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CO-MORBID SYMPTOMS OF DEPRESSION AND ANXIETY AND BIO-BEHAVIORAL RESPONSE TO STRESS IN PATIENTS WITH HEART FAILURE

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CO-MORBID SYMPTOMS OF DEPRESSION AND ANXIETY AND BIO-BEHAVIORAL RESPONSE TO STRESS IN PATIENTS WITH HEART FAILURE

DISSERTATION

A dissertation submitted in partial fulfillment of the
requirements for the degree of Doctor of Philosophy in the
College of Nursing at the University of Kentucky

By
Abdullah Subhi Alhurani

Lexington, Kentucky

Director: Dr. Debra K. Moser, Professor of Nursing

Lexington, KY

2016

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ABSTRACT OF DISSERTATION

CO-MORBID SYMPTOMS OF DEPRESSION AND ANXIETY AND BIO-BEHAVIORAL RESPONSE TO STRESS IN PATIENTS WITH HEART FAILURE

Heart failure (HF) is a major public health problem throughout the world. It accounts for one death certificate among nine in the United States. Heart failure and sudden death combined are responsible for the largest number of deaths in America. The total costs of HF in the United States are estimated to be $37 billion each year. Despite substantial medical and surgical advances related to treatment of HF, it remains a very costly condition with high mortality and morbidity rates. Although biological factors contribute to high morbidity and mortality in HF, there are many unexplored psychosocial factors that also likely contribute to these rates. Thus, the purpose of this dissertation was to examine the association between some of the psychosocial factors (i.e. depression, anxiety, comorbid depression and anxiety, stress, cognitive appraisal, and coping) and health outcomes as defined by rehospitalisation and mortality among HF patients.

The first paper is a report of longitudinal study of 1,260 patients with HF. The purpose of the study was to determine whether co-morbid symptoms of depression and anxiety are associated with all-cause mortality or rehospitalization for cardiac causes in patients with HF. Anxiety and depression were treated first as continuous level variables, then as categorical variables using standard published cut points. Patients were then divided into four groups based on the presence of symptoms of anxiety and depression. When depression and anxiety were treated as continuous level variables, both comorbid depression and anxiety, and depression alone were significant predictors of all-cause mortality. However, when depression and anxiety were treated as categorical variables, comorbid depression and anxiety was a predictor of all-cause mortality, while anxiety and depressive symptoms considered alone were not independent predictors of the same outcome. None of those variables were significant predictors of cardiac rehospitalization outcome, regardless of whether entered as continuous or categorical level variables.

The second paper is a report of a study that was conducted to (1) examine the association of stress with 6-month cardiac event-free survival; (2) examine the relationship of stress with salivary cortisol; and (3) examine the association of salivary cortisol level with 6-month cardiac event-free survival. The study sample was 81 HF patients. A prospective design was used in which patients were followed for 6 months to determine occurrence of 6-month cardiac event-free survival, defined as time to the

combined endpoint of cardiac rehospitalization or all-cause death. Stress was not a significant predictor of event-free survival in HF, salivary cortisol was a significant predictor of event-free survival in the unadjusted model, but not in the adjusted model, and stress was not a significant predictor of salivary cortisol level.

The final paper is a report of prospective design study that aimed to describe self-reported stress level, cognitive appraisal and coping among patients with HF, and to examine the association of cognitive appraisal and coping strategies with event-free survival based on a proposed model of HF patients' response to stressors that been suggested according to literature to date. The study sample consisted of 88 HF patients who been followed for 6 months to determine occurrence of the combined endpoint of rehospitalization for cardiac causes or all-cause death. The study showed that stress level was associated with harm and loss cognitive appraisal. Harm/loss and threat cognitive appraisals were associated with avoidant emotional coping. Furthermore, harm/loss cognitive appraisal was a significant predictor of avoidant emotional coping and event free survival. Finally avoidant emotional coping was a significant predictor of event free survival among HF patients in the unadjusted model, but not in the adjusted model.

The findings from this dissertation provided further evidence of the importance of psychosocial factors to health outcomes in HF patients. It also filled important gaps in the body of knowledge related to health outcomes among those with HF by demonstrating the need for cognitive and behavioral therapy among HF patients who negatively appraise their health condition.

