state or trait NA is a predictor of morbidity among CABG candidates, and explore the association with coping strategies.

The present findings contrast to previous studies with CABG patients where it has been found that preoperative depressive symptoms measured with two items from the medical outcomes study health questionnaire are associated with all-cause readmissions (Saur et al., 2001). Also, Oxlad et al. (2006a) found that preoperative depression and postoperative anxiety, measured with the DASS, increased the risk for cardiac readmissions adjusted for time spent on cardiopulmonary bypass. The difference in findings may be partly explained by variation in methodology. For example, Oxlad et al (2006b; 2006a) measured depression and anxiety symptoms, but not general stress, on average 50 days before surgery and only recorded CHD readmissions. Whereas in this study we assessed mood in the week preceding CABG surgery and included surgery related readmissions (e.g. infections, atypical chest pain). Furthermore, the recent study of Oxlad et al. (2006a) did not control for medical comorbidity in hazard models. This may confound results as it has been previously reported that CABG patients may endorse depression and anxiety items due to physical discomfort rather than emotional disturbance (Andrew et al. 2000). Given the paucity of research on this important outcome variable, further research is required to determine the impact of these negative emotions and the role of somatic symptoms on hospital readmission. It is largely unknown whether the DASS variables are related to other outcomes such as quality of life, graft patency and repeat revascularization in CABG populations, and further research should explore such endpoints.

The present findings have important practical and theoretical implications. Indeed, these results suggest interventions should target both anxiety and depression symptoms, rather than either in isolation. There are few RCTs to treat depression and anxiety post-CABG, with one nurse led intervention paradoxically associated with more readmissions compared to a control group (Lie et al. 2007), while another reported lower depression levels in the control group compared to the intervention group whom underwent exercise and behaviour modification (Sebregts et al. 2005). Recently, a nurse led cognitive-behavioural intervention demonstrated greater depressive symptom reduction at three months though at six months there was modest difference (Doering, Cross, Vredevoe, Martinez-Maza, & Cowan, 2007). The findings of a diverse range of RCT interventions for anxiety (e.g. education, phase I rehabilitation, telenursing) have also been inconsistent with some interventions associated with lower anxiety (Ku, Ku, & Ma, 2002; Sorlie, Busund, Sexton, Sexton, & Sorlie, 2007), while others have reported no treatment effects (Shuldham, Fleming, & Goodman, 2002; Tranmer & Parry, 2004). Interventions targeting general stress or NA are limited with a recent notable exception reported by Karlsson and colleagues (2007) who showed that patients randomised to expanded cardiac rehabilitation after MI or CABG had reduced depression, anxiety and Type-D personality trait scores. Several RCT

interventions have targeted depression following a myocardial infarction with anti-depressant medication or cognitive-behavioural intervention with reductions in mood but not mortality (Berkman et al. 2003; Glassman et al. 2002). It is not known whether these results will necessarily translate to patients undergoing an invasive surgical revascularization procedure such as CABG. Regardless, reducing emotional distress before and after CABG is likely to be important to an uncomplicated physical recovery and improved subjective quality of life. The prevalence of major depression is widely reported to be around 20% among CABG patients (Connerney et al., 2001; Fraguas Junior et al. 2000) though the prevalence of clinically relevant anxiety varies between 8.3% and 55% depending on the type of self-report measure or diagnostic interview (Rafanelli, Roncuzzi, & Milaneschi, 2006; Rothenbacher et al., 2007; Rothenhausler et al., 2005; Rymaszewska, Kiejna, & Hadrys, 2003). These patients may benefit from individually tailored psychological and rehabilitation support to maintain health promoting behaviours and educate patients (Hermele, Olivo, Namerow, & Oz, 2007; Rozanski et al., 1999). Given the present findings, it could be argued that distressed CABG patients may benefit from an intervention targeting negative emotions and fostering useful coping strategies commenced before scheduled surgery and maintained in the postoperative period alongside cardiac rehabilitation with lengthy follow-up.

This study's main strength is that we have interpreted the contribution of negative affect to readmission outcomes using a theoretical framework supported by empirical research. Secondly, this study has also adopted blinded coding of hospital readmissions. One limitation of this study is however that the DASS may not capture the full breadth of symptomatology endorsed by the tripartite model (Crawford & Henry, 2003), and that the symptoms of other pertinent negative emotions such as anger and hostility were not measured (Kubzansky et al., 2006). We did not gather any information from patients on non-pharmacological treatments such as visiting a psychologist or psychiatrist or attendance at cardiac rehabilitation. In addition, this study was performed on patients recruited from a single hospital site with 72 endpoints. The study would have been underpowered to determine large differences in analyses with dichotomised variables, while the hazard models with adjustment for numerous covariates are potentially biased according to regression model criteria (Babyak, 2004). Furthermore, we have excluded patients with dementia and those undergoing emergency surgery or a concomitant procedure, suggesting our results may not necessarily generalize to higher risk populations. We also draw the reader's attention to this study's endpoint inclusive of non-CHD related readmissions (e.g. infection, respiratory complications) when interpreting these findings.

In conclusion, this preliminary study showed that preoperative physiological hyperarousal anxiety symptoms and postoperative anhedonic depressive symptoms are

associated with a significantly increased risk of readmission following CABG. Further research should investigate the role of tripartite factors in cardiac outcomes, and explore the association with different coping styles. These findings highlight the need to develop suitable interventions for anxiety and depression before and after CABG surgery.

Chapter V Study Three

Negative Emotions and Quality of Life Six Months After Cardiac Surgery: The Dominant Role Of Depression Not Anxiety Symptoms

Statement of contributors

Phillip Tully (*Candidate*)

Responsible for study conception, literature review, data analysis, manuscript drafting and preparation, manuscript submission, response to reviewers and revisions.

Signed: Date: 4/01/2011

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We provided ongoing supervision throughout the research programme that lead to this publication and there was ongoing collaboration between Mr. Tully and us in refining the direction of the research. Mr. Tully was responsible for writing this paper; our role was to comment on drafts, make suggestions on the presentation of material in the paper, and to provide editorial input. We also provided advice on responding to comments by the journal reviewers and editor. We hereby give our permission for this paper to be incorporated in Mr. Tully's submission for the degree of Doctor of Philosophy from the University of Adelaide.

Signed: Robert Baker   Date: 4/01/2011

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Signed: Helen Winefield   Date: 4/01/2010

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Abstract

The specific syndromal aspects of depression and anxiety have not been explored in relation to changes in health related quality of life after cardiac surgery. The purpose of this study was to examine the impact of general stress, depression and anxiety on health related quality of life after coronary artery bypass graft (CABG) surgery. Utilising a tripartite conceptual model of depression and anxiety, it was hypothesised that general stress symptoms, rather than unique depressive or anxious symptoms, would be associated with lower health related quality of life six months after CABG surgery. Elective CABG patients (n = 226) completed baseline and postoperative self-report measures of negative emotions and health related quality of life, and 193 patients completed these measures at six-month follow-up. Multiple linear regression analyses and logit link analyses were performed to test the hypothesis. Elevated depression symptoms before and after surgery showed an association with lower and worse health related quality of life for vitality and social role functioning and physical and general health. This study adds to previous research by outlining discrete associations between specific health related quality of life domains, and is perhaps the first to test a theoretical model of depression and anxiety in relation to cardiac CABG patients' perceptions of health related quality of life. These findings encourage further research on negative emotions and health related quality of life in cardiac surgery patients and the practical implications of these findings are discussed.

Introduction

Coronary artery bypass graft surgery is a commonly performed cardiothoracic revascularization procedure to treat coronary artery disease CAD (Eagle et al., 2004; Morrow et al., 2005). While physical impairments and activity restrictions are common in the immediate postoperative period, patients reporting unipolar depressive symptoms tend not to exhibit improvements in health related quality of life in the longer term (Goyal et al., 2005; Mallik et al., 2005; Perski et al., 1998; Ruo et al., 2003; Stafford et al., 2007). Given that the global burden of heart disease and unipolar depression is predicted to exceed all other medical illness by year 2020 (Murray and Lopez 1997), this anticipated morbidity burden underscores the importance of accurately identifying the specific aspects of psychological distress that have a deleterious impact on health related quality of life. This may facilitate early intervention and ultimately improve health related quality of life for many patients (Doering et al., 2007).

The nebulous term health related quality of life is a multidimensional construct comprised of physical, mental and social aspects of health and the ability to perform everyday activities including socially and occupationally (Bosworth et al., 2000; Boudrez & De Backer 2001; Wilson & Cleary 1995). These aspects of health related quality of life are not only important indicators of surgical success but are salient to patients.

The etiological and prognostic role of depression in adverse CAD morbidity outcomes has been supported by two independent consensus panels (Ballenger et al., 2001; Davidson et al., 2006). Despite sharing substantial conceptual and symptom overlap with depression, the role of anxiety in CAD has been researched less extensively though recent studies support an association to outcomes such as health related quality of life among others (Hemingway & Marmot 1999; Höfer et al., 2005; Kubzansky et al., 2006; Rothenbacher et al., 2007; Tully et al., 2008a). The accumulating evidence implicating anxiety in morbidity coincides with two independent reviews that concluded conceptualisations of psychological distress should be refined to accommodate the related symptoms shared by anxiety and depression when studying health related quality of life in CAD (Duits et al., 1997; Suls & Bunde 2005). Specifically, Suls and Bunde (2005) and later Stafford et al. (2007) declared that a common disposition towards NA might underlie the purported psychogenic links with CAD morbidity and health related quality of life.

The recommendation to develop sophisticated disease-affect models parallels theoretical conceptualisations of depression and anxiety that emphasized the importance of

unique and common symptoms to better differentiate these overlapping negative emotions. In their seminal paper, Clark and Watson (1991) posited that depression and anxiety share a common disposition towards general NA that is associated with neuroticism, the symptoms of which may include distress, worry, pessimism and irritability (Watson, 2000). This model also specified that anxiety symptoms exclusively reflect physical hyperarousal and somatic tension (e.g., trembling, shakiness) whereas depressive symptoms are uniquely characterized by anhedonia (i.e., the loss of interest or pleasure) and the absence of positive affectivity (PA) and typical symptoms include hopelessness, crying and suicidal ideation (Clark & Watson, 1991). Although the diagnostic implications of the tripartite model were subsequently expanded upon (Mineka, Watson & Clark, 1998), the original latent symptom structure has been supported in psychiatric and community samples (Cook et al., 2004; Teachman et al., 2007; Watson et al., 1995a, 1995b) and cardiac populations (Marshall et al., 2003). Importantly, among CAD populations there has been minimal theory development or integration of existing empirical data into theoretical models (Dreher 2004; Höfer et al., 2005) in a burgeoning field where review articles are published as frequently as etiological and prognostic studies (Frasure-Smith & Lespérance, 2005). Therefore, the inclusion of theoretically driven research on CAD patient outcomes is requisite to foster novel understandings of disease-affect relationships in behavioural medicine, and to date this remains a major shortcoming and warranted criticism of the field (Dreher, 2004).

In light of the theoretical structure of depression and anxiety, a limitation of CABG health related quality of life research is that typically only depression is assessed thus confounding estimates of effect size by precluding the role of conceptually related and overlapping affective states, namely anxiety. It is also possible that limited gains in health related quality of life previously attributed to depression or anxiety were confounded by general and therefore non-differentiating NA symptoms within poorly constructed self-report measures (Clark & Watson, 1991). Specifically, the Hospital Anxiety and Depression Scale and State-Trait Anxiety Inventory have been demonstrated to contain a large component of NA, thus compromising the psychometric validity of these scales (Barth & Martin 2005; Caci, Bayle, Dossios, Robert, & Boyer, 2003; Martin et al., 2003). Therefore, it is necessary to explore the roles of the unique and discriminating aspects of depression and anxiety on CAD patient outcomes by accounting for the general influence of NA (Kubzansky & Kawachi 2000) and this study attempts to fill such a gap in the literature. A second limitation of CABG research is that typically aggregate health related quality of life scores are analysed, thus neglecting discrete patterns of association with individual health related quality of life domains. Indeed, studies with the methodological limitations noted above are likely to neglect sensitive associations with health related quality of life that may inform patient centred rehabilitation, education and intervention practices.

To overcome these shortcomings of previous CABG studies we propose to explore whether individual health related quality of life domains are predicted by psychometrically distinct measures of depressive and anxious symptoms and NA, in this study measured as general stress, utilising the tripartite model (1991) as a theoretical framework. Consistent with recent review evidence (Stafford et al., 2007; Suls & Bunde 2005), it was hypothesized that the symptoms of general stress, theoretically linked to NA, would remain significantly associated with lower health related quality of life six months after CABG surgery rather than anxiety and depression, when all three psychological variables are taken into account.

Methods

Patients

The patient sample for this study consisted of first time CABG surgery patients between January 1999 and December 2005 at the Flinders Medical Centre, a public hospital in Adelaide, South Australia, as reported previously (Tully et al., 2008a). Briefly, 681 CABG cases were evaluated for enrolment in the study after satisfying the inclusion criteria of age > 18 years, isolated CABG procedure with cardiopulmonary bypass, able and willing to provide informed consent. There were 443 patients excluded from the study as depicted in Figure 4, of whom 53 had declined to participate (22.3% refusal rate). A total of 238 patients were recruited at baseline, with patients excluded from final analysis for the following reasons; death before surgery (n = 1), surgery postponed indefinitely (n = 3), switched to surgery without cardiopulmonary bypass intraoperatively (n = 8). Due to patient dropout, 33 (14.6%) baseline recruited patients did not complete six month follow-up for the following reasons; deceased before 6 months (n = 1), refused (n = 15), health reasons (n = 8), lost to follow-up (n = 7) and other reasons (n = 2), leaving a final sample of n = 193 for analysis. All patients provided written informed consent and this study had received ethics approval from the respective hospital and university institutions. Patients completed self-report measures of health related quality of life and psychological distress in the week preceding scheduled surgery, and patients completed the psychological distress measure again after surgery on the hospital ward. Patients were contacted via mail out with reply paid envelope six months after surgery to complete the follow-up measures.

Eligible for recruitment
(n = 681)

Excluded (n = 443):

Residency outside South Australia (n = 156)
Language, reading, writing or vision difficulty (n = 82)
Emergency surgery (n = 60)
Refused (n = 53)
Dementia or confusion with Short Portable Mental Status
Questionnaire (SPMSQ) (n = 27)
Participating in another cardiac surgery study (n = 26)
Other (n = 14)
Unable to give informed consent (n = 12)
Psychotic, personality or developmental disorder (n = 8)
Health reasons (n = 5)

Consenting patients preoperatively
(n = 238)

Excluded before baseline (n=12):

Death (n = 1)
Surgery postponed indefinitely (n = 3)
Intraoperative change to off pump (n = 8)

Completed baseline assessment
(n=226)

Excluded by six months (n=33):

Death (n=1)
Refused (n=15)
Health reasons (n=8)
Lost to follow-up (n=7)
Other (n=2)

Completed six month assessment
and included in final analysis
(n = 193)

Figure 4. A Flow Chart of the Patients Throughout the Study Recruitment Period

Psychological Distress Measure

Psychological distress symptoms were measured with the DASS (Lovibond & Lovibond, 1995a, 1995b), a 42 item self-report measure that consists of three scales (depression, anxiety and stress) (Lovibond, 1998). Participants were asked to rate how often they experienced each symptom over the preceding week on a four point likert-type scale, and higher scores indicate greater psychological distress. Examples of depression scale items include ''I couldn't seem to experience any positive feeling at all'' and ''I just couldn't seem to get going.'' The anxiety scale contains such items as ''I felt scared without any good reason'' and ''I felt I was close to panic.'' The stress scale includes items such as ''I tended to over-react to situations'' and ''I found myself getting impatient when I was delayed in any way.'' The DASS has excellent psychometric properties including a uniform factor structure, high internal consistency and test retest reliability (Clara et al., 2001; Crawford & Henry 2003), and has previously been used among cardiac surgery patients (Andrew et al., 2000).

Lovibond and Lovibond (1995b) developed the DASS with the intention to maximally discriminate depression and anxiety symptoms and this is analogous to the tripartite model's principals. Confirmatory factor analysis has supported a latent tripartite structure of anhedonia, physiological hyperarousal and general distress factors (Brown et al., 1997a; Clara et al., 2001). Notably, confirmatory factor analysis of the DASS responses among n = 4,039 school aged adolescents showed that stress was synonymous with NA as a stress factor distinct from NA could not be extracted due to a linear dependency between these latent factors (Tully, Zajac, & Venning, 2009). By permitting all DASS items to load on the NA factor, correlations between depression and anxiety factors reduced from $r = .90$ to $r = .32$ for younger adolescents and from $r = .83$ to $r = .27$ for older adolescents, suggesting the NA factor is reflective of variance common to both anxiety and depression.

Though principally designed as a state-affect measure, the DASS scales correlates well with the trait dimensions of NA and PA as measured with the Positive and Negative Affect Schedule. For example, the DASS depression scale has been shown to correlate highest with the PA scale of the Positive and Negative Affect Schedule compared to the DASS anxiety and stress scales among clinical ($r = -.45$) (Brown et al., 1997a) and non-clinical samples ($r = -.48$) (Crawford & Henry 2003). With respect to the DASS stress scale, this scale correlated highest to Positive and Negative Affect Schedule-NA among the clinical ($r = .72$) (Brown et al., 1997a) and non-clinical populations ($r = .67$) (Crawford & Henry 2003). In addition, the DASS scales tap into affective constructs that are temporally stable over time as reported by Lovibond (1998) who administered the scale to n = 822 university students with three to eight years follow-up. Specifically, correlations between the depression, anxiety,

and stress scales with their respective follow-up measure were significant, $r = .29$, $r = .41$ and $r = .39$, respectively, (all $p < .01$) supporting the temporal stability of the DASS.

Quality of Life Measure

Health related quality of life was measured using the SF-36 (Ware 1993), a self-report instrument with validated psychometric properties that measures generic health status (McHorney et al., 1993). The SF-36 consists of eight scales assessing physical functioning, bodily pain, and perception of ability to perform physical, emotional, and social role functions, as well as sense of vitality and of mental and general health. These broad dimensions are consistent with the recommendations of the World Health Organization (WHOQOL Group, 1993) for a generic health related quality of life instrument, and the SF-36 has been endorsed as a reliable and valid measure to assess subjective health related quality of life among cardiac patients (Dempster & Donnelly, 2000). The individual items that comprise each of the eight quality of life domains measured by the SF-36 were summed and transformed in the prescribed fashion (Ware, 1993). Each SF-36 scale has a mean of 50 and a SD of 10, and higher scores indicate improved quality of life. Despite the overlap of health related quality of life measures such as the SF-36 mental health and emotional role subscales with depression and anxiety, we pursued analysis of associations between these variables to remain consistent with other research (Al-Ruzzeh et al., 2005; Beck, Joseph, Belisle, & Pilotte, 2001; Denollet, Vaes, & Brutsaert, 2000; Goyal et al., 2005).

Statistical Analysis

Data analyses were performed with SPSS 15.0 software package (SPSS Inc., Chicago, IL). Patients completing the study were compared to those unavailable for assessment on baseline demographic and self-report measures. Quantitative data were compared with independent samples t-tests or Mann–Whitney U-tests, while categorical data were analysed with the χ^2 statistic and Fisher's two-tailed exact test as appropriate. The normality of distributions for continuous variables was checked with the one-sample Kolmogorov–Smirnov test.

To examine the association between stress, depression and anxiety with 6 month health related quality of life ratings, a series of multivariable linear regressions were performed. The aim was to determine whether the dimensions of the tripartite model as measured by the DASS (independent variables) were associated with six month health related quality of life (dependent variables), adjusted for relevant clinical, demographic and

surgical covariates. The preoperative and postoperative psychological DASS scores (continuous variables) were analysed separately. A series of univariable regression analyses also examined each DASS subscale in isolation as a predictor of SF-36 with adjustment for covariates to determine the non-partialled effects.

The following covariates were selected from previous CAD health related quality of life research (Chocron et al., 2000; Falcoz et al., 2003; Goyal et al., 2005; Höfer et al., 2005; Mallik et al., 2005; Panagopoulou, Montgomery, & Benos, 2006; Perski et al., 1998; Rumsfeld et al., 2004; Ruo et al., 2003). The binary coded variables (0 = no; 1 = yes) included; female sex, hypertension, urgent surgery (versus non-urgent surgery), history of tobacco smoking, chronic lung disease, congestive heart failure, hypercholesterolemia, PVD, diabetes mellitus, renal failure, an acute myocardial infarction $\leq$ 30 days, revascularization without use of left internal mammary artery, postoperative encephalopathy or stroke and unplanned cardiovascular or surgery related hospital readmission (Tully et al., 2008a). Age was examined as a continuous variable and preoperative SF-36 scores for each respective scale were also entered as covariates. All medical data was collected prospectively from resident medical officers and surgical staff.

For each binary covariate, six month health related quality of life functioning was tested for its relationship to the variable of interest, and age was analysed as a continuous variable. All abovementioned covariates were entered in block fashion at the first step of the regression regardless of significance, followed by the continuous stress score at the second step, with depression and anxiety scores entered at the third step. The analysis strategy was planned to determine whether depression and anxiety were associated with health related quality of life beyond the variance attributable to stress. To avoid multicollinearity, tolerance, the variance inflation factor and eigen values were used to measure the strength of the linear relationships between the independent variables; a tolerance value of $\geq$ 0.2 and/or variance inflation factor $\leq$ 4 and/or an eigen value >.01 was regarded as acceptable. There were two scales that did not meet the requirements for linear analysis: role emotional and role physical. These data were analysed according to a binomial distribution with the generalized linear model logit link function and data are presented as OR's and CI's with adjustment for covariates (Bosworth et al., 2000). Both multivariable and univariable analyses were examined.

Results

The final patient sample (n = 193) consisted primarily of males (82.4% of total) and the mean age was 62.9 (SD = 9.5) (see Table 9 for final sample descriptives). Comorbid risk factors such as hypertension, hypercholesterolemia and tobacco smoking were evident in more than half of the sample (61.1, 71.8 and 66.8% of total respectively). Patients not available for follow-up at 6 months (n = 33) were found to have longer hospital length of stay (M = 7.6, SD = 5.9) than those completing six month assessment (M = 5.7, SD = 1.4, p = .07) and these results are shown in Table 9. The unavailable patients were also more likely to have tobacco smoking history (87.9 vs. 66.8%, p = .02), and diabetes (33.3 vs. 18.7%, p = .06). The patients not completing the study tended to spend more time in intensive care unit and have longer overall hospital stay, while evidence of encephalopathy was higher in this group (2.1 vs. 15.2%, p < .01). Patients not available for assessment at six months were found to have generally comparable scores on both the SF-36 and DASS at baseline, all p > .05 (results not shown). In this sample, internal consistency was favourable for the depression anxiety and stress scales (see Table 10) and inspection of the correlations suggest moderate to strong interrelation between the scales before and after surgery.

Table 9. Comparison of Baseline Demographic, Clinical and Surgical Variables Between Patients Able and Unable to Complete the Study (n = 226)

Descriptive variables [a]	Completed study (n = 193)		Unable to complete study (n = 33)		P
Demographic and clinical					
Female sex	34	(17.6)	4	(12.1)	.44
Mean age (*SD*)	62.9	(9.5)	64.3	(10.9)	.46
Urgent surgery	30	(15.5)	8	(24.2)	.22
Canadian Cardiovascular Society Angina class	54	(28.0)			
I			5	(15.2)	
II	73	(37.8)	17	(51.5)	
III	36	(18.7)	4	(12.1)	
IV	30	(15.5)	7	(21.2)	.23
Acute myocardial infarction <30 days	16	(8.3)	3	9.1%	.88
Congestive heart failure	14	(7.3)	2	(6.1)	.81
Left ventricular ejection fraction					
normal ≥60%	143	(74.1)	23	(69.7)	
Mild 45 – 59%	32	(16.6)	6	(18.2)	
moderate 30 – 44%	13	(6.7)	4	(12.1)	
Severe ≤ 29%	5	(2.6)	0	0	.56
Hypertension	118	(61.1)	21	(63.6)	.79
Hypercholesterolemia	135	(71.8)	21	(65.6)	.48
PVD	27	(14.0)	8	(24.2)	.13
Diabetes	36	(18.7)	11	(33.3)	.06
Renal disease	4	(2.1)	1	(3.0)	.55
Tobacco smoking history	129	(66.8)	29	(87.9)	.02
Chronic lung disease	37	(19.2)	7	(21.2)	.78
Surgical and hospital parameters					
Number anastomoses ≥ 3	100	(51.8)	15	(45.5)	.50
Left internal mammary graft	172	(89.1)	1	(3.0)	.21
Median procedure time (mins) (interquartile range)	145.0	(113-170)	155.0	(118-168)	.82
Median cardiopulmonary bypass time (mins) (interquartile range)	53.0	(42-68)	55.5	(42-66)	.84
Median complete cross-clamping time (mins) (interquartile range)	31.5	(23-42)	30.0	(15-37)	.17
Median time in ICU (hours) (interquartile range)	23.0	(23–26)	24.0	22-45	.03
Median length of hospital stay (days) (interquartile range)	5.0	(5-6)	6.0	5-7	.04
Postoperative stroke or encephalopathy	4	(2.1)	5	(15.2)	<.01
Unplanned hospital readmission	59	(30.6)	13	(39.4)	1.32

a. all data are presented as N (%) unless otherwise indicated

Table 10. Internal Consistency and Correlation Coefficients for Depression, Anxiety and Stress

	1.	2.	3.	4.	5.	6.
Baseline						
1. Depression	(.87)					
2. Anxiety	.77	(.80)				
3. Stress	.75	.73	(.92)			
Postoperative						
4. Depression	.52	.44	.42	(.94)		
5. Anxiety	.44	.52	.46	.73	(.86)	
6. Stress	.54	.52	.55	.75	.79	(.94)

Cronbach's alpha shown in parentheses

Quality of Life

The association between preoperative DASS scores and SF-36 subscales at six months analysed with multivariable linear regression is shown in Table 11. A negative Beta value suggests higher and worse distress measured with the DASS is associated with lower SF-36 scores and therefore worse health related quality of life at six months.

Preoperative psychological distress and six month quality of life: multivariable analyses.

The final regression model for the vitality scale accounted for 27% of variance, and the only significant covariate was the baseline vitality score that accounted for 1.2% of variance (β = .12, p < .05). Among the psychological predictors, increased and worse depression scores were significantly associated with lower and therefore worse vitality scores (β = -.35, p < .01) and accounted for 1.7% of the variance, though no effect was supported for stress or anxiety. For bodily pain, the regression model explained 25% of variance, though the only significant covariate was baseline bodily pain scores that explained 11.0% of variance (β = .41, p < .001), and no psychological scale scores were significantly associated with bodily pain. The final model for social role functioning explained 25% of variance, and patients with hypercholesterolemia had lower scores on this SF-36 scale at six months, (β = -.16, p = .03) and this variable explained 2% of the variance. At step two stress was associated with social role (β = - .29, p <.001) and replaced by an effect for preoperative depression scores at six months, (β = -.47, p <.001) and explained 6.6% of the variance, and anxiety was not significant. The general health model accounted for 32% of variance; age (β = -.15, p = .04) explained 1.8% of variance, baseline general health scores (β = .08, p <.001)

explained 6.8% of variance. An effect for stress at step two (β = -.27, p <.001) was replaced by a significant effect for depression scores that explained 2.9% of variance (β = -.32, p =.008), and anxiety was not significant in the model.

The mental health scale regression explained 39% of variance, and baseline scores specifically accounted for 7.7% of the variance (β = .08, p <.001). Patients with hypercholesterolemia were also found to have worse mental health scores (β = -.24, p = .05) though this variable explained only 1.3% of variance. Stress was associated with mental health scores (β = -.16, p = .05) though this effect was reduced and none of the baseline DASS scales were associated with SF-36 mental health at the final step. With regards to the physical health subscale, this model explained 36% of variance. Among the covariates, age was a significant predictor (β = -.26, p <.001) and explained 5.4% of variance, congestive heart failure (β = -.23, p = .001) explained 4.2% of variance, and acute myocardial infarction (β = -.13, p = .05) accounted for 1.4% of variance. Among the psychological predictors, stress was significant at step two (β = -.17, p = .01), but replaced by an effect for depression scores that explained 1.7% of variance (β = -.23, p = .04), and anxiety was not significant in this model.

Preoperative psychological distress and six month quality of life: univariable analyses.

The univariable regression results were largely unchanged with respect to depression that was a significant predictor of vitality, social role, physical health and general health (data not shown). Despite not being significant in multivariable analyses, anxiety when examined in isolation was a significant predictor of social role functioning (β = -.25, p < .01) and general health (β = -.18, p = .01). Significant effects were also found for stress on social role functioning (β = -.29, p < .001) and general health (β = -.29, p < .001.) and these results can be observed in Table 10 at step two, though they did not remain significant when depression was entered into the model. These results suggest that preoperative depression, anxiety and stress influence social role and general health, however when considered simultaneously the effect for depression remains the strongest predictor of limitations in these health related quality of life domains.

Table 11. Multivariable Linear Regression for Quality of Life after Cardiac Surgery Associated with Baseline Negative Emotions
(n = 193)

SF-36 Scale [a]	Step 1 R^2	Step 2 R^2	R^2 change	Stress (β)	Step 3 R^2	R^2 change	Covariates [b, c] Intraoperative and medical	Stress (β)	Depression (β)	Anxiety (β)	$F_{(19, 192)}$
Vitality	.22	.23	.01	-.07	.27	.04	-	-.08	-.35**	.14	3.35***
Bodily pain	.23	.24	.01	-.04	.25	.01	-	-.10	-.21	.03	3.02***
Social role	.12	.18	.06	-.29***	.25	.07	Hypercholesterolemia*	-.07	-.47***	-.16	3.00***
Mental	.36	.37	.01	-.16*	.39	.02	Hypercholesterolemia*	-.20	-.16	.18	5.70***
Physical health	.30	.33	.03	-.17*	.36	.03	Age*** CHF** Recent MI*	-.11	-.23*	-.12	5.05***
General health	.23	.29	.06	-.27***	.32	.03	Age*	-.21	-.32**	.23	4.26***

*p <.05, ** p <.01, p <.001***

a. Results for the non-normally distributed role emotional and role physical scales are shown in Table 12

b. only significant covariates listed

c. baseline SF-36 was significant in all models (p<.05)

Postoperative psychological distress and six month quality of life: multivariable analyses.

The postoperative multivariable results are shown in Table 12. The regression model for general health explained 27% of variance in total, and was predicted by baseline general health scores (β = .40, *p* <.001) that explained 12.6% of variance. The covariates stress was significant at step two (β = -.19, *p* = .009) and explained 2.9% of variance in the total scores, but this effect was not upheld with the inclusion of depression and anxiety, and no psychological predictors were significant. The pain subscale was predicted only by baseline pain scores (β = .43, *p* = <.001), and this predictor accounted for 15.2% of variance, with the total model explaining 25% of variance, though again no psychological predictors were significant. The physical health scale regression model explained 33% of variance. Age was a significant predictor explaining 4.4% of variance (β = -.24, *p* <.001), congestive heart failure explained a further 4.0% of variance (β = -.23, *p* <.001), and baseline physical health scores explained 3.5% of variance, (β = .23, *p* .003). Postoperative depression explained 1.8% of variance (β = -.25, *p* = .03) and no effect was evident for stress or anxiety.

The vitality model accounted for 27% of the variance, and baseline scores accounted for 10.9% of the variance (β = .38, *p* <.001), and depression predicted another 3.6% of variance (β = -.35, *p* <.01), while stress and anxiety were not significantly associated with vitality. The social role function model explained 20% of variance and baseline scores accounted for 2.8% of the variance (β = .18, *p* = .02), while hypercholesterolemia accounted for 2.2% (β = -.17, *p* = .03). At step two of the model stress explained 3.1% of the variance in social role (β = -.19, *p* = .01), though this effect was not maintained when depression was added to the model and postoperative depressive symptoms explained 5.3% of variance (β = -.43, *p* <.001), while no effect was evident for anxiety. For mental health, the model explained 37% of variance, and patients with hypercholesterolemia had worse quality of life with this variable explaining 1.4% of variance (β = -.14, *p* = .05). Baseline mental health scores accounted for 21.1% of variance (β = .54, *p* <.001), though none of the DASS scales were associated with six month mental health scores.

Table 12. Multivariable Linear Regression for Quality of Life after Cardiac Surgery Associated with Postoperative Negative Emotions
(n = 193)

SF-36 Scale [a]	Step 1 R^2	Step 2 R^2	R^2 change	Stress (β)	Step 3 R^2	R^2 change	Covariates [b, c] Intraoperative and medical	Stress (β)	Depression (β)	Anxiety (β)	$F_{(19, 192)}$
Vitality	.22	.23	.01	-.08	.27	.04	-	-.16	-.35**	-.05	3.40***
Bodily pain	.22	.23	.01	-.11	.25	.02	-	-.23	-.16	-.11	3.02***
Social role	.12	.15	.03	-.19**	.20	.05	Hypercholesterolemia*	-.01	-.43***	-.19	2.27**
Mental	.35	.36	.01	-.02	.37	.01	Hypercholesterolemia*	-.01	-.11	.14	5.27***
Physical health	.30	.31	.01	-.03	.33	.02	Age** CHF**	-.23	-.25*	-.08	4.46***
General health	.23	.26	.03	-.19**	.27	.01	Age*	-.09	-.21	-.09	3.34***

*p<.05, ** p<.01, *** p <.001
a. Results for the non-normally distributed role emotional and role physical scales are shown in Table 12
b. Only significant covariates listed
c. Baseline SF-36 was significant in all models (p < .05)

Postoperative psychological distress and six month quality of life: univariable analyses.

The independent of depression on health related quality of life was evident for vitality, social role and physical health in univariable analyses while an effect was also evident for general health (β = -.21, *p* =.002) that was not supported by the multivariable analysis above. Other discrepant results among univariable results were evident for postoperative anxiety that was associated with social role functioning β = -.15, *p* =.05 and general health (β = -.15, *p* = .03), as was the case with baseline anxiety scores. The significant effect of postoperative stress on social role and general health in univariable analysis was not supported by the multivariable analysis.

Non-linear regression analyses: multivariable.

The non-linear SF-36 scales are presented in Table 13. A negative and significant beta weight for DASS variables would suggest that increased negative emotional symptoms are associated with lower and therefore worse health related quality of life measured with the SF-36. The baseline analysis of emotional role functioning suggested that increased age (OR = .98; 95% CI .97 - 1.00, *p* = .05) and hypercholesterolemia (OR = .69; 95% CI .48 - .99, *p* = .04) were associated with poorer emotional role functioning, and baseline depression scores were also significant in this model, though anxiety and stress were not. This was not the case when postoperative DASS scores were analysed and only diabetes was associated with poorer emotional role functioning (OR = .66; 95% CI .44 - .98, *p* = .04) and no psychological variables. Multivariable analysis of physical role function showed that worse physical role functioning was associated with age (OR = .96; 95% CI .94 - .98, *p* <.001), hypercholesterolemia (OR = .51; 95% CI .36 - .72, *p* <.001), PVD (OR = .45; 95% CI .28 - .70, *p* <.001), chronic lung disease (OR = .64; 95% CI .43 - .93, *p* = .02), and also depression among the psychological predictors, but not anxiety or stress. In postoperative analysis, no DASS predictors were significant in the model and the results for covariates were largely unchanged, suggesting medical comorbidity accounts for limitations in physical role.

Non-linear regression analyses: univariable.

Univariable analysis of emotional role suggested that each baseline DASS scale was significantly associated with poorer functioning, whereas multivariable analysis only supported depression. Postoperative DASS scores were not associated with emotional role, supporting the multivariable analysis. When physical role function was analysed, all baseline DASS scales were associated with poorer health related quality of life, though the multivariable analysis attenuated these effects so that only depression remained significant. Univariable analysis with postoperative DASS scores suggested that no scales were significantly associated with physical role, supporting the multivariable analysis.

Table 13. Multivariable Regression Analyses for Non Normally Distributed SF-36 Scales (n = 193)

	B	Odds Ratio	Lower 95% CI	Upper 95% CI	*P*
Role emotional					
Baseline					
Stress	.01	1.01	.97	1.04	.75
Depression	-.08	.92	.88	.96	<.001
Anxiety	.01	1.01	.96	1.05	.77
Postoperative					
Stress	.02	1.02	.99	1.06	.22
Depression	-.02	.98	.95	1.01	.18
Anxiety	-.02	.98	.95	1.02	.35
Role physical					
Baseline					
Stress	.01	1.01	.98	1.04	.59
Depression	-.09	.91	.87	.96	<.001
Anxiety	.01	1.01	.97	1.06	.52
Postoperative					
Stress	-.01	1.00	.96	1.03	.93
Depression	-.03	.97	.94	1.01	.12
Anxiety	.01	1.00	.97	1.04	.96

Baseline SF-36 scales were significant in all models (p <.05)

Discussion

This study generally showed that pre and postoperative depression symptoms were associated with the normally distributed health related quality of life domains of vitality, social role, physical health and general health beyond the effects of general stress and anxiety six months after CABG surgery. Non linear analyses showed a general association between baseline depression and role emotional and role physical functioning. Taken together, these results did not support the primary hypothesis derived from review evidence (Duits et al., 1997; Stafford et al., 2007; Suls & Bunde, 2005) that the general and shared, rather than unique and differentiating, symptoms of depression and anxiety (i.e., general stress) would be associated with lower health related quality of life after CABG. While it is well known that emotional distress portends lower gains in health related quality of life (Goyal et al., 2005; Mallik et al., 2005; Perski et al., 1998; Ruo et al., 2003; Stafford et al., 2007), this study adds to previous research by outlining the discrete associations between specific health related quality of life domains, and was the first to test a theoretical model of depression and anxiety in relation to cardiac patients' perceptions of health related quality of life over time.