Keywords: Heart failure, Comorbid depression and anxiety, Stress, Health outcomes, Cognitive appraisal and Coping.

Abdullah S. Alhurani

Student's Signature

March 22, 2016

Date

CO-MORBID SYMPTOMS OF DEPRESSION AND ANXIETY AND BIO-BEHAVIORAL RESPONSE TO STRESS IN PATIENTS WITH HEART FAILURE

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CHAPTER ONE

Introduction

Heart failure (HF) is a complex, progressive clinical condition arising from any structural or functional cardiac disorder that affects the capability of cardiac ventricles to fill with or eject blood.[1] In the United States, HF is considered a major public health problem that affects around 5.7 million patients, with 670,000 newly diagnosed patients each year.[2,3] Heart failure and sudden death combined are responsible for the largest number of deaths in America.[4,5] The total costs of HF in the United States are estimated to be $37 billion each year, and this number will rise to around $70 billion by 2030.[2,6] By 2030, more than 8 million people in the United States will be diagnosed with HF.[6] Despite substantial medical and surgical advances related to treatment of HF, in 2010, there were about 279 000 deaths related to HF, which is as high as that reported in 1995 (287 000).[3] Heart failure also is the most common hospital discharge diagnosis among elders and the number of hospitalizations for HF is increasing substantially each year.[3,4]

The one-year mortality rate of HF patients with progressive symptoms still approaches 40%, which is the same for some types of aggressive cancer.[7,8] Even patients who have less serious HF symptoms usually experience impaired quality of life.[8] The high mortality and morbidity rates associated with HF are still not well explained. [9] Although biological factors explain some aspects of the high mortality and rehospitalization rates, it would not be surprising if other aspects of these rates are related to psychological factors such as depression, anxiety, and stress.[9] Patients with HF concurrently suffer from multiple psychological symptoms that affect patients' prognosis, physical health, and mental well-being such as symptoms of depression and anxiety.

Furthermore, HF is generally perceived as a very stressful experience that also likely contributes to the poor prognosis. [9-15]

Depression is a mood disorder that affect the patient's capability to deal with daily life activities.[16,17] Depression is associated with distinct symptoms such as changes in appetite, sleep disturbance, fatigue, agitation, feelings of guilt or worthlessness, and concentration problems.[11,18,19] In the context of HF, depression is considered a major clinical problem that affects around 48% of the outpatients who have HF with up to 20% of those are experiencing major depression symptoms.[20] Heart failure patients who suffer from depressive symptoms have two times the risk of being rehospitalized or dying compared to those who do not suffer from these symptoms.[21] Furthermore, patients who suffer from depressive symptoms often engage in unhealthy behaviors like smoking, excess alcohol use, drug use, and unsatisfactory adherence. [22,23] Pathophysiologically, depression is associated with negative effects on cardiac function through mechanisms such as hypercortisolemia, impaired platelet function, and reduced heart rate variability. [24-27]

When the individual is unable to predict, control, or even gain from a situation that is perceived by the individual as a threat, this will lead to a state of negative emotions called anxiety. [11,16] Like depression, anxiety is also associated with negative cardiac events such as coronary artery diseases and sudden cardiac death. [10,16] Anxiety also may be considered a mediator for some pathophysiological mechanisms that affect health outcomes such as cardiac arrhythmias, reduced heart rate variability, and baroreflex cardiac control. [28-30] Anxiety is considered a major clinical problem that affects 40% of HF Patients with a severity that is 60% higher than anxiety severity in healthy elders.

[11,31,32] Furthermore, anxiety severity in patients with HF tends to be higher than among patients with other cardiac, lung, and cancer diseases. [33,34] Conversely, there are contradictory results about the effect of anxiety on health outcomes among patients with HF.[33,34]

Multiple studies addressed the association of depression and anxiety, individually, with survival in HF patients; however, the association between co-morbid symptoms of anxiety and depression and survival is unknown. Thus, Chapter Two of this dissertation is a report of a study in which we investigated the association of co-morbid symptoms of depression and anxiety with all-cause mortality and cardiac rehospitalization in patients with HF. Chapter Two presents a secondary analysis from a longitudinal study of 1,260 patients with HF. The purpose of the study was to determine whether co-morbid symptoms of depression and anxiety are associated with all-cause mortality or rehospitalization for cardiac causes in patients with HF. Cox regression analysis was used to determine whether co-morbid symptoms of depression and anxiety independently predicted all-cause mortality and cardiac rehospitalization. The results showed that the interaction between symptoms of depression and anxiety (when the variable was considered at the continuous level) was a significant predictor of all-cause mortality but not cardiac hospitalization. In addition, comorbid depression and anxiety when the variable was considered at the categorical level was a significant predictor for all-cause mortality but not cardiac rehospitalization (versus no symptoms, or symptoms of anxiety or depression alone). Questions remaining are, (1) what factors lead to symptoms of depression and anxiety in patients with HF? And (2) why do HF patients suffer from depression and anxiety more than other populations?

Depression or anxiety symptoms often develop after stressful life events that are not cognitively processed in a healthy manner.[35] Thus, cognitive appraisal of the stressful events plays a major role in selecting a suitable coping strategy to handle stressful events.[36] Therefore, although stressful events play an integral role in producing symptoms of depression and anxiety, there are individual variances in how people respond to these events.[36] In a classic study conducted by Brown & Harris (1978)[37], stressful events rapidly led to depression within the first month after the event.[37] Other studies suggest that stressful events may cause depletion of several neurotransmitters such as norepinephrine, dopamine, and serotonin, which may lead to depression or anxiety symptoms.[38]

In a study conducted among Mexican-American college students, higher levels of stress were associated with higher levels of depression and anxiety symptoms.[39] Furthermore, coping mechanisms were predictors of depression and anxiety symptoms.[39] A study in which investigators studied the moderating effects of gender and cognitive avoidance coping on the negative life events–depressive/anxious symptoms relationship demonstrated that stressful life events predicted symptoms of depression and anxiety.[40] In addition, cognitive coping strategies were predictors of depression and anxiety symptoms in a study that investigated healthy adolescents and adults.[41]

Depression and anxiety symptoms are been well studied in HF population. However, there is limited information about the effect of stress and coping mechanisms in HF population. Thus, there is a need to establish a body of knowledge regarding stress and coping mechanisms in the HF population, so it can be used by both clinicians and researchers to decrease the high mortality and rehospitalization rates in HF patients. To

fully understand stress and coping in HF context, some of the concepts need to be defined in this chapter.

Stressors can be defined as environmental events or chronic conditions that objectively threaten the physical and/or psychological health or well-being of individuals.[42] Stressors may lead to a state in which a patient perceives that environmental demands exceed his or her adaptive capacity [43]; this state is called stress. The term "stress" also can be used to summarize the effects of psychological and environmental factors on the patient's physical and mental health. [44,45] Stressful events are unpredictable and seemingly uncontrollable events that affect individuals' lives. Given that HF is associated with many of the psychological distress factors that significantly affect patients' prognosis, physical health, and mental well-being, HF is a very stressful experience physically and psychologically.[11,12] [11,12]

There is limited information about stress and heart failure. However, in cardiac disease patients, stress was associated with multiple adverse effects on patient health outcomes.[46-48] For example, stress was associated with decreased blood supply to the coronary arteries and was a significant predictor of greater severity of cardiac disease.[49,50] In addition, a lower level of stress was a predictor of improved prognosis and cardiac function in cardiac disease patients.[51] Furthermore, stress had an effect on the immune system which may exacerbate disease processes and lead to further complications.[52] Finally, stress was significantly associated with an increased mortality rate among cardiac disease patients.[53]

Stress is defined physiologically as the condition in which the sympathoadrenomedullary system (SAM) and the limbic-hypothalamic-pituitary-adrenal

axis (HPA) are co-activated.[54] Stressors mainly activate two major neural pathways which are the HPA axis and the sympathetic nervous system. The activation of the sympathoadrenomedullary system is the initial and rapid acting response of the body to stress. However, HPA axis activation is the delayed body response to stress to restore homeostasis. [55]