The findings with respect to anhedonic depressive symptoms are generally consistent with previous research that has established an association between health related quality of life and depression after CABG surgery, percutaneous coronary intervention or myocardial infarction (de Jonge et al., 2006a; Denollet, Vaes, & Brutsaert, 2000; Goyal et al., 2005; Höfer et al., 2005; Mallik et al., 2005; Perski et al., 1998; Ruo et al., 2003; Stafford et al., 2007; Stoll et al., 2000). The results appeared robust in that whether pre or postoperative affect was considered, depression remained a significant predictor of health related quality of life. However, several differential patterns of association were revealed in univariable analysis and most notably that significant effects on social role and general health were attributable to all DASS scales. This is potentially explained by these particular health related quality of life domains' association with non-specific general stress or alternatively an inability to identify a single psychological predictor from such interrelated scales. Importantly, these data also showed that perioperative psychological variables bore no association with the bodily pain scale at six months, with baseline pain the best predictor for this variable, thus contrasting to work elsewhere that has supported a relationship between post-CABG pain and anxiety (Nelson et al., 1998). In contrast to our domain specific analyses, previous studies (Al-Ruzzeh et al., 2005; Goyal et al., 2005) have utilised aggregate summary scores and factor analysis based data reduction to yield composite indices of health related quality of life to demonstrate an association with depression among CABG patients. However our results appear to challenge the utility of analysing non-specific aggregate health related

quality of life scores as such composite indices are too cumbersome to yield the discrete patterns of association with perioperative negative emotions as reported here.

Emphasizing the discriminating rather than shared symptoms of depression and anxiety may elucidate possible mechanisms that effect health related quality of life. The results show that depression and anxiety were not simultaneously associated with any health related quality of life domains, possibly as a result of analysing unique residualised variance after the stress symptoms were entered in the regression models (Lynam et al., 2006). These results contrast to Höfer et al. (2005) who found health related quality of life was associated with Hospital Anxiety and Depression Scale depressive and anxious symptoms along with measures of trait anxiety, though these findings were potentially due to non-specific NA (Barth & Martin 2005; Martin et al., 2003).

Other findings suggested that stress was associated with mental health though the effect did not retain significance when depression and anxiety entered regression models. Research among community samples showed that NA was associated only with the mental and not physical component summary of the SF-36 (Kressin et al., 2000). However, with regards to the lack of multivariable association between depression, anxiety and SF-36 measures of mental health, these findings contrasts to those reported by Al-Ruzzeh et al. (2005) who showed that the mental summary score of the SF-36 was associated with anxiety albeit at trend level in a sample of 437 CABG patients (OR = 0.2; 95% CI .03 - 1.22, p = .08). A possible explanation is that the SF-36 mental health domain reflects general stress more so than anxiety or depression as reported elsewhere among 822 employees in the Ausburg cohort study (Kudielka et al., 2004). In the absence of measures of depression and anxiety general distress predicts health related quality of life at one and six months post CABG (Panagopoulou, Montgomery, & Benos, 2006). However, neuroticism, a broad marker of NA, has both direct causal and indirect effects on anxiety and depression across the recovery period from CABG (Duits et al., 1999). Given this underlying role of neuroticism, it is possible that the association between state NA on health related quality of life is attenuated by distinct markers of depression and anxiety.

The results suggest that depression and anxiety do not work in concert to moderate subjective reports of health related quality of life domains. Given the effect of depression on health related quality of life independent of general stress and anxiety, this affective domain appears to be an appropriate area for targeted rehabilitation and psychological intervention depending on patient health related quality of life and emotional needs. Although the behavioural mechanisms impacting upon health related quality of life are unclear, they may include lower adherence to cardiac rehabilitation (Komorovsky et al., 2008) and medication

regimens (Gehi et al., 2005) or problem focused coping or acceptance based coping (Wray et al., 2004). Also, given that medical and demographic covariates such as age, hypercholesterolemia, CHF and previous myocardial infarction influenced health related quality of life, depression may impact on subjective reports of certain health related quality of life domains particularly in the presence of other known risk factors.

The practical implications of this study may inform rehabilitation and psychological interventions in cardiac settings. The results provide new support for the isolated deleterious impact of depressive symptoms on health related quality of life above and beyond the effects of anxiety and general stress. This finding is bolstered by the claim that psychosocial risk factors cluster together (Rozanski et al., 2005). Specifically, the differential associations between health related quality of life domains and depression suggest that interventions may target specific areas in consultation with individual patients' needs and goals. Clearly, these results suggest that researchers and future interventions should consider depression consistent with other reports (Al-Ruzzeh et al., 2005). Given that depressive cognitive content is likely to influence perceptions of health related quality of life (Christensen et al., 1999). Moore et al. (2005) suggested that psychological interventions should aim to achieve realistic perceptions of health related quality of life and provide relief of distress symptoms. Indeed, these findings have important theoretical implications given that unique and not common affective symptomatology was most commonly associated with health related quality of life, highlighting the importance of negative emotions even when measured as psychometrically and theoretically distinct phenomena. The tripartite model may therefore provide a useful theoretical basis for researchers assessing health related quality of life among CAD patients (Marshall et al., 2003).

The main strengths of this study were that an empirically validated theoretical framework was employed to examine associations between psychological distress and health related quality of life. The results are presented with several limitations, in particular that the patients not available for follow up assessment had a higher proportion of comorbid conditions that may influence health related quality of life. Given that we have not recorded attendance at rehabilitation or medication adherence, these behavioural factors may partly explain our results and therefore limit our conclusions. This study utilised a generic health related quality of life measure that may not be sensitive to change compared to those designed for CAD populations (Schroter & Lamping, 2006). Another limitation of this study is that the DASS was not explicitly designed to capture the full breadth of symptoms endorsed by the tripartite model such as PA (Crawford & Henry, 2003). Moreover, it is not known how well the DASS scales represent their original constructs after partialling of variance in regression analyses (Lynam et al., 2006). Indeed, another limitation of the univariable

analysis employing each measure of depression and anxiety in isolation would likely be an overestimation of the effect given that each is correlated with general stress. In addition, this study has not measured broader negative emotions related to NA and known to be associated with cardiac outcomes namely vital exhaustion (Appels et al., 2006), Type D personality (Denollet, Vaes, Brutsaert, 2000) and anger/hostility (Chida & Steptoe, 2009) and this may further limit these findings. With specific regards to anger/hostility, while these negative emotions were not explicitly outlined in the tripartite model, Watson has recently conceptualized hostility as anger and irritability (Watson, 2009b) and this may be an avenue for future researchers to consider the links between NA and other negative emotions. A recommendation for future research is to draw on psychological theories of negative emotions for understanding the association with CHD outcomes such as sociotropy and autonomy (Stafford et al., 2009), cognitive content (Martens et al., 2006), hopelessness (Brothers & Andersen 2009) or tripartite (Tully et al., 2008a) and behavioural theories. It is not known whether cognitive theories of negative emotions without somatic symptomatology or whether behavioural theories might lend themselves more readily to improved understandings and outcomes for cardiac rehabilitation settings.

In conclusion, this study has shown that unique depressive symptoms, more than general stress, are associated with health related quality of life six months after CABG. The results support previous research that has shown health related quality of life following CABG is not accounted for entirely by medical risk factors with various behavioural and psychological mechanisms implicated (Hawkes et al., 2006; Lindsay et al., 2000). Improvement in health related quality of life following CABG procedures is typical (Lindsay et al., 2000; Tully et al., 2008b) but by no means universal (Hawkes & Mortensen, 2006), and therefore the challenge is to identify the ways in which certain psychological and behavioural mechanisms interact to limit the health related quality of life benefits usually afforded by CABG surgery.

Chapter VI Study Four

Neuropsychological Function Five Years After Cardiac Surgery And The Effect Of Psychological Distress

Phillip J. Tully, Robert A. Baker, John L. Knight, Deborah A. Turnbull, Helen R. Winefield (2009)
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We provided ongoing supervision throughout the research programme that lead to this publication and there was ongoing collaboration between Mr. Tully and us in refining the direction of the research. Mr. Tully was responsible for writing this paper; our role was to comment on drafts, make suggestions on the presentation of material in the paper, and to provide editorial input. We also provided advice on responding to comments by the journal reviewers and editor. We hereby give our permission for this paper to be incorporated in Mr. Tully's submission for the degree of Doctor of Philosophy from the University of Adelaide.

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Chapter VII Study Five

Anxiety, Depression And Stress As Risk Factors For Atrial Fibrillation After Cardiac Surgery

Phillip J. Tully, Jayme S. Bennetts, Robert A. Baker, Andrew D. McGavigan, Deborah A. Turnbull, Helen R. Winefield. (2011)

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We provided ongoing supervision throughout the research programme that lead to this publication and there was ongoing collaboration between Mr. Tully and us in refining the direction of the research. Mr. Tully was responsible for writing this paper; our role was to comment on drafts, make suggestions on the presentation of material in the paper, and to provide editorial input. We also provided advice on responding to comments by the journal reviewers and editor. Dr Bennetts individually reviewed the patient echocardiograms. We hereby give our permission for this paper to be incorporated in Mr. Tully's submission for the degree of Doctor of Philosophy from the University of Adelaide.

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Abstract

The objective was to determine whether pre and postoperative anxiety, depression and stress symptoms were associated with AF after cardiac surgery. Two hundred and twenty six cardiac surgery patients completed measures of depression, anxiety and general stress prior to surgery and 222 patients completed these measures after surgery. The outcome variable was new onset AF confirmed prior to the median day of discharge (day 5) after cardiac surgery during the index hospitalisation. There were 56 (24.8%) patients with incident AF and these patients spent more days in hospital (M = 7.3, SD = 4.6) than patients without AF (M = 5.5, SD = 1.4, *p* <.001). No baseline psychological predictors were associated with AF. When postoperative distress measures were considered, anxiety was associated with an increased odds for AF (OR = 1.09; 95% CI 1.00 – 1.18) *p* = .05). This analysis also showed that age was significantly associated with AF (OR = 1.07; 95% CI 1.03 – 1.12, *p* <.001). Analysis specific to the symptomatic expression of anxiety indicated that somatic (i.e. autonomic arousal) and cognitive-affective (i.e. subjective experience of anxious affect) symptoms were associated with incident AF. Anxiety symptoms in the postoperative period were associated with AF. Hospital staff in acute cardiac care and cardiac rehabilitation settings should observe anxiety as related to AF after cardiac surgery. It is not clear how anxious cognitions influence AF symptom experience and whether anxiety symptoms commonly precede AF.

Introduction

Review evidence indicates that the incidence of atrial arrhythmias, of which the most common is AF, after CABG surgery is between 20% and 60% (Echahidi, Pibarot, O'Hara, & Mathieu, 2008; Hogue, Creswell, Gutterman, & Fleisher, 2005). Though rarely requiring long-term therapy (Bradley et al., 2005), AF developing in the postoperative period is associated with increased mortality (Jung, Meyerfeldt, & Birkemeyer, 2006), higher incidence of stroke (Mariscalco et al., 2007) and increased length of stay and hospital costs (Aranki et al., 1996). In addition to medical risk factors including left ventricular dysfunction, hypertension and diabetes, studies among non-surgical populations have suggested that anxiety and other psychosocial factors may precede or be a symptom of arrhythmias (Sears et al., 2005; Suzuki & Kasanuki, 2004). Identifying psychological correlates of AF that are amenable to intervention is important as the results may inform CABG patient rehabilitation practices and provide new information regarding this common morbidity complication.

Research has suggested that panic disorder and agoraphobic symptomatology are common in persons with paroxysmal AF (Suzuki & Kasanuki, 2004). One plausible mechanism for the psychogenic links between negative emotions such as anxiety and arrhythmias is dysregulation of the autonomic nervous system, and consequently reduced parasympathetic and increased sympathetic nervous system activity (Carney, Freedland, & Veith, 2005; Moser & de Jong, 2006). Specifically, increased sympathetic nervous system response as a consequence of weak vagal tone may increase catecholamines, and thus disrupt refractoriness and or local re-entry atrial wavelets, directly or indirectly initiating AF during emotional or mental stress (Ziegelstein, 2007). Supporting this hypothesis of increased sympathetic modulation, Yavuzkir and colleagues (2007) showed that electrocardiogram P-wave dispersion, a predictor of atrial fibrillation after CABG (Aytemir, Aksoyek, Ozer, Aslamaci, & Oto, 1999; Chandy et al., 2004), was increased among patients with panic disorder compared to a control group. However the association between psychological variables and AF has not been confirmed with CABG patients. Limited research to date has focused on Type A behaviour patterns (Freeman, Fleece, Folks, Waldo, & Cohen-Cole, 1984; Krantz, Arabian, Davia, & Parker, 1982), paradoxically suggested that lower anxiety and depression were associated with AF (Freeman et al., 1984), and showed trend level association with hostility (Contrada et al., 2008).

The prevalence of psychological distress is reportedly 20% for depressive disorders, whilst anxiety has received less research attention among candidates for cardiac surgery (Borowicz et al., 2002; Dunkel et al., 2009; Tully, Baker, & Knight, 2008). Yet anxiety

dominates the scope of psychogenic correlates of AF among non-cardiac surgery patients therefore it is important to confirm these findings with respect to CABG patients. As part of the present study, the specific cognitive and somatic symptoms of anxiety were assessed in relation to postoperative AF. Also, given that anxiety and depression are conceptually interrelated (Clark & Watson, 1991) it is also requisite to consider whether anxiety is associated with postoperative AF independent of closely related but distinct psychological constructs. With this in mind, the objectives of the current study were to firstly examine whether cognitive-affective or somatic symptoms of anxiety were associated with AF after CABG, and secondly to determine whether anxiety was associated with AF after adjustment for general distress and depression.

Methods

Patient Sample

The sample for this study consisted of patients undergoing first time CABG surgery between January 1999 and December 2005 at the Flinders Medical Centre. Six hundred and eighty one patients scheduled for isolated CABG were evaluated against the inclusion criteria; age >18 years, CABG procedure with cardiopulmonary bypass, able and willing to provide informed consent, and undergoing elective or urgent surgery. Four hundred and forty three patients were deemed ineligible and the most common reason was residing outside the state of South Australia (n = 156). This exclusion criterion was adopted so that hospital readmissions and other long-term follow-up data could be documented as reported elsewhere (Tully et al., 2008a; Tully et al., 2009a). The final baseline sample of patients providing informed consent was N = 226. This study received ethics approval from the respective hospital and university institutions (approval numbers: 57/067, H-148-2006).

Arrhythmia Investigations

The main outcome variable was new onset AF confirmed from when the patient was admitted to the intensive care unit and prior to the median day of discharge (day 5) after CABG during the index hospitalisation. All patients underwent ambulatory electrocardiogram and transthoracic echocardiograph up to seven days prior to scheduled surgery, and were monitored daily on the hospital ward or intensive care unit following surgery with 24-hour Holter monitor for the first three postoperative days, and five daily electrocardiograms thereafter until discharge. Certified technicians used a 12-lead surface electrocardiogram. Both technician report of Holter-monitor and electrocardiogram were used to determine

incident AF. Patient electrocardiogram's were reviewed independent of the original assessors and blinded to patients' psychological distress scores. Agreement between technician and blinded reviewer electrocardiogram report as ascertained by Kappa was excellent (κ = .91).

Psychological Distress

Psychological distress was measured with the 42 item self-report DASS and readers unfamiliar with this instrument are referred elsewhere for a review (Lovibond & Lovibond, 1995a; Lovibond & Lovibond, 1995b). Briefly, three separate scales consisting of 14 items each tap into anxiety, depression and general stress states within the previous week of administration. Scored on a Likert-type scale from 0 (*Did not apply to me at all*) to 3 (*Applied to me very much of the time*), scores range from a high of 42 to a low of zero (lower scores are indicative of lower levels of each construct). On the three DASS scales a mild and potentially clinically relevant level of symptoms from normative data are; depression ≥ 10, anxiety ≥ 8, stress ≥ 15.

Confirmatory factor analysis supports a uniform structure, high internal consistency (Brown et al., 1997a; Lovibond & Lovibond, 1995a; Lovibond & Lovibond, 1995b; Tully, Zajac, & Venning, 2009) and temporal stability at 3 – 8 years follow-up has also been documented (Lovibond, 1998). Patient anxiety symptoms were of particular interest to the current study, and the DASS-Anxiety scale consists of four subscales two of which capture somatic and two of which capture cognitive symptomatology. The somatic subscales were as follows, with example items in parentheses; autonomic arousal which measures breathing difficulties and pounding of the heart (e.g. I was aware of the action of my heart in the absence of physical exertion) and skeletal musculature which reflects trembling and shakiness states [e.g. I had a feeling of shakiness (e.g. legs going to give way)]. The cognitive subscales were situational anxiety which reflects worry about performance and possible loss of control (e.g. I found myself in situations that made me so anxious I was most relieved when they ended) and experience of anxious affect which reflects apprehensiveness and panicky states (e.g. I felt scared without any good reason).

Patients were assessed before (*M* = 2, *SD* = 2 days) and after surgery on the hospital ward (*M* = 6, *SD* = 2 days). In this study, internal consistency of the depression, anxiety and stress subscales before surgery were α = .87, α = .80 and α = .92 respectively, whilst after surgery for these scales they were α = .94, α = .86 and α = .94 respectively.

Statistical Analysis

Data were analysed with SPSS® 18.0 statistical software package (SPSS Inc., Chicago, IL). Continuous data were examined with the general linear model while categorical data were examined with the chi-square statistic. Analysis of co-variance was employed adjusted for baseline DASS scores to determine whether patients with and without incident AF had discrepant subjective ratings of psychological distress. Previous research (Echahidi et al., 2008; Girerd et al., 2009; Hakala et al., 2002; Mariscalco et al., 2008; Sezai et al., 2009) was examined to select potential covariates for a predictive association with AF in univariable logistic regression and included age, sex, LVEF <30%, mitral incompetence, hypertension, urgent surgery (elective as reference category), diabetes, body surface area (m^2), Canadian Cardiovascular Society angina class, congestive heart failure, PVD, renal disease, number of anastomoses, revascularization with left internal mammary artery, total cross clamp time, intraoperative inotropic support. No patients required support with an intra-aortic balloon pump and thus this variable was not considered.

Regression model constraints necessitated that a limited number of covariates could be retained for multivariable analysis to avoid over fitting. The criterion adopted for retaining variables was increased OR for incident AF ($p < .20$) ascertained from univariable logistic regression and the Wald chi-square statistic (Babyak, 2004). The first analysis focused exclusively on DASS-Anxiety subscale scores given previous reports of association between anxiogenic symptomatology and AF (Sears et al., 2005; Suzuki & Kasanuki, 2004). For this analysis, DASS-Anxiety subscale scores were arranged according to one of four groups of item content as specified in the manual (Lovibond & Lovibond, 1995b), i.e. autonomic arousal, skeletal musculature, situational anxiety, and experience of anxious affect. For each of the four anxious item domains, the baseline anxiety subscale score was subtracted from the respective postoperative subscale score (positive change scores denote an increase in that aspect of anxiety and vice versa). This analysis aimed to determine whether spurious increases in somatic symptoms would confound an association between AF and anxiety. Retained medical and demographic covariates were entered (step 1), followed by anxiety subscale scores (step 2). Multivariable hierarchical logistic regression analyses were also performed with the continuous DASS scores completed preoperatively and postoperatively (independent variables). Retained medical and demographic covariates were entered (step 1), then stress (step 2), and depression and anxiety (step 3) to determine the effect of anxiety and depression on AF after the common variance with stress and medical covariates was accounted for as elsewhere (Tully et al., 2008a). Regression model fit indices were ascertained from the Hosmer and Lemeshow test, and multicollinearity was ascertained from inspection of correlations between regression coefficients.

Power calculation for log binomial tests showed that N = 120 patients would be required to yield sufficient power (.80) to test for a significant difference (α = 0.05) between distressed and non-distressed group AF rates given that large differences between groups would be considered important (effect size = 0.20), with a moderate between groups odds ratio, δ = 2.8. This calculation is based on the estimate of a 25% within hospital AF rate (Echahidi et al., 2008; Hogue et al., 2005), and the expectation that around 20% of patients will experience some psychological distress (Borowicz et al., 2002; Dunkel et al., 2009; Tully et al., 2008a).

Results

Fifty-six patients (24.8% of total) were identified as having postoperative AF and the descriptives of the sample and univariable predictors of AF are shown in Table 19. Retained predictors of AF from univariable logistic regression were older age, mitral incompetence, LVEF ≤30% and urgent procedure. Inspection of preoperative medications indicated that n = 3 patients in the sample had been prescribed preoperative warfarin, and one of these patients developed AF. Among the 56 patients who developed AF, 15 were managed with antiarrhythmic prophylaxis in the postoperative period and consisted of; amiodarone n = 4, digoxin n = 4, sotalol n = 1, combination of digoxin and sotalol n = 5, combination of amiodarone and digoxin n = 1. Analysis of postoperative length of hospital stay indicated that patients with incident AF spent more days in hospital on average (M = 7.3, SD = 4.6) than patients without incident AF (M = 5.5, SD = 1.4, t (224) = -4.53, p <.001), though AF patients tended to be older with poorer left ventricular output and mitral incompetence.

The analysis of co-variance suggested that there was a modest relationship between baseline DASS subscale scores and the respective subscale after surgery; partial η^2 = .19 - .24, all p <. 001. After adjustment for baseline DASS subscale scores however, there were no significant differences between the AF and non-AF group on postoperative DASS subscale scores. Inspection of Table 19 suggests that patients were on average in the normal range for depression, anxiety and stress. The interrelation between depression and anxiety scales pre (r = .77) and post surgery (r = .73) indicated a modest association, whereas for anxiety and stress the correlations were r = .73 and r = .79 respectively, whilst correlations between depression and stress were r = .75 at each of the two assessment times, all p <.05.

Table 19. Descriptives Comparisons of Sample and Univariable Predictors of Atrial Fibrillation

| Descriptive variable [a] | Incidence of AF | | | Odds for AF | | |
	No AF (n = 170)	Postoperative AF (n = 56)	P	OR	95% CI	P
Female sex	28 (16.5)	10 (17.9)	.79	1.10	.50–2.44	.81
Age ‡	61.6 (9.7)	67.7 (8.3)	<.001	1.08	1.04–1.12	<.001
Canadian Cardiovascular Society angina class III/IV	60 (35.3)	17 (30.4)	.50	.80	.42-1.53	.50
Acute myocardial infarction <30 days	15 (8.8)	4 (7.1)	.69	.80	.25-2.50	.70
Congestive heart failure	12 (7.1)	4 (7.1)	.98	1.01	.31-3.28	.98
Left ventricular ejection fraction ≤ 30%	2 (1.2)	3 (5.4)	.10	4.76	.77-29.2	.09
Mitral incompetence	6 (3.5)	7 (12.5)	.02	3.91	1.25-12.16	.02
Hypertension	108 (63.5)	31 (55.4)	.28	.71	.39-.1.31	.28
PVD	24 (14.1)	11 (19.6)	.32	1.49	.68-3.28	.32
Diabetes	38 (22.4)	9 (16.1)	.31	.67	.30-1.48	.32
Renal disease	4 (2.4)	1 (1.8)	1.00	.76	.08-6.90	.80
Chronic lung disease	32 (18.8)	12 (21.4)	.67	1.28	.56-2.48	.67
Body surface area m^2‡	2.01 (.32)	1.98 (.21)	.52	.67	.19-2.33	.52
Surgical and hospital parameters						
Elective surgery (reference category)	145 (85.3)	43 (76.8)	.14	-	-	-
Urgent surgery	25 (14.7)	13 (23.2)		1.75	.83-3.71	.14
Number of anastomoses ≥ 3	86 (50.6)	29 (51.8)	.88	1.05	.57-1.92	.88
Left internal mammary artery revascularization	155 (91.2)	49 (87.5)	.42	.68	.26-1.76	.42
Total complete cross-clamping time (mins) ‡	31.8 (12.7)	30.6 (14.1)	.55	.99	.97-1.02	.55
Intraoperative inotropes	21 (12.4)	7 (12.5)	.77	1.01	.41-2.53	.98
Psychological distress [b]						
Preoperative depression ‡	5.69 (5.93)	5.34 (5.83)		-		
Postoperative depression ‡	5.65 (6.79)	6.91 (8.01)	.31	-		
Preoperative anxiety ‡	6.49 (6.72)	6.32 (6.09)		-		
Postoperative anxiety ‡	8.98 (6.46)	9.18 (8.36)	.92	-		
Preoperative stress ‡	9.36 (8.60)	9.86 (7.70)		-		
Postoperative stress ‡	7.15 (7.01)	8.52 (9.10)	.18	-		

a. presented as N(%) unless otherwise indicated with ‡ which denotes mean, and standard deviation in parentheses
b. Analysis of co-variance results for postoperative DASS scores according to atrial fibrillation group adjusted for baseline scores

Perioperative Anxiety And AF

Analysis of the perioperative change in DASS anxiety symptoms showed that an association with AF was evident for autonomic arousal and subjective experience of anxious affect, as shown in Table 20. Specifically, autonomic arousal increased the risk for incident AF (OR = 1.16; 95% CI 1.02 – 1.32, *p* = .02). In contrast, subjective experience of anxious affect reduced the risk for AF (OR = .68; 95% CI .51 - .89, *p* < .01).

Preoperative Distress And Atrial Fibrillation

The regression model for baseline DASS scores showed that no psychological variables were significantly associated with AF, as displayed in Table 21. Each increasing year of age was associated with an 8% increased odds for AF (OR = 1.08; 95% CI 1.03 – 1.12, *p* < .001). Trend level association with AF was evident for LVEF ≤ 30%, mitral valve incompetence and stress.

Table 20. Logistic Regression Results for Atrial Fibrillation Predicted From Perioperative Anxiety Change Score and Medical Covariates (n = 222)

	OR	95% CI Lower	95% CI Upper	*P*
Age	1.08	1.03	1.12	<.001
Elective procedure (reference)	-	-	-	-
Urgent procedure	1.64	.67	4.01	.13
LVEF ≤ 30%	8.18	1.07	16.64	.04
Mitral incompetence	2.24	.64	7.88	.10
<u>Change in anxiety</u> [a]				
Autonomic arousal	1.16	1.02	1.32	.02
Skeletal musculature	1.26	.90	1.77	.18
Situational anxiety	.97	.76	1.23	.78
Subjective experience of anxious affect	.68	.51	.89	<.01

CI, confidence interval; DASS, Depression, Anxiety and Stress Scales; LVEF, left ventricular ejection fraction; OR, odds ratio

a. Anxiety change score calculated for each of the four anxiety subscales as postoperative DASS-Anxiety subscale score subtract baseline DASS-Anxiety subscale score

Table 21. Logistic Regression Results for Atrial Fibrillation Predicted from Preoperative Distress and Medical Covariates (n = 226)

	OR	95% CI Lower	95% CI Upper	P
Age	1.08	1.03	1.12	<.001
Elective procedure (reference)	-	-	-	-
Urgent procedure	1.57	.68	3.60	.29
LVEF ≤ 30%	5.03	.75	13.81	.10
Mitral incompetence	3.26	.96	11.08	.06
Preoperative stress	1.06	.99	1.14	.09
Preoperative depression	.95	.86	1.04	.27
Preoperative anxiety	.99	.90	1.08	.79

CI, confidence interval; LVEF, left ventricular ejection fraction; OR, odds ratio

Postoperative Distress And AF

When postoperative distress was considered a one point increase in anxiety scale score translated to increased odds for developing AF of around 9%, OR = 1.09 (95% CI, 1.00 – 1.18), *p* = .05, as shown in Table 22. Like the preoperative analysis every year increase in age was associated with around 7% increased odds for AF, OR = 1.07 (95% CI = 1.03– 1.12), *p* < .001. Trend level association was again evident for LVEF ≤ 30% and mitral valve incompetence.

Table 22. Logistic Regression Results for Atrial Fibrillation Predicted from Postoperative Distress and Medical Covariates (n = 222)

	OR	95% CI Lower	95% CI Upper	P
Age	1.07	1.03	1.12	<.001
Elective procedure (reference)	-	-	-	-
Urgent procedure	1.33	.55	3.21	.52
LVEF ≤ 30%	6.08	.85	14.68	.07
Mitral incompetence	2.80	.82	9.53	.10
Postoperative stress	.96	.89	1.04	.31
Postoperative depression	.96	.89	1.03	.23
Postoperative anxiety	1.09	1.00	1.18	.05

CI, confidence interval; LVEF, left ventricular ejection fraction; OR, odds ratio

Discussion

This study showed that postoperative anxiety was associated with increased odds for AF after CABG and generally supports work elsewhere in non-CABG populations (Ong et al., 2006; Suzuki & Kasanuki, 2004). These findings do not support that anxiety is predictive of AF, but rather suggest that anxiety is associated with concurrent AF, and a differential pattern was revealed with respect to cognitive-affective and somatic anxiety symptoms.

Postoperative autonomic arousal symptoms were associated with AF, a not surprising finding given overlapping symptoms of this DASS anxiety subscale (Lovibond & Lovibond, 1995b) and that experienced in AF such as palpitations and shortness of breath. Subjective experience of anxious affect however reduced the risk of AF. Research supports that the cognitive interpretation of physical symptoms plays a role in patient reports of AF (Sears et al., 2005). Intriguingly Hansson and colleagues (2004) reported that mental stress was the most commonly recalled 'trigger' of arrhythmia among patients with idiopathic paroxysmal AF, while anxiety was reported by more than half of patients during an arrhythmia attack. The findings of the present study are preliminary among CABG patients however, and it is not clear whether anxiety symptoms precede AF or whether anxious cognitions succeed and work to impact on AF symptom reports. One explanation of these data is that a cognitive rather than somatic focus of anxiety symptoms is beneficial for CABG patients at risk of, or already experiencing, AF.

Despite the lack of findings with respect to depression symptoms an association with AF cannot be ruled out. The DASS measure tapped into cognitive-affective rather than somatic-vegetative depressive symptoms (Lovibond & Lovibond, 1995b) and this may partly explain the lack of association with incident AF. Nevertheless work elsewhere has suggested that cognitive-affective depressive symptoms are associated with a two-fold increased risk of recurrence of AF among successful electrical cardioversion patients (HR = 2.7; 95% CI 1.05 – 1.72, p = .046) (Lange & Herrmann-Lingen, 2007). It was also possible that depressive symptoms are associated with arrhythmias in the longer term after cardiac surgery, rather than incident and potentially paroxysmal AF. Supporting this, previous research has demonstrated that patients reporting depressive symptoms one month after cardiac surgery had a greater proportion of unspecified dysrrhythmias at five year follow-up (Borowicz et al., 2002).

The 24.8% incidence of AF was within published rates in the literature (Echahidi et al., 2008; Hogue et al., 2005) and the longer hospital stay of patients with AF was consistent with other reports (Aranki et al., 1996). The finding with respect to age, impaired left

ventricular function and mitral incompetence was consistent with work elsewhere (Girerd et al., 2009; Hakala et al., 2002; Sezai et al., 2009) though the precise aetiology of AF is likely multifactorial. Typically, AF arises from multiple ectopic pacemakers or sites of rapid re-entry circuits in the atria. The suspected physiological mechanisms contributing to arrhythmiogenesis in the cardiac surgery patient include atrial manipulation and injury, venous cannulation, inflammation, oxidative stress, and imbalance of electrolytes and the autonomic nervous system (Echahidi et al., 2008; Hogue et al., 2005) though no operative factors were significantly associated with AF in these data.

These data have important practical implications that may serve to highlight the role of postoperative anxiety in AF after CABG. This finding is indeed important in the acute cardiac care and rehabilitation context given that guidelines for the assessment of coronary heart disease psychosocial risk factors recommend exploring depression and hostility but not anxiety (Orth-Gomer et al., 2005), and only recently have cardiac rehabilitation recommendations been refined to advocate psychosocial evaluation of anxiety in addition to depression (Balady et al., 2007). Recent CABG studies show that anxiety is associated with myocardial infarction and mortality (Rosenbloom, Wellenius, Mukamal, & Mittleman, 2009; Tully, Baker, & Knight, 2008) and unplanned hospital readmission (Tully et al., 2008a), which when coupled with current findings, suggest that hospital staff should consider patient self-reported anxiety as an important correlate of morbidity, including AF, after CABG. With respect to interventions, cognitive-behavioural rehabilitation may reduce distress among patients undergoing implantation with an implantable cardioverter defibrillator (Lewin, Coulton, Frizelle, Kaye, & Cox, 2007). It is not known whether such findings may also afford a benefit to CABG patients with dysrrhythmias, though cognitive-behavioural interventions have showed favourable results for reducing distress among cardiac surgery patients generally (Freedland et al., 2009; Lie, Arnesen, Sandvik, Hamilton, & H. Bunch, 2007) as has been reported for interventions involving education, phase I cardiac rehabilitation and telenursing (Ku, Ku, & Ma, 2002; Sorlie, Busund, Sexton, Sexton, & Sorlie, 2007).

The results here are presented with several limitations as only postoperative AF was assessed thus precluding the role of psychogenic stress on AF in the longer term, nor allowing us to document whether patients had experienced paroxysmal AF or went on to experience persistent or permanent AF in the longer term. Thus in these CABG surgery patients the role of pre and postoperative psychogenic stressors on classification of AF cannot be determined. Indeed, the findings may also be limited in generalizability given the high proportion of males, geographic location, interrelation between depression and anxiety, and that only isolated CABG surgery patients were included in the study. The modest number of patients reported to have AF also restrained regression models to a limited

number of covariates, and the width of the confidence intervals suggests this may limit the generalizability of the findings.

In conclusion, in the first study of this kind, an association was evident between AF and anxiety after CABG surgery, independent of the effects of depression and general stress and medical covariates. These findings support broader work elsewhere implicating anxiety in AF, and hospital staff in acute cardiac care and cardiac rehabilitation settings should observe anxiety as related to AF. It is however not established whether anxiety symptoms commonly precede AF or whether anxious cognitions succeed and exacerbate AF symptoms. Further research with larger samples is required to explore the psychogenic links between negative emotions and AF in cardiac surgery patients and cardiology patients generally.

Chapter VIII Study Six

Depression, Anxiety Disorders And Type D Personality As Risk Factors For Delirium After Cardiac Surgery

Phillip J. Tully, Robert A. Baker, Helen R. Winefield, Deborah A. Turnbull (2010)
Australian and New Zealand Journal of Psychiatry, 44(11), 1005-1011.

Statement of contributors

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We provided ongoing supervision throughout the research programme that lead to this publication and there was ongoing collaboration between Mr. Tully and us in refining the direction of the research. Mr. Tully was responsible for writing this paper; our role was to comment on drafts, make suggestions on the presentation of material in the paper, and to provide editorial input. We also provided advice on responding to comments by the journal reviewers and editor. We hereby give our permission for this paper to be incorporated in Mr. Tully's submission for the degree of Doctor of Philosophy from the University of Adelaide.

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NOTE:
This publication is included on pages 126-137 in the print copy
of the thesis held in the University of Adelaide Library.

Chapter IX Study Seven

Cardiac Morbidity Risk and Depression and Anxiety: A Disorder, Symptom and Trait Analysis Among Cardiac Surgery Patients

Phillip J. Tully, Susanne S. Pedersen, Helen R. Winefield, Robert A. Baker, Deborah A. Turnbull, Johan Denollet (in press, accepted 27/12/2010)
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We provided ongoing supervision throughout the research programme that lead to this publication and there was ongoing collaboration between Mr. Tully and us in refining the direction of the research. Mr. Tully was responsible for writing this paper; our role was to comment on drafts, make suggestions on the presentation of material in the paper, and to provide editorial input. We also provided advice on responding to comments by the journal reviewers and editor. Data analysis and conception for this study was during a laboratory visit to Universiteit van Tilburg, The Netherlands, in May 2009. We hereby give our permission for this paper to be incorporated in Mr. Tully's submission for the degree of Doctor of Philosophy from the University of Adelaide.

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Psychology, Health & Medicine, v. 16(3), pp. 333-345.

Chapter X Study Eight

Depression and Anxiety Disorders, Symptoms and Traits Among Cardiac Patients: A Receiver Operating Characteristic Study of the Mood and Anxiety Symptom Questionnaire

Phillip J. Tully & Brenda W. J. H. Pennix (Submitted)

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This study was conceived during Mr Tully's visit to VU University, The Netherlands, in October, 2010. I provided feedback on the study methods and manuscript that lead to this publication and there was ongoing collaboration between Mr. Tully and myself in refining the direction of the research. Mr. Tully was responsible for writing this paper; my role was to comment on drafts, make suggestions on the presentation of material in the paper, and to provide editorial input. I also provided advice on responding to comments by the journal reviewers and editor. I hereby give my permission for this paper to be incorporated in Mr. Tully's submission for the degree of Doctor of Philosophy from the University of Adelaide.