The SAM system is activated through the hypothalamus and brain stem, which sends an activation signal to the adrenal medulla that releases stored epinephrine into the blood circulation. The release of epinephrine will promote changes in the tissues that supplied by beta-adrenoreceptors such as cardiac, blood vessels, liver, adipose tissues and musculoskeletal. [56] The activation of beta-adrenoreceptors promote changes such as increased heart rate and contractility, vasodilatation, glycogenolysis, lipolysis, and bronchodilation.[56] In the heart failure context, most patients are routinely treated with beta-adrenergic blockade, which makes the study of the stress response challenging because SAM stress responses are inhibited by beta blockers.[57,58] Much of the literature on animals and humans suggests that psychological factors can influence the HPA axis, which controls the release of cortisol, an important glucocorticoid that is secreted by the adrenal cortex. Over the past decades, many investigators have concluded that physical and psychological stressors are capable of activating the HPA axis and increasing cortisol level in the blood stream.[59] However, the effects of psychological stressors on this physiological system are variable.[60] This variability is likely a result of differences in an individual's cognitive appraisal of a stressor.

The thalamus and frontal lobes of the brain put together the sensory information and assess the significance or meaning of environmental stimuli in a process called

cognitive appraisal. Based on this appraisal, an emotional response will be generated through connections from the prefrontal cortex to the limbic system. The limbic system, which is connected to the hypothalamus, serves as the primary conduit for HPA activation. The activation begins when the hypothalamus exudes the corticotropin releasing hormone (CRH) which stimulates the anterior pituitary to secrete adrenocorticotropin hormone (ACTH), which in turn stimulates the adrenal cortex to secrete cortisol in the blood.[61,62]

Through cortisol, the HPA supports physiological functions and regulates other systems. Cortisol plays a major role in metabolism through the glycogenolysis process that converts amino acids and fats to glucose in the liver to meet body requirements. In addition, cortisol inhibits the immune system and regulates the inflammation process.[59] Furthermore, the sympathetic nervous system requires a certain level of cortisol to perform physiologic functions effectively, such as inducing vasoconstriction or increasing heart rate.[59] However, prolonged cortisol activation due to frequent exposure to stressors is associated with many negative biological effects such as suppression of aspects of the immune system, damage to hippocampal neurons, and development and progression of certain chronic diseases like diabetes and hypertension.[52,63] In heart failure, cortisol may contribute to the progression of cardiac damage by acting as a mineralocorticoid receptor (MR) agonist in cardiac muscle, which causes cortisol to mimic the physiological and pathophysiological effects of aldosterone.[64-67]

In a study conducted by Guder et al., higher levels of serum cortisol and aldosterone were independent predictors of mortality in HF patients.[67] Thus, determining whether the stressors that are associated with HF activate the cortisol system and

contribute to the onset or exacerbation of certain health outcomes is crucial. Based on this literature, measurement of cortisol is an appropriate reflection of response to stressors in patients with HF.

In the third chapter of this dissertation we aimed to examine the association of stress with cardiac event-free survival; examine the relationship of stress with salivary cortisol; and examine the association of salivary cortisol level with cardiac event-free survival. This study was a longitudinal study with a sample of 81 HF patients. We hypothesized that stress and salivary cortisol are predictors of event-free survival in HF patients. In addition, we hypothesized that stress is a predictor of salivary cortisol level in HF patients. Cox regression analyses and multiple linear regression were used for data analysis. Stress was not a significant predictor of event free survival in HF. Salivary cortisol was a significant predictor of event free survival in the unadjusted model but not in the adjusted model. Stress was not a significant predictor of salivary cortisol level. But do these results suggest that stress is not a predictor of health outcomes in HF patients or is there an indirect association of stress with outcomes that is mediated through another construct that remains unexplored.