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Abstract

The objectives were to determine affective disorder screening properties of a self-report dimensional measure of depression, panic and general anxiety disorders among cardiac patients. Measures of state and trait negative affect were also evaluated. Patients awaiting coronary revascularization (N = 158; 20.9% female; median age = 65, interquartile range 58 - 73) underwent structured interview with the MINI International Neuropsychiatric Interview before surgery to determine caseness for major depression, panic disorder and general anxiety disorder. The MASQ was completed measuring low positive affect, anxious arousal and general distress symptoms. Patients also completed a Type D personality measure. Self-report measures were evaluated with ROCs. Prediction of 12 panic disorder cases (7.6%) by the MASQ anxious arousal scale yielded an area under the curve (AUC) = .784 and 75.0% sensitivity and 68.5% specificity. Prediction of 27 major depression cases (17.1%) by the MASQ low positive affect scale yielded AUC = .811 and 70.4% sensitivity and 77.1% specificity. Prediction of 16 general anxiety disorder cases (10.1%) yielded AUC = .780 and 68.8% sensitivity and 77.5% specificity for the general distress scale. The Type D negative affect scale ROCs were optimal in prediction of the composite any affective disorder, AUC = .745 and 54.5% sensitivity and 91.3% specificity. The MASQ dimensions performed best when predicting concordant disorders, but did not predict discordant disorders. This supports discriminant validity of the MASQ. The absence of latent NA in the MASQ anhedonia and anxious arousal scales may mitigate the sensitivity and specificity of the MASQ for diagnostic classification of affective disorders purported to contain a NA component. Therefore the MASQ should be employed cautiously considering other established and validated distress screening measures.

Introduction

The prognostic impact of major depressive disorder on cardiac morbidity and mortality is extensively documented (Rugulies, 2002; Suls & Bunde, 2005; Van der Kooy et al., 2007) though not conclusive (Nicholson, Kuper, & Hemingway, 2004). Comparatively, the evidence basis for anxiety upon such endpoints is reportedly on par with that for depression (Kubzansky & Kawachi, 2000). Though sorely under researched, evidence implicates panic disorder (Chen, Tsai, Lee, & Lin, 2009) and generalized anxiety disorder (Frasure-Smith & Lespérance, 2008) in adverse cardiac outcomes. Treatment of such affective disorders is contingent on identifying the at risk population when, for example, nearly 50% of depressed persons are not detected by medical specialists (Harris et al., 1996), and less than half of those detected are commenced on appropriate treatment (Koenig, 2007). Practically however, substantial interrelation between depression and anxiety complicates identification of the affective disorders when employing self-reported dimensions (e.g. correlation) and diagnostic categories (e.g. comorbidity and symptom overlap). Although the sensitivity and specificity of self-report depression measures has been systematically reviewed (Thombs et al., 2008) the diagnostic identification of specific anxiety disorders among cardiac patients has been reported on less commonly (Frasure-Smith & Lespérance, 2008). In fact common practice upon evaluation of anxiety screening measures amongst cardiac populations has been to examine multiple heterogeneous anxiety disorders together (Haworth, Moniz-Cook, Clark, Wang, & Cleland, 2007). This practice neglects discrepant affective dimensions or phenotypes (Craske et al., 2009; Watson, 2009a) or, in other words, the variance that makes each anxiety disorder relatively unique. Indeed inconsistent conceptual definitions for anxiety, reviewed previously (De Jong & Hall, 2006) are evident across a multitude of psychosocial screening measures available to hospital and research staff. Evidently, clear conceptual definitions may aid distinction of anxiety from depression, but also within the heterogeneous anxiety disorders themselves (Craske et al., 2009; Watson, 2009a).

The MASQ shows promise to aid the distinction between core unipolar depression and panic dimensions (i.e. anhedonia/low positive affect and anxious arousal/somatic tension respectively) while specifying a non-specific and therefore general distress dimension (Watson et al., 1995a, 1995b). Such a three-dimensional coherent factor structure has been extensively empirically validated to support what is known as the tripartite model of anxiety and depression (Watson et al., 1995a, 1995b). To the best of our knowledge we are not aware of a previous study among non-psychiatric medical in patient populations to evaluate the screener properties using ROCs for the MASQ (Watson et al., 1995a. 1995b), i.e. the true and false positive detection rates. Secondly, we are not aware of a previous study that

documents the ROCs of a single self-report depression and anxiety questionnaire in relation to affective disorders other than major depression, general anxiety or combinations of heterogeneous anxiety disorders among cardiac samples.

The current study attempts to address these limitations. Considering empirical findings and theoretical conceptualisations (Craske et al., 2009; Watson, 2009a) it was hypothesized that ROCs would be optimal when the MASQ scale (i.e. anhedonia/low positive affect, anxious arousal/somatic tension) was affect-congruent with the criterion disorder (i.e. depression and panic respectively). As the general distress scale is relatively non-specific and presumed to reflect latent NA common to many disorders we hypothesized this scale to be predictive of depression, panic and general anxiety. As a comparison, and in further consideration of general distress, the specific combination of NA and socially inhibited personality style (i.e. Type D personality) reportedly increases the risk for cardiac outcomes (Denollet, 2005). However research suggests that Type D personality is discrepant and largely unrelated to both MDD and LVEF (Denollet et al., 2009). Therefore, considering the possible common NA dimension to depression and anxiety, here we also investigated the ROCs for the Type D personality trait NA scale in relation to depression, panic and general anxiety disorder.

Methods

Patients

Eligible patients were aged > 18 years scheduled for non-emergency CABG ± concomitant valve procedure. Recruitment took place at the preadmission clinic of two institutions, Flinders Medical Centre and Flinders Private Hospital, between February 2007 and March 2009. From 252 approached patients, 94 were excluded as described elsewhere (Tully et al., 2010). All patients provided written informed consent, and this study received ethics approval from the respective institutions (H-010-2007, 112/067). Patients were interviewed and completed questionnaires at the hospital preadmission clinic in the week before surgery or on the hospital ward if an urgent patient, inter-hospital transfer or rural patient.

Psychiatric Status

The MINI version 5.0.0 served as the criterion for current affective disorders administered by an intern psychologist (first author). The MINI assesses a range of mood, anxiety and other disorders (Watson et al., 1995a. 1995b) with high sensitivity and specificity. Kappa coefficients (κ = .86 - .96) suggest favourable agreement with the structured clinical interview for DSM-III-R patients (Sheehan et al., 1997), and also the composite international diseases interview (κ = .43 - .73) (Sheehan et al., 1998). Here only major depression, panic disorder and general anxiety disorder were analysed with respect to the MASQ considering the importance to cardiac research (Chen, Tsai, Lee, & Lin, 2009; Frasure-Smith & Lespérance, 2008) and also the low base rates (<5%) of other affective disorders in the sample. Patients meeting current other MINI criteria were excluded for the following reasons: current psychosis and/ or taking anti-psychotic medications (n = 3), current or past alcohol and/ or substance abuse (n = 5).

Self-Reported Distress

The MASQ consists of a list of statements and respondents indicate for each item how much they have felt or experienced these feelings or thoughts in the past week using a Likert type scale from 1 "not at all" to 5 "extremely." Items reflecting positive affect are reverse scored. Responses to the MASQ were employed to derive the same 30-items described by Wardenaar et al (2010) from community and psychiatric samples. The advantages of a shortened MASQ are brevity for screening purposes in cardiac or primary care settings. Consistent with Wardenaar et al's work (2010), 10-items each were allocated to an anxious hyperarousal/somatic tension scale (originally 17 items) characteristic of panic and an anhedonia/low positive affect scale (originally 22 items) characteristic of depression. The general distress scale (originally 15 items) is non-specific and moderately associated with depression, panic and generalised anxiety disorder, though differentially associated to the phobic anxiety disorders (Watson, 2009a). Factor analysis suggests that the MASQ is a reliable and valid measure with excellent discriminant and divergent validity and internal consistency (Bredemeier et al., 2010; Keogh & Reidy, 2000; Reidy & Keogh, 1997; Watson et al., 1995a, 1995b).

The DS14 measure of Type D personality consists of two scales, seven items each, that measure NA and social inhibition respectively. Previous research has corroborated favourable psychometric properties (Denollet, 2005). Here only the NA subscale, tapping into

dysphoria, worry, and irritability, was employed based on previous empirical models (Watson, 2009a) and our hypotheses.

Statistical Analysis

Analyses were two-tailed and an alpha value p <.05 was considered statistically significant (SPSS Inc 18.0, Chicago, IL). The MINI diagnosis served as the external criterion for major depression, panic disorder and generalised anxiety disorder. The AUC from ROCs evaluated the accuracy of the MASQ subscales to screen for a particular psychiatric disorder. Instances where AUC = 0.5 the screening measure does no better than chance and AUC = 1.0 corresponds to perfect accuracy. Optimal cut points are reported for AUC p <.05 and were determined by maximizing sensitivity (i.e. identification of true positives) and specificity (i.e. identification of true negatives) with the Youden statistic (Y = sensitivity + specificity − 100). The positive predictive value and negative predictive values are also reported. The ROCs for Type D trait NA were evaluated for all abovementioned affective disorders in the same fashion.

Consistent with previous MASQ research (Buckby, Yung, Cosgrave, & Killackey, 2007) a series of logistic regressions were performed to predict the presence of a disorder according to affect congruent MASQ subscales, general distress, and Type D personality NA. Both continuous score and categorical analyses were employed with the latter adopting the ROCs optimal cutpoint determined by maximizing the Youden index. In the case that a categorical cutpoint could not be determined from ROC AUC >.5 then the upper 25% for a given scale was selected. Regression model overfitting concerns did not permit analysis of multiple affect scales simultaneously.

Results

Descriptives

Patients excluded from the study were not discrepant from participants on comorbid conditions but were more likely to identify as Aboriginal χ^2 (1) = 5.85, p = .02. A descriptive comparison between those persons with and without an affective disorder did not suggest any significant differences in comorbidity as reported elsewhere (Tully et al., 2010). Briefly, N = 158 patients were recruited (20.9% female; 11.4% concomitant valve surgery; median age

M = 65, interquartile range 58-73). Highly prevalent comorbidity was evident for hypercholesterolemia and hypertension (74.7% and 64.6% respectively), while heart failure and low ejection fraction <45% were evident among 25.3% and 11.4% of patients respectively. The MINI classified 27 cases with major depression (17.1%), 12 cases with panic disorder (7.6%) and 16 cases with GAD (10.1%). A total of 60 affective disorder criteria for major depression, panic disorder and generalised anxiety disorder combined were among n = 47 individuals comprising the *any* affective disorder group.

Receiver Operator Characteristics

The ROC results are reported in Table 30. The anxious arousal scale was the only scale to reach ≥75% sensitivity in relation to an affect concordant disorder (i.e. panic disorder). Anxious arousal and general distress were both predictive of GAD though general distress was associated with higher AUC. Results are displayed graphically for panic disorder, major depression and generalised anxiety disorder in Figure 6, Figure 7 and Figure 8 according to affect-concordant MASQ subscales of anxious arousal, anhedonia and general distress scale respectively. The ROCs for affect discordant anhedonia and arousal scales were no better than chance to predict panic disorder and major depression respectively. High sensitivity but poor specificity was evident for the general distress scale in relation to any affective disorder. Also, the general distress scale AUC was no better than chance to predict panic disorder and major depression suggesting non-specificity of the scale (Watson et al., 1995a, 1995b). By contrast the Type D NA trait showed favourable ROCs particularly for prediction of the composite any affective disorder.

Table 30. Receiver Operating Characteristics of Short MASQ Subscales, Trait NA and Major Depression, Panic and General Anxiety (N = 158)

	AUC (*SE*)	95% CI	Optimal cutoff	Sensitivity (True +)	Specificity (True -)	Youden	PPV	NPV
Any Affective Disorder (n = 47)								
Low Positive Affect	.756 (.047)	.664 -. 848	17	58.1	79.1	37.3	54.1	81.7
General Distress	.746 (.046)	.657 - .836	19	81.4	42.6	39.2	37.5	84.4
Anxious Arousal	.780 (.043)	.696 - .864	22	65.1	73.9	39.0	51.3	83.3
Trait negative affect	.745 (.046)	.655 - .835	11	54.5	91.3	44.8	49.0	92.9
Major Depression (n = 27)								
Low Positive Affect (concordant)	.811 (.048)	.716 - .906	17	70.4	77.1	47.5	38.8	92.7
General Distress	.457 (.065)	.329 - .585	-	-	-	-	-	-
Anxious Arousal (discordant)	.543 (.065)	.416 - .670	-	-	-	-	-	-
Trait negative affect	.713 (.057)	.601 - .825	12	52.9	87.8	39.6	39.9	92.4
Panic Disorder (n = 12)								
Anxious Arousal (concordant)	.784 (.079)	.587 - .908	23	75.0	68.5	43.5	16.5	97.1
General Distress	.610 (.094)	.426 - .795	-	-	-	-	-	-
Low Positive Affect (discordant)	.529 (.105)	.322 - .735	-	-	-	-	-	-
Trait negative affect	.781 (.065)	.654 - .908	11	66.7	82.9	49.5	37.4	97.2
General Anxiety (n = 16)								
General Distress	.780 (.063)	.657 - .903	20	68.8	77.5	46.2	25.6	95.7
Low Positive Affect	.538 (.077)	.387 - .690	-	-	-	-	-	-
Anxious Arousal	.667 (.074)	.522 - .812	23	68.8	69.0	37.8	20.0	95.2
Trait negative affect	.677 (.077)	.527 - .827	11	56.3	83.1	39.3	33.8	92.5

CI, confidence interval; MASQ, mood and anxiety symptom questionnaire; NPV, negative predictive value; PPV, positive predictive value; SE, standard error
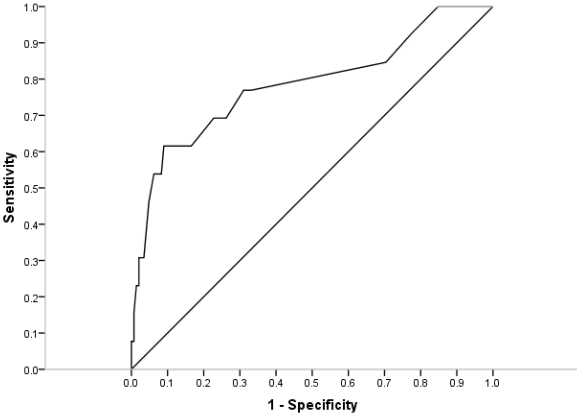
Figure 6. Graph of Receiver Operating Characteristic Curve for Detection of Panic Disorder by Mood and Anxiety and Symptom Questionnaire Anxious Arousal Scale Showing Sensitivity and 1 – Specificity
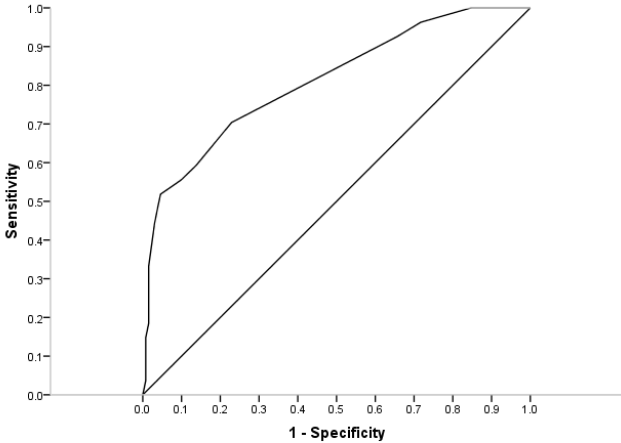
Figure 7. Graph of Receiver Operating Characteristic Curve for Detection of Major Depressive Disorder by Mood and Anxiety and Symptom Questionnaire Low Positive Affect Scale Showing Sensitivity and 1 – Specificity
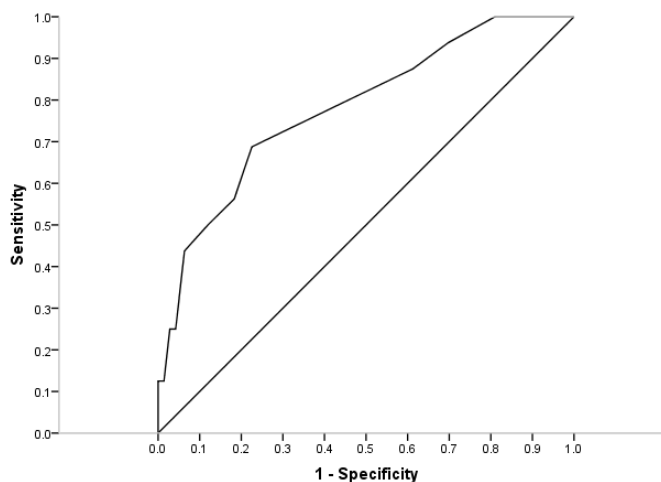
Figure 8. Graph of Receiver Operating Characteristic Curves for Detection of Generalised Anxiety Disorder by Mood and Anxiety and Symptom Questionnaire General Distress Scale Showing Sensitivity and 1 – Specificity

Logistic Regression Prediction

The logistic regression results predicting affective disorders are presented in Table 31 separately for each of the MASQ dimensions. All affect concordant scales were significantly associated with the respective disorder as expected though anxious arousal was associated with generalized anxiety disorder. A separate series of analyses showed that general distress and Type D NA was also associated with major depression, panic and generalised anxiety disorder.

Table 31. Logistic regression analyses for specific affective disorders by dimensional and general distress symptoms

	β	Wald	OR	95% CI lower	95% CI upper	P
Major Depression (n = 27)						
Continuous						
Positive Affect (concordant)	.39	20.89	1.48	1.25	1.75	<.001
MASQ General Distress	.36	19.34	1.44	1.22	1.69	<.001
DS14 Trait NA	.15	15.23	1.17	1.08	1.26	<.001
Categorical						
Positive Affect (concordant)	2.08	19.57	8.00	3.18	20.09	<.001
MASQ General Distress	1.93	17.95	6.87	2.82	16.74	<.001
DS14 Trait NA	2.05	19.08	7.74	3.09	19.39	<.001
Panic Disorder (n = 12)						
Continuous						
Anxious Arousal (concordant)	.22	13.12	1.24	1.10	1.40	<.001
MASQ General Distress	.18	4.78	1.20	1.02	1.40	.03
DS14 Trait NA	.14	8.37	1.15	1.05	1.27	<.01
Categorical						
Anxious Arousal (concordant)	1.70	7.07	5.49	1.56	19.25	<.01
MASQ General Distress	1.08	3.16	2.95	.90	9.70	.08
DS14 Trait NA	2.27	12.17	9.68	2.71	34.65	<.001
General Anxiety (n = 16)						
Continuous						
Anxious Arousal	.26	19.02	1.30	1.16	1.46	<.001
MASQ General Distress	.33	15.40	1.39	1.18	1.64	<.001
DS14 Trait NA	.11	6.94	1.12	1.03	1.22	.01
Categorical						
Anxious Arousal	2.21	13.23	9.17	2.78	30.27	<.001
MASQ General Distress	2.02	12.36	7.56	2.45	23.37	<.001
DS14 Trait NA	1.84	11.18	6.32	2.15	18.63	.001

CI, confidence interval; MASQ, Mood and Anxiety Symptom Questionnaire; NA, negative affect; OR, odds ratio,

Discussion

This was perhaps the first ROC examination of a single self-report distress measure comprising depression, anxiety and NA subscales in relation to depression, panic and general anxiety disorders among cardiac patients. Anxious arousal appeared to be the only subscale to achieve 75% sensitivity to detect true positive cases of a specific disorder, i.e. panic disorder. This was an encouraging finding considering the overlap between somatic manifestations of anxiety and visceral fear and those of heart disease (Craske et al., 2009; Watson, 2009a). Distinguishing between anxiety and depression can be problematic owing to shared NA (Watson, 2009a). The affect discordant MASQ subscales were curiously no better than chance to detect major depression and panic disorder here. This finding is conspicuously discrepant from some other self-report measures that have shown comparable sensitivity and poor specificity in detection of major depression when employing either depression or anxiety scales (Bambauer, Locke, Aupont, Mullan, & McLaughlin, 2005).

The results diverge from poor specificity of the MASQ anxious arousal scale reported elsewhere (Buckby, Yung, Cosgrave, & Killackey, 2007; Boschen, & Oei, 2007) to predict *any* heterogeneous anxiety disorder including samples derived predominantly of simple phobia and social phobia. The current results concerning anxious arousal and panic disorder corroborate recent theory (Watson, 2009a) and dimensional findings elsewhere (Joiner et al., 1999). One explanation is that anxious arousal is characteristic primarily of panic disorder while social phobia is related to anhedonia along with fear (Hughes et al., 2006). Intriguingly, the Hospital Anxiety and Depression Scale-anxiety subscale has been demonstrated to tap into hyperarousal symptoms (Martin, Thompson, & Barth, 2008) characteristic of panic disorder (Joiner et al., 1999) and reported to have favourable sensitivity (90.7%) and specificity (61.4%) for scores ≥8 with respect to generalised anxiety disorder (Frasure-Smith & Lespérance, 2008). Here, the MASQ general distress ROCs were more favourable than that of anxious arousal with respect to generalised anxiety disorder. However the logistic regression results also indicated that generalised anxiety disorder is marginally associated with self-reported autonomic arousal corroborating pending diagnostic taxonomy revisions (American Psychiatric Association, 2010). With respect to depression a recent systematic review reported median sensitivity 84% (range 39% - 100%) and specificity 79% (58% - 94%) of various depression measures among 11 cardiac studies (Thombs et al., 2008). The MASQ anhedonia scale was within the abovementioned ranges though lower than the desirable 75% sensitivity for predicting true major depression cases. A possible explanation is that the MASQ anhedonia/low positive affect scale precluded analysis of somatic

symptoms that form an important part of a cardiac patient's depression experience (Fraguas Junior, Ramadan, Pereira, & Wajngarten, 2000).

It is not surprising that Type D personality trait NA was associated with favourable ROCs in prediction of any affective disorder. However the MASQ state distress scale was not, suggesting a clear divergence between the state and trait general distress in their association with the composite affective disorders. Yet the logistic regression data corroborated that affective disorders were significantly associated with both unique and shared variance, and could be taken to support previous theoretical contentions (Watson, 2009a). However the MASQ diagnostic classification utility is possibly jeopardized by delineating a general distress scale, separate from that of anhedonia and anxious arousal. That is, these disorder specific symptoms may, paradoxically, sub-optimally predict major depression and panic disorder given that intrinsic latent NA variance is omitted. This could explain generally inferior ROCs for the MASQ here by comparison to measures such as the Hospital Anxiety and Depression Scale (Frasure-Smith & Lespérance, 2008), Beck Depression Inventory (Thombs et al., 2008) or multiple component scales (Young, Ignaszewski, Fofonoff, & Kaan, 2007) where latent NA variance is evident among the scales (Martin, Thompson, & Barth, 2008; Shafer, 2006). Of course, the MASQ is comprised of two additional general distress scales tapping more closely into depression and anxiety respectively (Watson et al., 1995a, 1995b). While analysis of these scales has typically been omitted for parsimony (Wardenaar et al., 2010; Watson, 2009a) it is possible that such MASQ scales could contribute to the diagnostic identification of affective disorders. Here general NA was no better than chance in prediction of specific affective disorder caseness except for the *any affective disorder* group supporting the non-specificity of the scale (Watson et al., 1995a, 1995b) and theoretical assumptions (Watson, 2009a). Among cardiac patients, diagnostic classification of affective disorders such as major depression, generalised anxiety disorder and panic disorder is perhaps likely to be optimized when self-report measures contain a degree of NA variance within depression and anxiety subscales. That being said, NA laden depression and anxiety measures confound the examination of cardiac morbidity outcomes (Smith & MacKenzie, 2006; Suls & Bunde, 2005). Careful portioning out the unique affect/disorder variance from that of general NA may disentangle the role of specific constructs from broader NA and neuroticism traits in cardiac outcomes research (Tully et al., 2008a).

Practically, previous authors have recommended psychosocial screening at the patient bedside (Ketterer et al., 2007) and nursing staffs typically have high patient contact with hospitalized cardiac patients on the hospital ward and admission clinics. The balance between the MASQ sensitivity, specificity and predictive values should be considered in

context of the intended purpose, whether that be for research or diagnostic screening. The findings here support that the 10-item MASQ anxious arousal established by Wardenaar et al (2010) could serve as a brief screening measure for panic disorder among cardiac populations. This suggestion is within the abovementioned limitations concerning omission of latent NA variance from the anxious arousal scale and the low prevalence of panic disorder and predictive values. Nevertheless, high presentation rate of persons with panic disorder presenting with non cardiac chest pain (Fleet et al., 1996) may warrant further investigation to establish validity of MASQ anxious arousal scale to determine diagnostic screening benefits.

These data should be interpreted acknowledging several limitations including that a shortened MASQ was utilised (Wardenaar et al., 2010) rather than the full version (Watson et al., 1995a, 1995b) and only low positive affect items reflected the depression construct. Thus no items concerned loss of interest a potentially important construct among cardiac surgery patients who face physical activity and social restrictions (Tully et al., 2009a). As Ketterer and colleagues (2007) suggest measures that employ ratings of Behavioral frequency may fare better with respect to screening accuracy. Also, low base rates of the affective disorders are reflected in the width of the 95% CI AUC values, standard errors and the positive and negative predictive values. The MINI had the advantage of identifying primary affective disorders however inevitably precluded potentially informative comorbidity between major depression and generalised anxiety disorder. Patients had established heart disease necessitating coronary artery bypass graft surgery and thus the ROC for the MASQ is not known among heterogeneous cardiac samples.

Conclusion

The MASQ dimensions performed best when predicting affect concordant disorders. Discordant dimensions performed no better than chance supporting the discriminant validity of the MASQ. The absence of latent NA in the MASQ anhedonia and anxious arousal scales may the sensitivity and specificity of the MASQ for diagnostic classification of affective disorders purported to contain a NA component. Therefore the MASQ should be employed cautiously considering other established and validated distress screening measures. Further research should validate the diagnostic utility of affective dimensions and examine these in relation to adverse cardiac outcomes.

Chapter XI Discussion

General Considerations

This chapter provides a general overview of the dissertation results and describes what these data add to the extant literature. The practical implications, future directions and limitations are discussed over and above what is described in the individual Chapters. With regards to the thesis aim to apply conceptual models of depression and anxiety to improve understanding of cardiac surgery outcomes, differential patterns were observed in relation to morbidity, mortality, rehospitalisation, health related quality of life, AF and delirium while no consistent association was found for neuropsychological function. The findings clearly support the second hypothesis that only after examination of the shared variance attributable to NA would the morbidity risk attributable to depression and anxiety become evident. Despite demonstrated utility among the prognostic studies to identify discrete associations with cardiac outcome, the results of the final study do not support the utility of MASQ affect dimensions to screen for depression and anxiety disorders among cardiac patients. A brief summary of the findings in relation to the dimensional and categorical affective constructs is outlined below.

Summary And Synthesis Of Main findings

As discussed in Chapter I, a range of psychological factors have been exhaustively documented as related to adverse CHD outcomes though in particular, depression has been described as a robust prognostic risk factor (Barth, Schumacher, & Herrmann-Lingen, 2004; Rugulies, 2002; Suls & Bunde, 2005; Van der Kooy et al., 2007). The research among cardiac surgery patients has paralleled the broader heart disease literature focussing more on depression than other conceptually and statistically interrelated psychological factors such as anxiety (e.g. Blumenthal et al., 2003; Connerney et al., 203). Across the eight separate cardiac surgery studies described here it was found that disorders, symptoms and traits reflecting depression, anxiety and general stress exhibited differential associations with mortality, readmission, health related quality of life, cognitive performance, delirium, arrhythmia and morbidity. The general findings regarding anxious arousal and somatic tension anxiety suggested that heightened levels of this affective construct before surgery were associated with long-term mortality and six month unplanned hospital readmission. Cognitive and somatic anxiety symptoms were associated with decreased and increased odds for AF respectively. Diagnostically ascertained panic disorder before surgery was not

associated with delirium or a combined morbidity endpoint. Also, self-reported anxiety and depression suggested at least 50% shared variance, while anxiety and depression disorders were strongly associated with state and trait NA. Therefore collectively, the findings support closer examination of the role of anxiety in heart disease patients beyond simply depression, whilst taking into consideration non-specific distress.

That being said, the results with regards to self-report anhedonic depression symptoms suggested a particular association to vitality and social role functioning, physical and general health quality of life six months after surgery. In addition characteristic depression symptoms were associated with hospital readmission though only when postoperative distress measures were analysed. Though depression symptoms were linearly related to six month and five year cognitive functioning these were not reflective of neuropsychological decline *per se*. In contrast, diagnostically ascertained major depression was also associated with incident transient delirium controlling for the effects of overlapping diagnostic criteria. The present depression related results, in context of previous research, indicate that depression may have particular, and not universal, associations to cardiac surgery outcomes. The novel findings concerning depression, and also anxiety, however, were partly due to simultaneous adjustment for general distress in some studies. The findings would therefore strongly support the contention that in order to identify what appear to be discrete associations between affect and cardiac outcomes, the variance attributable to general NA should be controlled for.

The hypothesis that general distress, more so than depression and anxiety, would be associated with morbidity outcomes after cardiac surgery seemed only supported in Study Seven where state distress and trait NA were marginally associated with postoperative morbidity. The combination of Type D personality traits was also marginally associated with delirium in Study Six. Although the affective disorders themselves were significantly associated with state and trait NA in Study Eight, the association with cardiac outcome was minimal once unique partialled depression and anxiety variance was examined with respect to cardiac surgery outcomes (Studies Two to Four). The findings of Study Three corroborated that general stress was significantly associated with some health related quality of life domains though this effect was not significant once depression and anxiety entered the regression models.

The moderate to large correlations between general distress with depression and anxiety can be taken to support Watson's (2009a) theoretical contention that these affective states are inherently related to latent NA. Similarly, the regression findings of Study Eight also support a state and trait component to major depression, panic disorder and generalised

anxiety disorder. Consequently these significant findings implicating depression and anxiety in adverse cardiac outcomes reflect the effects of NA to some degree. That being said, as the results of Study Eight showed, the MASQ's delineation of a NA scale distinct from *unique* depression and anxiety dimensions may hinder screening attempts to identify affective disorders.

Indeed, the discrepancy in findings with respect to affective states, traits and disorders support the recommendation to simultaneously examine *unique* aspects of depression and anxiety with theoretical models (Kubzansky & Kawachi, 2006; Suls & Bunde, 2005). There are several key implications from these findings. Firstly, it is apparent that NA should be sufficiently controlled for to uncover discrete patterns of association between anhedonia and anxious arousal with cardiac outcomes. Secondly, self-report measures of unique depression and anxiety dimensions, separate from NA, may not meet sufficient psychometric requirements to screen for affective disorders.

The conclusions that can be drawn from the current findings are in context of the *a priori* hypothesis and conceptual definitions of affective constructs. According to Clark and Watson (1991), the temperamental disposition toward NA could manifest as anxiety and/ or depression in some individuals, at different times, in different situations, due to idiosyncratic circumstances, coping resources and other personality factors. Thus from a cross-sectional assessment of patients prior to a major surgical operation it is hardly surprising that the clinical presentation of distress reflected a clustering of interrelated negative emotion symptoms differentially related to cardiac outcomes. The accumulated evidence presented here might also suggest, however, that the psychogenic correlates of cardiac surgery endpoints are dependent on which morbidity outcome(s) are investigated and how each particular negative emotion is conceptualised and measured. The unique variability in each study's endpoints, and degree to which covariate control captured causative factors, can explain why the psychological risk factors displayed inconsistent associations. Together the results reflect the complexity of psychogenic correlates of CAD morbidity and encourage broadening of psychological risk factors beyond depression among cardiac surgery and heart disease patients alike.

New Findings From These Studies

Study One addressed a gap in knowledge concerning the effect of anxiety and general distress upon post-CABG all-cause mortality. The findings provided preliminary evidence that anxiety may contribute to adverse CABG surgery outcomes, thereby noticeably

contrasting to other research that had not examined the role of anxiety upon CABG mortality (e.g. Blumenthal et al., 2003; Connerney et al., 2010). Moreover the study adjusted for medical comorbidity whereas an earlier study had not (Szekely et al., 2007). Despite an improvement in methodology supporting the anxiety and post-CABG mortality association, not all authors agree this to be sufficient evidence (Jiang & Xiong, 2011). One limitation was that the simultaneous or synergistic effects of anxiety, depression and general distress were not investigated (Strik et al., 2003; Watkins et al., 2006).

To reconcile the methodological limitation concerning what Smith describes as "portioning at the joints" of naturally co-occurring affective constructs (Smith & Cundiff, in press), depression, anxiety and general distress were analysed simultaneously in Studies Two to Five. Study Two in particular was perhaps the first published report employing a theoretical model of depression and anxiety in relation to cardiac prognosis. Apart from the conceptual and methodological differences, adjustment for medical comorbidity was also a likely explanation for the contrast to other post-CABG surgery readmission studies (Oxlad et al., 2006a).

Study Three was perhaps the first application of the tripartite model in relation to health related quality of life among any population. The discrete findings challenged the assumption that depression impacts broader composite aspects of general and mental health related quality of life after CABG surgery (Al-Ruzzeh et al., 2005; Goyal et al., 2005). A second important finding from the study was that significant effects for state distress on health related quality of life became non significant when depression and anxiety were added to the regression models. In fact, depression was consistently associated with vitality and social role functioning and physical and general health over and above the effects of general distress. Considering previous findings (Panagopoulou, Montgomery, & Benos, 2006), general distress may be associated with health related quality of life in the absence of measures of depression and anxiety.

Study Four reported probably the first conceptual approach to control for affect in relation to cognitive dysfunction after cardiac surgery. Previously there were some inconsistent findings regarding whether distress was associated with neuropsychological performance (Andrew et al., 2000; McKhann et al., 1997; Newman et al., 2001a; Stroobant & Vingerhoets, 2008; Tsushima et al., 2005). Studies were, in some cases, confounded by biased statistical methods (Newman et al., 2001a). The findings here, in context of previous research, suggested that emotional distress is not significantly associated with cognitive dysfunction considering the SRB estimates derived from a non surgical control group. Also

the findings did not support Newman and colleagues (2001a) who overestimated the magnitude of neuropsychological dysfunction to be 42% of all CABG surgery patients.

Though research had investigated psychogenic correlates of AF previously (Hansson et al., 2004; Sears et al., 2005; Suzuki & Kasanuki, 2004; Yavuzkir et al., 2007), Study V was perhaps the first to investigate depression, general distress and also anxiety symptom clusters in relation to incident AF following a CABG procedure. The substantial overlap between anxious arousal and AF symptoms, and the fact that patients may have been endorsing somatic anxiety items in response to AF, highlighted a methodological obstacle for future studies. It also raises the possibility whether differentiation between cognitive and somatic symptoms might provide further information as to the association between distress and AF.

Previous systematic reviews are inconsistent in describing the effects of depression and anxiety upon delirium, while overlapping diagnostic criteria pose a caveat to investigating a prognostic association. In perhaps the first depression study to stringently modify delirium criteria among cardiac surgery patients, the findings suggested that major depression was a risk factor for delirium after CABG surgery, without the confound of overlapping psychiatric criteria. Another new finding from Study Six was that Type D personality might be associated with delirium (OR = 2.85, 95% CI .97 – 8.38).

The interplay between psychosocial factors and CHD risk is undoubtedly complex and may reflect disorder, symptom and trait associations. Prior to Study VII the dissertation had addressed many limitations of previous research offering new understanding of simultaneous psychological risk factors. Yet a comprehensive methodology applying, in turn, varying dimensional, categorical and trait theoretical conceptualisations were sorely lacking. Indeed, as Smith and Cundiff (in press) recommended, to build an informative and cumulative knowledge base the CHD literature requires adoption of more consistent disorder, symptom and trait models of affect. Thus Study Seven integrated, probably for the first time, more than one empirically validated theory of emotion to derive *a priori* hypotheses concerning prognostic cardiac outcomes (i.e. Type D and hierarchical/tripartite). Study Seven was also likely the first study to report a similar proportion of panic disorder and generalised anxiety across high state and trait NA groups, regardless of the tendency to be socially inhibited.

Study Eight was probably the first to assess the ROCs of the MASQ amongst a cohort of patients defined by a medical condition such as CAD. The study also extended Study Sevens' results by investigating the extent to which the Type D personality and

Watson's model could be integrated. The findings further supported Watson's (2009a) assertion that depression, panic and general anxiety are associated with NA and unique disorder specific variance. New data suggested that the MASQ low positive affect and physical arousal symptoms would not necessarily translate to suitable disorder screening measures amongst cardiac patients.