Cognitive appraisal is the patient's perception of a stressor with an assessment to the stress level that caused by it. It also includes an assessment of the patient's goals and resources available to face that stressor.[68,69] Psychologists have long realized that people have considerable differences in their appraisals of and response to stressors. Thus, cognitive appraisal became a core theory in many stress models.[59,68] Cognitive appraisal has the following forms: (1) irrelevant when the situation has no effect on the patient, (2) benign positive when the situation is appraised as positive, (3) or stressful.[68] When the

event is viewed as stressful, then it can be appraised in three categories: (1) Harm / loss, which refers to a harmful occurrence like illness or damage to self or social esteem; (2) Threat, which refers to suspected harm that does not occur; and (3) Challenge, in the opportunity occurs for gain and growth. [68] In a study conducted by Harvey et al.,[70] cognitive appraisal played an important role in stress responses, which have been proven to impair health performance. Harm/loss and threat cognitive appraisals were associated with impaired performance, lower quality of life, and poor health outcomes when compared to challenge cognitive appraisal.[71,72]

The cognitive appraisal mechanism can give a general view or prediction about patients' psychological and physical coping. [73] The stress appraisal and coping model, developed by Lazarus and Folkman,[68] was a starting point for recent research in which stress and coping were investigated. Lazarus and Folkman[68] define coping as "Constantly changing cognitive and behavioral efforts to manage specific external and/or internal demands that are appraised as taxing or exceeding the resources of the person." Coping can be also defined as cognitive or behavioral attempts to manage, master, or alter the stressor by reducing it or by tolerating it.[74,75] Two major types of coping have been addressed. [68] The first is emotion-focused coping, which describes the patient attempts to control his or her emotional response without changing the stressor because the patient believes no change can be made on the stressor. [68,76] Emotion-focused coping can be divided into two categories (active emotional coping and avoidant emotional coping) based on the strategies that are used by the patient to reduce or manage the emotional distress relating to the stressor.[77,78] Active emotional coping includes venting, positive reframing, humor, acceptance, and emotional support strategies. Avoidant emotional

coping includes self-distraction, denial, behavioral disengagement, self-blame, and substance use.[79,80] The second major type of coping is problem-focused coping, which occurs when the individual responds to attempt to control, alter, and manage the stressor. [68,76] Problem-focused coping contains cognitive and behavioral strategies such as planning, positive reinterpretation and growth, reaching out for instrumental support, and religion.[79,80]

The predominant view of emotion-focused coping in the stress and coping literature is that it is a maladaptive form of coping associated with poor health outcomes.[81,82] In contrast, problem-focused coping that aims to alter or manage the stressor is positively associated with better adjustment and outcomes in the literature.[82] According to Folkman,[75] emotion-focused coping strategies are used in situations with high levels of uncertainty, where patient identifies few opportunities for effective beneficial change. In contrast, problem-focused coping strategies are used in situations where patient feels a sense of personal efficacy and perceives the possibility for making positive change.[75] Patients with HF who used problem focused coping experienced positive health-related quality of life and lower levels of depression. [83-85] In contrast, patient who used emotion focused experienced a negative effect on health-related quality of life and higher levels of depression.[83-85] Practically, avoidant emotional coping is significantly associated with higher levels of anxiety, poorer health outcomes, and lower health-related quality of life. [86,87] Avoidant emotional coping is associated with lower health-related quality of life in patient with head and neck cancer disease.[87]

In a study conducted by Ransom et al.[88], cancer patients, who focused on their illnesses by concentrating their efforts on managing symptoms and seeking out

information about their illness, experienced more positive changes in their physical health and quality of life. [88] Another study conducted on job stress, employees who used problem-focused coping experienced better performance as compared with other employees who used emotion- focused coping.[58] Furthermore, when a challenge (versus a threat) is perceived, problem-focused coping ensued, which leads to better health outcomes. In contrast, threat, harm and loss cognitive appraisals are significantly correlated with emotional-focused coping, which leads to unsatisfactory health outcomes.[71,89-93]