Overall Significance

Many authors have repeatedly opposed the assumption that psychological factors are independent and implored cardiac researchers to address conceptual ideas of multiple emotional distress factors (Bleil et al., 2008; Denollet, 2008; Kubzansky & Kawachi, 2000; Smith & Cundiff, in press; Suls & Bunde, 2005). Uptake of such recommendations has however been sorely lacking (see Appendix A). Notably, the dissertation represents perhaps the first application of an empirically supported theoretical model of depression and anxiety in relation to adverse outcomes among cardiac patients. This thesis attempted to inform a critical gap in knowledge, highlighted by Kubzansky and Kawachi's review (2000), which questioned whether psychological theories of emotion could help answer whether *pure* anxiety or *pure* depression are associated with cardiac outcomes. In other words, various methods were employed to test emotional construct commonality versus emotional construct specificity with respect to cardiac outcomes. The findings corroborated that simultaneous adjustment for NA and empirically validated models of affect may reveal discrete associations between depression, anxiety and cardiac outcomes. It is likely that without the theoretical basis to investigate emotion commonality and specificity, such discrete associations between affect and cardiac outcome would not have been found. The integrative approach may further help to identify specific cardiopathogenic elements of affect and concentrate efforts to testing hypothesised mechanisms (Smith & MacKenzie, 2006).

Identifying cardiac patients at an increased risk of adverse outcome and resource use after interventional surgery is likely to be of intrinsic interest to researchers, hospital executives, governments and health system stakeholders alike. These data may assist mental health and allied healthcare workers, cardiology staff, consensus panels and policy makers as to the deleterious impact of psychological factors on cardiac surgery outcomes. The current research concerning multiple affective components also informs the design of psychological interventions with respect to identifying the *at risk* population (Smith & Cundiff, in press; Laurent & Ettelson, 2001) for particular adverse CABG surgery outcomes. The volume of annual CABG surgery operations among increasingly older and sicker patients,

coupled with the observation that nearly one in five patients experience major depression for example, highlight these patients as a precarious group indeed.

Practical Treatment Implications

These data belie the assumption that depression may act as a stand-alone risk factor for cardiopathogenesis thereby supporting the use of emotion theory to investigate broader psychogenic risk factors. There are several clues from recent psychological and pharmacological RCTs that a broader approach to distress reduction might be of benefit in CHD populations. In a RCT targeting major depression post-CABG, nearly half of CABG patients were diagnosed with a comorbid anxiety disorder (Rollman et al., 2009). A systematic review of six treatment studies among cardiac populations reported modest effect sizes in depression symptom reduction (Hedges *g* 0.20 – 0.38; Thombs et al., 2008). There are mixed reports concerning the efficacy of inter-personal therapy, an intervention specifically tailored toward depression, among CAD patients (Koszycki, Lafontaine, Frasure-Smith, Swenson, & Lespérance, 2004; Lespérance et al., 2007). Reductions in incident cardiovascular events and improved survival from depression treatment RCTs have not been consistently demonstrated (Berkman et al. 2003; Glassman et al. 2002). Significantly lower depression levels among a control group compared to an exercise and behaviour modification group (Sebregts et al., 2005) challenge the benefits of behavioural activation alone for reducing depressive symptomatology post CABG surgery.

As Denollet (2008) suggested it is perhaps too soon to restrict intervention trials to the narrow scope of depression. Unfortunately, paradoxical results are not isolated to depression RCTs among cardiac populations. Some studies report lower anxiety (Ku, Ku, & Ma, 2002; Sorlie, Busund, Sexton, Sexton, & Sorlie, 2007), while others have reported no treatment effects (Shuldham, Fleming, & Goodman, 2002; Tranmer & Parry, 2004) or, paradoxically, increased readmissions and healthcare utilisation (Lie et al., 2007).

Needless to say that treatment and intervention should be made available for clinically distressed cardiac patients regardless of whether a survival benefit is documented. It cannot be assumed that the results from other cardiac populations will necessarily generalise to CABG surgery patients. Further investigation is required with what is, comparatively, an older population with substantial proportion of medical comorbidity. Previous depression RCTs have focussed exclusively on depression treatment in the postoperative period (Rollman et al., 2009; Freedland et al., 2009) discounting early detection of distressed and possibly anxious patients before surgery, as described recently

elsewhere (Appendix B). Conversely, anxiety focussed intervention is typically applied in the preoperative period and patients are not supported after surgery.

In context of the current dissertation results it is possible that contemporary general stress reduction techniques such as mindfulness and supportive stress management techniques may provide a novel opportunity pre and post cardiac surgery, as has been applied to other medically ill populations (Brown & Ryan, 2003). One advantage of general distress reduction interventions is the applicability to persons with varying levels and varying clinical presentations of emotional distress, discomfort and physical comorbidity. Optimally, such intervention would include multidisciplinary collaboration and be integrated into existing care such as community and hospital rehabilitation. A disadvantage however is that general stress reduction is not directly focussed on individual client needs (Rozanski et al., 2005). Also, the evidence basis for general distress interventions among diverse cardiac populations is quite mixed (see Goldston & Baillee, 2008) and has not been systematically reviewed amongst CABG surgery patients.

Nevertheless, it is difficult to derive strong recommendations for treatment from these data other than that depression is clearly not the only psychological factor associated with post CABG morbidity. Therefore, psychosocial intervention among CABG surgery patients should not be restricted to the narrow focus of depression. Secondly, the extent to which psychosocial intervention would affect neuropsychological function is modest.

Practical Implications at the Study Hospital

A direct application of these findings is that, commencing in January 2010, the Department of Cardiothoracic Surgery at Flinders Medical Centre has administered the SF-12 health related quality of life measure before and six months after surgery to all patients undergoing a cardiothoracic procedure. The implementation of the SF-12 into routine clinical practice relates to quality of life being considered by clinicians as a relevant functional outcome for individual patients, and will additionally serve to bolster research studies. Some authors have also recommended screening CABG surgery patients for depression following surgery as a way to improve pathways to recovery (Charlson & Isom, 2003). Of course the evidence basis, costs, benefits, and stigma associated with routine screening for depression in CAD have garnered much debate (Blumenthal & O'Connor, 2010; Thombs, Jewett, Knafo, Coyne, & Ziegelstein, 2009; Ziegelstein, Thombs, Coyne, & de Jonge, 2009). At Flinders Medical Centre, the Patient Health Questionnaire-9, that asks respondents the DSM-IV diagnostic criteria for depression and provides a rating scale of severity, was adopted for

research purposes. The decision to employ diagnostic screening for depression, but not anxiety, may reflect institutional staff preference and brevity of this measure. Given the inherent difficulty in screening for the heterogenous anxiety disorders, and it was not clear from these data and other research whether particular disorders, or anxiety in general, are important for CABG surgery outcomes. Nevertheless, as it was shown in Study Eight, the MASQ and DS14 did not exhibit favourable sensitivity and specificity with respect to prediction of depression, panic and general anxiety.

Future Research Directions

Previous depression and CHD research omitting anxiety, among other factors, is severely oversimplified, to the detriment of identifying affective components related to poorer cardiac outcome. Widening the research scope to embrace psychosocial constructs interrelated with depression may shift away from what has traditionally been a *piecemeal* approach to health psychology and behavioural cardiology. Such an empirical stance may also avoid the undesirable situation of prematurely endorsing a sole psychosocial variable as has historically been the case with Type A or coronary prone behaviour pattern (for a review see Razzini et al., 2008). Intriguingly, it is currently the case that the American Heart Association recommends universal screening for depression among patients (Lichtman et al., 2008), yet at the same time, the widely publicised adverse prognostic impact of depression upon CHD is not universally agreed upon (Nicholson et al., 2006). Of course, conversely espousing that numerous psychological risk factors portend worse medical outcome is equally undesirable and once relegated psychosomatic medicine in the 1940s and 1950s into near discredit as Holroyd and Coyne once noted (1987). Therefore it appears that a balance must be found between the numerous, if not superfluous, emotional risk factors with an empirical demonstration of independent risk from interrelated emotional constructs. Thus, as was hypothesised in the dissertation *a priori*, it seems that only a systematic comparison of interrelated constructs, under an empirically validated framework, in a methodologically robust manner, can explicate the independent effects of psychological factors upon cardiac outcome. Moreover, research methodology will have to take into consideration moderator and mediation effects between these variables and health outcomes (Stanton, Revenson, & Tennen, 2007).

Anxiety and to an extent NA confound depression focused research on cardiopathogenic mechanisms and prognosis. Here, even supposedly differentiating and unique anhedonic and somatic tension symptoms were moderately correlated with each other and NA. As Smith and Cundiff (in press) point out, researchers in behavioural medicine

routinely imply that different labelled measures tap into distinct constructs when they may be highly overlapping if not equivalent constructs. Smith and Cundiff (in press) also cite this as evidence of what Block (1995) previously described as the "jangle fallacy." Such caveats suggest that cardiac outcome research requires clear psychosocial construct definition, differentiation from related constructs and transparency (see Appendix C). A case in point is that of psychological, mental and environmental *stress*. Upon synthesising expert recommendations and previous systematic reviews, an Australian National Heart Foundation position paper suggested that stress was so poorly defined in the literature that it was essentially meaningless to amalgamate such research findings in context of heart disease (Bunker et al., 2003).

Methodological obstacles that complicate further research include conceptually defining elements from a vast scope of self-report measures reflecting various somatic, cognitive, state, trait and symptom clusters (for review see Clark & Watson, 1991). Like the erroneous assumptions of the "jangle fallacy," de Jong and Hall (2006) noted in their review of anxiety measures that cardiac researchers rarely define anxiety. Even at the disorder level there appears to be varying degrees of categorical comorbidity and construct interrelation (Mineka, Watson, & Clark, 1998) suggesting that relative, and not necessarily absolute, associations should be explored. Also, as it appears unlikely that anxious arousal and somatic tension symptoms is representative of all anxiety disorders, further research should therefore incorporate other anxiety constructs and processes into disorder based research. In the vein of NA and anxious arousal/somatic tension, anxiety sensitivity, that is fear of anxiety symptoms, is differentially related across the anxiety disorders (Deacon & Abramowitz, 2006; Olatunji & Wolitzky-Taylor, 2009) and has not been investigated among cardiac patients. As anxiety sensitivity is negatively reinforcing, it is more likely associated with chronic symptoms (Deacon & Abramowitz, 2006). One suggestion would therefore be to examine anxiety sensitivity with respect to the somatic sensations commonly experienced in CAD such as chest pain and fatigability. Of course other anxiogenic symptoms, behaviours and cognitive processes should also be considered (e.g. catastrophising, worry, hypervigilance, avoidance, anxiety sensitivity, rumination, self-processing, attention to threat) and identifying explicit eliciting stimuli (e.g. medical procedures, hospitals, social situations, chest pain) (Craske et al., 2009; Mathews & MacLeod, 2005).

Like anxiety, depression related symptoms, behaviours and cognitive processes require further investigation among cardiac patients (e.g. rumination, guilt, behavioural withdrawal, melancholia, negative memory bias, mastery, sociotropy) (Mathews & MacLeod, 2005). Also similar to the heterogeneous anxiety disorders and anxiety related constructs, less is seemingly known about minor depressive disorder, dysthymia, melancholic

depressive subtypes and bipolar disorder among heart disease patients. Also within these depressive variants, cardiac patients may experience substantial differences in cognitive and somatic symptoms potentially reflecting cardiac illness or depressogenic cognitions (Martens et al., 2006; Thombs et al., 2009). Research among myocardial infarction patients suggests that new onset or incident depression but not lifetime history of depression portends worse cardiac prognosis (Grace et al., 2005; de Jonge, van den Brink, Spijkerman, & Ormel, 2006). Further research should similarly establish whether lifetime, current and incident affective disorders, enduring or transient distress, and personality traits portend discrepant risk among CABG surgery patients.

Yet adoption of purely categorical classifications restricts researchers to taxonomic rules (Brown, Chorpita & Barlow, 1998) as was evident in Study Seven. This precludes an examination of the dimensional nature of disorders. Future research could thus benefit from incorporating both dimensional and categorical measures to optimally investigate the association with morbidity outcomes, whether that is for depression or anxiety. Simultaneous investigation of depression and anxiety in CHD populations will also necessitate developments within the field towards comprehensive systematic review and meta-analytic methods. That is, meta-analytic techniques should strive to address psychosocial moderator variables and, as Rosenthal and Di Matteo (2001) point out, testing of theory (e.g. commonality of NA and CHD outcomes).

Further Empirically Validated Theoretical Research

The tripartite and hierarchical models provide solid empirical grounding to identify the links between depression, anxiety and even NA upon cardiac outcomes. However there are no universally accepted models for the relatedness of anxiety and depression. It is possible that depression and anxiety; are opposites on the same continuum, are alternative manifestations of a single disorder/disease process or vulnerability factor, are differentiable syndromes with some shared diagnostic features, that one disorder causes the other, and that co-occurrence are merely a chance result (Sherr & Trull, 1996). Therefore, investigation among cardiac patients should further explore alternative theoretical models and be critically informed by clinical psychology and psychiatry. Recent examples include cognitive content specificity (Martens et al., 2006) and sociotropy and autonomy (Stafford et al., 2009) though the latter theory explicitly precludes anxiety. Theoretical models should also bridge the gap between empirical understandings of affect and behaviour. The field may therefore consider integrating explanatory models within cardiac research such as valence arousal (Heller &

Nitschke, 1998), behavioural activation/inhibition systems (Gray, 1987, 1994) and approach-withdrawal (Davidson, 1998; Sutton & Davidson, 1997).

Any theoretical model of affect, personality, or human behaviour inevitably oversimplifies complex individual processes and social contextual factors. Therefore subsequent cardiac research should investigate proximal indicators such as affect, personality and behaviour and expand to encompass evidence implicating interpersonal processes (Smith & Ruiz, 2002), ethnicity, geographic location, economic status, access to healthcare and other social factors (Chaix, 2009; Dreher, 2004).

Type D Personality

Some limitations of Type D personality construct were described in Chapter I. Type D personality research predominantly dichotomises continuous NA and social inhibition measures to create a personality *type*. Comparisons between Type D patients with persons high on NA in the absence of social inhibition (as per Study VII), and also socially inhibited persons with low NA, can provide more detailed information of how these personality types deleteriously influence CAD prognosis. As Smith and MacKenzie (2006) noted, the *distressed* personality type assumes unique prognostic information despite the incremental effect of two personality traits, or the interaction, being rarely investigated. Study VII suggested that NA and not the NA*social inhibition interaction was associated with adverse morbidity outcome among CABG surgery patients. Future research should strive to determine the incremental prognostic risk attributable to NA and social inhibition traits and evaluation of these traits on a continuum to consider dimensional distributions of personality (Ferguson et al., 2009).

Another limitation to be addressed in the future concerns the extent to which the *distressed* traits are conceptually related to, and possibly surrogate markers for, existing psychiatric taxonomies (e.g. social anxiety disorder, avoidant personality disorder). Notwithstanding previous criticisms, another limitation warranting clarification is the overlap between avoidant personality disorder criteria of preoccupation with being criticised or rejected in social situations and the Type D social inhibition trait. Indeed, the extent to which social anxiety disorder and avoidant personality disorder are marked by NA (Watson, 2009a) and anhedonia (Hughes et al., 2006) will influence the association to Type D personality traits. That being said, substantial interrelation between Type D personality and social anxiety disorder and avoidant traits might stimulate suggestions for treatment to target

avoidance and maladaptive schemas (Sperry, 2006; Wells, 1997b) given that Type D intervention recommendations are lacking.

Future Interventions

Though affective disorder treatment is important in any context, it has not been sufficiently investigated whether interventions among cardiac patients can promote and maintain health related behaviour change (Hermele, Olivo, Namerow, & Oz, 2007). Another limitation that should be addressed in the near future concerns RCT for patients with co-morbid depression and anxiety. Also, revascularisation patients that experience significant postoperative morbidity are typically excluded from psychological therapy RCTs and thus less is known about the long term treatment outcomes with respect to patients with extended length of time spent intubated and in the intensive care unit, persons with stroke, deep sternal wound infection, sternal dehiscence or postoperative renal failure requiring dialysis. Such patients are possibly at risk for incident distress, documented to be a stronger predictor of cardiac morbidity than pre-existing psychiatric disorders (Grace et al., 2005; de Jonge, van den Brink, Spijkerman, & Ormel, 2006).

Perhaps not all psychosocial interventions among cardiac patients should be limited to persons meeting clinically relevant levels of distress. General interventions concern prevention of future, non-current, psychological distress. It is feasible that preventative psychosocial approaches could be imbedded within cardiac rehabilitation programmes informed by psychologists and psychiatrists. Consistent with the findings that both depression and anxiety were related to poor outcomes, there is potential efficacy and cost-effectiveness from delivery of transdiagnostic approaches that target general distress vulnerability factors common to depression and anxiety, rather than depression or anxiety alone. Dozois and colleagues (2009) recently described that common and modifiable vulnerability risk factors for depression and anxiety include negative cognitive content processes, stress and coping, and behavioural inhibition and avoidance.

Concerning post-CABG cognitive function; these data do not support a role of affective distress in permanent neuropsychological decline after CABG surgery. Therefore above described interventions would not be expected to lead to improvements in post-CABG neuropsychological function, but may impact transient delirium. Further research should continue to explore cardiac risk factors (e.g. PVD, diabetes) and also technical aspects related to surgery (e.g. cross clamping techniques) that portend worse permanent cognitive dysfunction. A research shift toward identifying cognitive domains rather than absolute

number of heterogenous cognitive deficits may also prove beneficial to explicating the mechanisms of cognitive dysfunction.

Limitations

Sampling.

The individual studies and recommendations from this thesis must be interpreted bearing in mind certain limitations including the geographic location and sampling of patients from only two South Australian institutions. The prospective studies were less likely to include Aboriginal patients, suggesting that these findings would not generalise to this Indigenous population. To this end, it was also the case that the dissertation did not incorporate culturally sensitive and relevant concepts of subjective wellbeing, as opposed to mental health *per se*, for the recruited Aboriginal participants. The fact that Aboriginal and Torres Straight Islander cardiac surgery patients face poor health such as a high proportion of diabetes, renal disease, heart failure and rheumatic heart disease (Alizzi, Knight, & Tully, 2010) should serve to highlight the health of these Indigenous groups as a future research priority.

Though data were collected prospectively, the retrospective audit is subject to chance variation within the data set that may not necessarily generalise. Data concerning sociodemographic factors such as low income, social support, and marital and work stress were not documented that can impact on a persons' perception of emotional distress and potentially influence CAD outcomes. In all studies the patients undergoing emergency procedures were not recruited, highlighting the pragmatic difficulties inherent in recruiting patients who are likely to experience acute emotional distress and are at high risk for morbidity.

Distress onset, distress precursors and follow-up.

The current study is largely limited by the cross-sectional assessment of patient distress typically in the week before surgery. Some evidence suggests that anxiety levels in particular are highest when on the waiting list with an unknown surgery date (Fitzsimons et al., 2003; Koivula et al., 2002). Transient versus chronic and enduring distress may differentially impact upon cardiac surgery patient health related behaviour, coping and morbidity outcomes. Likewise, the absence of comprehensive post-surgery follow-up

compromises how these findings should be interpreted. There was no documentation of psychotropic medication use and engagement with clinical therapy (e.g. psychologist, psychiatrist). Depression and anxiety remission may have reduced the effect sizes for adverse outcome attributable to distress. Indeed, it is somewhat remarkable that a once off perioperative assessment of distress is associated with poorer outcome many years after CABG surgery. However, such cross-sectional assessments inevitably fail to capture important health and life related events that, for CABG surgery patients, could reasonably include redundancy, retirement, nursing home institutionalisation, and other medical diagnoses (e.g. cancer, sexual dysfunction).

Negative affect.

Not all research findings have been supportive of a positive association between NA and cardiac outcomes. Smith's (2001) systematic review concluded that CHD and negative emotional states merely co-exist as opposed to sharing any specific pathophysiological effects. Also Watson and Pennebaker's (1989) review of studies among healthy populations suggested that there was no relationship between NA and CHD risk factors such as blood pressure and serum cholesterol. They went on to suggest that NA may act as a *nuisance* variable in health research. It should also be noted that research concerning personality factors in cancer populations, and also Type A or coronary prone behaviour, has historically fallen largely out of favour in the scientific community (Holroyd & Coyne, 1987). Likewise, within psychopathology research it has been suggested that neuroticism is not a sufficient vulnerability factor in the aetiology of depression and anxiety (Ormel, Rosmalen, & Farmer, 2004).

Conceptual and measurement issues.

The attempt to conceptually distinguish between affective constructs should not imply that the current body of work empirically achieved this difficult aim (Suls & Bunde, 2005). Moderate to large correlations between self-report measures, as reported in Study III and Study VII, suggest discriminant validity issues (Smith & Cundiff, in press). Also these measures are confounded by measurement error, poor sensitivity and specificity reflecting the diagnostic disorders (e.g. Study VIII), and are by no means exhaustive in terms of symptomatology. Despite a tripartite-like factor structure for the DASS, the stress scale was conceptualised as a distinct syndrome (Lovibond & Lovibond, 1995). Also anxious arousal/somatic tension, as reflected in the DASS and MASQ, is strongly associated with panic disorder but has also been incorporated into diagnostic criteria for pending generalised

anxiety disorder (American Psychiatric Association, 2010). This corroborates the assertion by Mineka and colleagues (1998) that symptom specificity is relative and not absolute. Similarly, anhedonia was conceptualised here and by Watson (2009a) as a distinct affective marker of unipolar depression. Yet anhedonia is commonly observed among persons with psychosis and dementia related disorders (Winograd-Gurvich, Fitzgerald, Georgiou-Karistianis, Bradshaw, & White, 2006) suggesting non exclusivity of anhedonia. Also the emphasis on unipolar depression precludes the largely unknown role of bipolar disorders on heart disease patient outcomes. With respect to symptom measurement, the shortened MASQ outlined by Wardenaar et al (2010) reflects only low positive affect and not loss of pleasure *per se*.

In further consideration of affective phenotypes, Studies VI-VII employed general NA as a close approximation to broad generalised anxiety dimensions and not symptoms *per se*. General anxiety can be conceptualised via worrisome cognitions and also meta-cognitions, i.e. worry about worry (Wells, 1997a), and the self-report instruments employed here did not reflect such a clinical meta-cognitive framework. Also, though indeed generalised anxiety disorder has a high NA and irritability component, pending diagnostic revisions have incorporated the requirement also for somatic tension (American Psychiatric Association, 2010).

This thesis resides largely on the assumption that depression and anxiety comorbidity is not an artificial bi-product of diagnostic *splitting* (Mineka, Watson, & Clark, 1998) of related disorders. A limitation of disorder-based studies (e.g. Study VI - VII) is that low base rates necessitate a large recruitment pool, and dysthymia, obsessive-compulsive disorder, post-traumatic stress disorder and specific phobia were excluded from any analyses. A related point concerns the hierarchical exclusion rule specified by the MINI for major depression and generalised anxiety disorder that would inevitably result in lower prevalence and comorbidity rates despite phenotypic and genetic overlap (Watson, 2009a). Inconsistent diagnostic classification rules may result in varying prevalence estimates among CABG surgery patients compared to the Structured Clinical Interview for DSM-IV (Rafanelli et al., 2006; Rothenhausler et al., 2005), Diagnostic Interview Schedule (Connerney et al., 2001) and Clinical Interview Schedule (Fraguas et al., 2000).

Statistical and methodological issues.

The present investigation exclusively employed regression based techniques (linear, logistic, hazard and logit link). In most studies employing a low frequency outcome variable the regression models were constrained to a limited number of covariates. Though remaining

within conventional regression guidelines for overfitting (Babyak, 2004), important variance in the outcome variable was inevitably omitted, evidenced by low c-statistics in study VI and VII. Multicollinearity also poses as a statistical limitation here among the studies reporting the effects of interrelated self-report distress measures. Taking the finding from Study II that lower readmission risk was attributable to stress highlights how multicollinearity may lead to parameter estimates of incorrect sign, incorrect magnitude or large standard errors of the estimate (Slinker & Glantz, 2008). Indeed, the correlations between DASS and MASQ measures were typically $r > .7$ highlighting that the issue of multicollinearity is one of degree rather than presence. Similar likely multicollinearity effects can be observed in Al-Ruzzeh and colleagues' (2005) study where reduced odds for poor health related quality of life after cardiac surgery was attributable to increasing anxiety scores when Type D personality was included in the regression model. In an attempt to circumvent multicollinearity here by adjusting for NA, the analyses concerned only residualised depression and anxiety variance and not pure construct variance *per se* (Lynam et al., 2006).

Alternative approaches in the cardiac literature have included deriving orthogonal factors from self-report measures (Kubzansky et al 2006; Frasure-Smith & Lésperance, 2003). The methodological limitations of such an approach include the statistical manipulation and therefore artificial independence of naturally co-occurring and interrelated distress variables as Smith and Cundiff have pointed out (in press). Resembling the partialled variance limitation in the present study, it is questionable what variance for a given factor remains once all variance shared with another factor is removed. The field is yet to consistently overcome the methodological complexity of investigating interrelated and collinear psychogenic risk factors for CAD morbidity.

Conclusion

These data support the Society of Thoracic Surgeons report that psychological factors can deleteriously impact upon cardiac surgery patient health and morbidity outcomes (Eagle et al., 2004). Investigation of theoretical models of emotion identified discrete risk patterns for adverse cardiac surgery outcomes. Identifying unique psychogenic risk factors for cardiac outcomes is in the nascent stages, with many aspects of emotional distress phenomenology not yet described consistently, whether in relation to mechanisms of cardiopathogenesis or cardiac outcome. The fact that non-specific NA is diffusely embedded within many self-report distress measures and appears to be relatively and not absolutely associated with affective disorders cannot be understated. Needless to say those previous authors' recommendations are resonated here whereby independence between depression

and anxiety risk for cardiac outcome has not been sufficiently established. To build a cumulative and not disjointed knowledge basis our understanding of the interrelationships between psychological factors and cardiac outcomes must therefore be informed by empirically validated theories of emotion. Nevertheless, a single psychological affective construct, or theory, is overly simplistic to determine cardiac risk. Moreover, these models fail to encompass the complexity of individuals' behaviours and neglect social context such as access to healthcare, ethnicity and income. Therefore further research should combine theoretical models of affect with theories of behaviour and broader social and economic factors, to better understand incident CHD and adverse cardiac morbidity risk among CABG surgery and other populations.

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APPENDIX A

Tully PJ. (2010) Theories of depression and anxiety and cardiovascular outcomes in psychosomatic medicine and behavioural cardiology. *Psychosomatic Medicine*, 72(2), 224-225. [Letter]

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paucity of theory and reluctance to address overlapping psychosocial risk factors for cardiovascular morbidity. The absence of theory development in behavioural cardiology with respect to depression and anxiety, among other emotions, perhaps reflects reluctance to adopt theoretical perspectives, low priority, or a lack of awareness (or boldness) to base research around a theoretical framework. Whatever the reason, one unfortunate consequence is the scarcity of well-formulated and testable hypotheses as to whether a single depressive construct and/ or symptoms (versus those characteristic of anxiety), combinations of depression and anxiety, or common dimensions shared between depression and anxiety are related to cardiovascular outcomes. It is the latter hypothesis and the associated theoretical perspectives that are briefly discussed herein.

As a starting point, Dr. Watson (2009) described the seminal tripartite, integrative hierarchical and quadripartite model of depression and anxiety as a comprehensive account of the interrelation between depressive and anxiogenic disorders and symptoms. Specifically, Watson (2009) reviewed nearly 400 research papers to arrive at this conclusion, and highlighted that simply because a self-report measure has the word "depression" in the title does not imply measurement of the depressive construct at all. The authors originally postulated that substantial overlap between depression and anxiety is explained by latent negative affect (NA) or neuroticism. Moreover, depression and anxiety are differentiated based on unique symptoms tapping into anhedonia/ low positive affect (PA), and aspects of somatic arousal, respectively, though the latter was found to be most related to Panic Disorder. Likewise, Barlow et al. (2006) described anhedonia as unique to depression, and further specified that somatic arousal is closely associated with fear, whereas general distress is a manifestation of anxiety. One potential advantage of considering general distress is that this approach can be applied to categorical and dimensional approaches of depression and anxiety (Watson, 2009), whilst encompassing other negative emotions, such as anger and possibly other constructs important to cardiovascular outcomes defined by a central NA trait (e.g., Type D personality). Of interest, in an examination of the tripartite model that hypothesized general distress would be related to six-month outcomes post coronary artery bypass graft surgery, depression was commonly associated with lower and worse quality of life (Tully et al., 2009), whereas anxiety was associated with increased risk of cardiac and surgery-related hospital readmissions (Tully et al., 2008).

Our understandings of depression and anxiety in Behavioral cardiology and psychosomatic medicine are developing. Dr. Watson's model is but one developing theory of depression and anxiety, and one of few employed with hypotheses to predict morbidity outcomes in cardiovascular patients (Tully et al., 2008; 2009). Some alternative perspectives on depression and anxiety, or combinations of the following that may also prove equally

fruitful include Barlow's emotion-based theory (1996), a two-factor NA/ positive affect model (Watson & Tellegen, 1985), and Beck's (1976) cognitive-content specificity hypothesis. Hopefully, the suggestion by Dr. Rutledge et al. (2010) and other authors is resonated here that consideration of theories of depression and anxiety and other emotions may help shift away from analysis of unitary constructs in isolation that has unfortunately fostered a piecemeal approach and absence of hypotheses in behavioural cardiology and psychosomatic medicine. Regardless of whether researchers formulate testable hypotheses and give any credence to theoretical perspectives of emotion, some as yet to be reconciled methodological obstacles relate to comorbidity at the diagnostic level, heterogeneity of the anxiogenic disorders and defining symptoms, whereas multicollinearity and symptom overlap may affect studies employing self-report measures. One potential solution for self-report studies is to employ measures of anxiety that adequately discriminate between anxiety and depression symptoms on separate scales at the same time measuring general distress. Coincidentally, Dr. Watson's hierarchical model (2009) may assist resolving the latter methodological limitations related to self-report measurement of anxiety and depression symptoms.

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Appendix B

Tully PJ. (2010). Telephone-delivered collaborative care for post-CABG depression is more effective than usual care for improving mental-health-related quality of life. *Evidence Based Medicine*, 15(2), 57-58

Invited commentary on: Rollman, B.L., Belnap, B. H., LeMenager, M.S., *et al.* (2009). Telephone-delivered collaborative care for treating post-CABG depression: a randomized controlled trial. *Journal of the American Medical Association*, 302, 2095–2103.

Rollman and colleagues' randomised control trial (RCT) concerns treatment of depression after coronary artery bypass graft (CABG) surgery. Increased mortality risk attributable to depression after CABG (Connerney et al., 2001) and myocardial infarction (van Melle et al., 2004) is a pressing reason to identify effective depression treatment in these patients.

The RCT involved an 8-month, bi-weekly nurse-led, telephone-delivered intervention for depression after on pump' or 'off pump' surgery across seven hospitals in Pennsylvania, USA. Patients were randomised to intervention (n = 150) or usual care (n = 152), and 151 non-depressed individuals served as a control group. The intervention, tailored to patient preference, consisted of psychoeducation, antidepressant pharmacotherapy, referral to a community mental health specialist (MHS), behavioural activation and pleasant activity scheduling, avoidance of tobacco, alcohol and unhealthy foods, a depression handbook and 'watchful waiting'.

Primary analyses involved the intervention and usual care groups on baseline to 8-month change in Mental Composite Score from the SF-36, with an effect size of 0.30 (95% CI 0.17 to 0.52). Secondary analyses of physical functioning and mood symptoms also indicated intervention treatment effect sizes of approximately 0.30.

After 8 months of intervention, scores on the Mental Composite Score and Hamilton Rating Scale for Depression among the treatment and usual care groups did not reach the baseline level of the non-depressed group. Female patients did not benefit from the intervention despite greater pharmacotherapy use; male patients were more likely to report use of the depression workbook. Low intervention MHS visits (4% vs 6% usual care) would not have contributed to treatment effect sizes. Among the study's limitations is the failure to report the number of MHS referrals, participation in cardiac rehabilitation targeting mental

and physical health and behaviours, or intervention cases where 'watchful waiting' was applied. The trial protocol (Rollman et al., 2009) indicated an analysis of secondary end points consisting of employment and treatment costs, but these are yet to be reported.

The clinical implications relate to the efficacy and practicality of telephone-delivered psychological support after CABG surgery, and to determining whether a particular component of this multifaceted, individually tailored intervention is associated with depression remission. Cardiology departments would probably require staff with specialist training in psychiatry, psychology and cardiology to balance the clinical and cost-effectiveness of such a collaborative care package, particularly as the intervention spanned 8 months and 20% of a hospital's CABG patient caseload would be candidates for depression treatment (Dunkel et al., 2009). Moreover, depression is more common among female CABG patients (Dunkel et al., 2009) and favourable results were generally not documented for women in secondary analyses by gender. There may also be some barriers to collaborative care relating to the individual primary care physician, hospital culture, work practices and psychiatry registrar or allied health professional workload (Wade et al., 2005) in addition to MHS costs, cardiologist/surgeon preference and overlap with cardiac rehabilitation services.

The results of this study generally support those of a recent RCT (Freedland et al., 2009) in suggesting that psychological and pharmacological intervention after CABG is beneficial in reducing depressive symptoms. However, it is not known whether a particular component of the intervention here contributed substantially to depression remission and improved quality of life. It cannot be assumed that the findings from other RCTs of treatment following myocardial infarction or unstable angina can be extrapolated to patients undergoing CABG; further research like that of Rollman and colleagues will help clarify the particular outcomes for CABG patients. Identifying adverse morbidity outcomes before depression treatment (eg, prolonged intensive care unit stay, renal failure, sternal wound infection) may provide insight into factors impeding depression remission rates. Research to date has typically examined unitary psychological constructs, whereas in this RCT nearly 40% of depressed patients were identified with a co-morbid anxiety disorder. A gap in knowledge that remains for CABG patients and cardiovascular populations alike relates to determining optimum treatment of heterogeneous anxiety disorders and the effects of anxiety on cardiovascular outcome alongside depression.

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Appendix C

Tully, P. J. (in press). On post traumatic stress disorder and neuropsychologic impairment among cardiac surgery patients, *Journal of Cardiac and Vascular Anesthesia*

The article by Hudetz et al (2010) covers the exhaustively documented topic of neuropsychologic impairment after cardiac surgery among a sample of 86 male patients recruited from a Veterans Affairs hospital. The potentially novel information provided by this study is the comparison of persons supposedly with and without post-traumatic stress disorder (PTSD) undergoing cardiac surgery. A sample of nonsurgical hospital patients with coronary artery disease, as specified by medical notes, also was recruited. Whether these patients were also screened for a history of PTSD was not reported although 29% had a history of depression.

Unfortunately, the major limitation of Hudetz et al's study (2010) is the lack of descriptive information pertaining to how, when, and by whom the original PTSD diagnosis was made. It was reported that a preoperative PTSD interview was not performed although it is not clear why this was the case given that all patients underwent face-to-face psychometric testing. Similarly, it was not reported how the sleep disorders, history of alcohol dependence, and mood disorders were ascertained in any of the recruited patients, surgical or otherwise. The authors implied that at some point in time a PTSD diagnosis was made for 30 of the 86 cardiac surgery patients, suggesting a 34.9% lifetime prevalence, which may reflect the elder male veteran sample. Recently, Dao et al's (2010) discharge record database study reported that 14.7% of cardiac surgery patients had a PTSD diagnosis, whereas another 9.0% had comorbid PTSD and depression. Both of these reports seem large compared with another recent study in which less than 5% of cardiac surgery patients met current criteria for PTSD in the week before cardiac surgery after diagnostic interview (Tully, Baker, Winefield, & Turnbull, 2010). This highlights the potential discrepancy in prevalence derived from databases versus clinical interviews for psychiatric disorders among cardiac surgery patients; each having their strengths and limitations.

Presumably, the patients recruited from the Veterans Affairs hospital in Hudetz et al's study (2010) would have at some point, possibly after combat, been identified as meeting some form of diagnostic criteria for PTSD. Indeed, the PTSD criteria used may vary over time as diagnostic criteria change and also vary across diagnostic instruments. Although the authors' Veteran Affairs sample is likely to have experienced trauma during combat, it should be pointed out to readers that civilians living in combat zones; persons receiving a diagnosis

of a life-threatening illness; survivors of physical violence, rape, motor vehicle accidents, and natural disasters; witnesses to the previously mentioned events; and those hearing such news regarding loved ones may also develop PTSD. However, only thorough psychiatric evaluation and structured diagnostic interview will accurately identify current PTSD, as is the case for depressive disorders.

A second limitation of Hudetz et al's study (2010) concerns the neuropsychologic analyses. The authors' analysed differences between patients with and without PTSD at baseline but not postoperatively. Moreover, the authors calculated a composite z score from a nonsurgical group but did not consider demographic predictors, test-retest reliability, and measurement error in the calculation as others have recommended (Tully, Baker, Kneebone, & Knight, 2008). Indeed, amalgamating heterogenous neuropsychologic domains into a composite measure immediately after surgery may obscure potential mechanisms of brain injury, and, thus, the clinical utility of these possibly transient amalgamated cognitive impairments is debatable. Nevertheless, although PTSD was significantly associated with the composite neuropsychologic z score, the amount of variance explained in cognitive functioning was not reported, and no adjustment was made for other known demographic and medical predictors of neuropsychologic performance. Given the previously mentioned limitations, the clinical impact of current PTSD on cognitive function after cardiac surgery remains largely unknown.

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