Due to the need to understand these concepts in HF population, a descriptive longitudinal study with a sample of 88 HF patients was conducted and presented in Chapter Four of this dissertation. The purpose of Chapter Four was to describe self-reported stress level, cognitive appraisal and coping among patients with HF, and to examine the association of cognitive appraisal and coping strategies with event-free survival. A model based on the literature to date [10-15,44,45,70-72,77-80,94, 81,82] (see Figure 1) was proposed and presented in Chapter Four in a trial to understand the relationships between the different variables through testing the proposed model. Two tailed Pearson correlation was used to determine relationships among the variables. Cox regression analyses were used to determine if coping style or cognitive appraisal type predicted event-free survival. Linear and multiple regressions were used to determine the association of stress with coping style and cognitive appraisal type, and the association of cognitive appraisal type with coping style. Results showed that stress level was significantly associated with harm and loss cognitive appraisal. Harm and loss cognitive appraisal was significantly associated with avoidant emotional coping. Threat cognitive

appraisal was also significantly associated with avoidant emotional coping. Linear and Cox regression showed that harm loss cognitive appraisal was a significant predictor of avoidant emotional coping and event free survival. Finally avoidant emotional coping was a significant predictor of event free survival among HF patients in the unadjusted model. All other relations in the model were not significant.

In Chapter Five, an integrated summary and conclusions from the findings of the previous four chapters is presented. Recommendations for clinical practice and future research are included in this chapter. The findings from each chapter in this dissertation fill a gap in knowledge about HF patient health outcomes related to psychosocial factors that may contribute to poor outcomes. The dissertation also recommend future research studies and suggested interventions to limit the effect of the negative psychosocial factors on the health outcomes in HF population.

CHAPTER TWO

The Association of Co-morbid Symptoms of Depression and Anxiety with All-Cause Mortality and Cardiac Rehospitalization in Patients with Heart failure

Introduction

In the United States, heart failure (HF) is a major public health problem that affects around 5.7 million patients, with 670,000 newly diagnosed patients each year [2].The total costs of HF in the United States are estimated to be $37billion each year[2]. Although there have been significant therapeutic advances in pharmacological and surgical treatment of HF, the one-year mortality rate of HF patients with progressive symptoms still approaches 40%, which is the same for some types of aggressive cancer [7,8]. Even patients who have less serious HF symptoms usually experience impaired quality of life [8]. The high mortality and morbidity rates associated with HF are still not well explained [9]. Patients with HF simultaneously experience multiple psychological symptoms that affect health outcomes such as symptoms of depression and anxiety.

Depression is a mood disorder that interferes with an individual's ability to perform daily life activities [16,17]. Depression is characterized by specific symptoms such as changes in appetite, sleep disturbance, fatigue, agitation, feelings of guilt or worthlessness, and concentration problems [11,18,19]. Depression is a significant clinical problem that is found in a substantial number of patients with HF; around 20% of outpatients who have HF have major depressive symptoms, and up to 48% of outpatients experience clinically significant depressive symptoms. [20] Furthermore, HF patients who are depressed are two times more likely to be hospitalized and face death than those who are not depressed [21]. Depression is associated with unhealthy behaviors like smoking and

unsatisfactory patient compliance. [22,23] Moreover, depression is associated with pathophysiological mechanisms that negatively affect cardiac conditions, such as hypercortisolemia, impaired platelet function, and reduced heart rate variability. [24-27]

Anxiety is a negative emotional state resulting from the perception of threat, and is described as the result of a perceived inability to predict, control, or gain from the threatening situation. [11,16] Anxiety is significantly associated with a higher occurrence of adverse cardiac events and cardiac death in the general population and in patients with coronary artery disease. [10,16] Anxiety also has been linked to pathophysiological mechanisms that could mediate negative outcomes such as reduced heart rate variability and baroreflex cardiac control, cardiac arrhythmias, and sudden death. [28-30] Patients with HF have a 60% higher level of anxiety compared to healthy elders; 40% percent of patients suffer from major anxiety. [11,31,32] In addition, patients with HF tend to have higher levels of anxiety compared to other cardiac disease patients or even cancer and lung patients. There are, however, contradictory results about the association between anxiety and health outcomes in patients with HF.[33,34]

Individually, depression and anxiety are associated with survival in HF patients; however, the association of co-morbid symptoms of anxiety and depression with morbidity and mortality in patient with HF is unknown. Thus, the purpose of this study was to examine whether co-morbid symptoms of depression and anxiety are associated with all-cause mortality or rehospitalization for cardiac causes in patients with HF.

Method

Design, sample, and setting

Data from this study were from the Heart Failure Health-Related Quality of Life Collaborative Registry [95], housed at the University of Kentucky College of Nursing. This is a longitudinal database that includes data from patients from across the United States and from several international sites (n = 4076). From this database, we analyzed data from all patients who had data on anxiety, depression, and mortality and rehospitalization outcomes (n = 1,260). The demographics (i.e., age, gender, and ethnicity) and New York Heart Association (NYHA) class of the sample used in the current study were compared statistically to those in the registry who did not have data on anxiety, depression and outcomes. There were no differences between these two groups on these four variables. The database was accessed through the Research and Interventions for Cardiovascular Health (RICH) program at the University of Kentucky. Inclusion criteria for the original database were patients with a confirmed diagnosis of HF with impaired or preserved left ventricular systolic function. Patients were excluded if they had valvular heart disease, were referred for heart transplantation, had a history of cerebrovascular accident or myocardial infarction in the past 6 months, and had a co-existing terminal illness. Data on mortality and rehospitalization were collected over 12 months. [96,97]

Measures

Symptoms of Depression and Anxiety

Depressive symptoms. The Patient Health Questionnaire (PHQ-9)[98,99] was used to measure depressive symptoms in this study. The PHQ-9 is a 9-item, self-reported measure of depression that reflects the severity of depressive symptoms over the past two

weeks. [100,101] Patients respond to each item by using a Likert scale in which responses range from 0 (not at all) to 3 (nearly every day). The total summary score can range from 0 to 27; a higher score reflects more severe depressive symptoms. Good internal consistency, stability, construct and concurrent validity of the PHQ-9 have been supported. [97,101] The standard published cut point of 10 was selected in this study for PHQ-9 to identify those in the sample who were depressed and those who were not depressed. [97] This cut point was reported to have 88% sensitivity and 88% specificity for diagnosing major depression.[100,101]

Anxiety. The Brief Symptom Inventory (BSI) anxiety subscale was used to measure current symptoms of anxiety. [102,103] The subscale consists of 6 questions, each of which are scored by patients using a scale that ranges from 0 (not at all) to 4 (extremely). The total score is calculated by summing all 6 item scores and taking the mean. Thus, the possible range of scores for the anxiety scale is 0 to 4 with higher scores indicative of higher levels of anxiety. The BSI has demonstrated internal consistency, stability, construct and concurrent validity in other studies. [102,103] In this study, the Cronbach's alpha of the anxiety scale was 0.82.A standard published mean of 0.35 was used in this study for BSI to identify those in the sample who were anxious and those who were not anxious. [104]

Mortality and Rehospitalization Outcomes

All-cause mortality, or rehospitalization for cardiac causes were the outcome variables in this study. By monthly phone call follow up and by reviewing electronic and non-electronic hospital medical records, all dates of and reasons for hospitalization and

death were collected. Furthermore, death certificates were acquired to confirm the cause of death. Patients were followed for at least 12 months.

Demographic and clinical variables

Data on demographic variables and clinical characteristics were collected by reviewing medical records and interviewing patients. These variables included age, gender, ethnicity, and New York Heart Association (NYHA) class. The NYHA class indicates the level of functional impairment reported by patients as a result of symptoms and was rated by trained research nurses. These variables were selected because of their effects on the outcome variable as suggested in the literature. [97,100]

Statistical Analysis

Data were analyzed using SPSS software, version 20.0 (SPSS Inc., Chicago, IL). Descriptive statistics, including mean, standard deviation and frequency distribution, were used to describe sample characteristics. In the main analysis, anxiety and depression were treated first as continuous level variables, then as categorical variables. In order to create the categories, variables were created for each individual describing the presence of depression and anxiety using published, standard cut points (10 and 0.35, respectively). Patients were then divided into the following four groups: 1) patients who had neither depression nor anxiety; 2) patients who had depression; 3) patients who had anxiety; and 4) patients who had comorbid anxiety and depression. Sample socio-demographic and clinical characteristics (i.e., age, gender, ethnicity, NYHA class, anxiety level and depression level) between the four groups were compared using X^2or ANOVA as appropriate to the level of measurement. Hierarchal Cox regression analyses were used to determine whether co-morbid symptoms of depression and anxiety,

independently, predicted mortality alone, or cardiac rehospitalization alone. Data were forced into the regression in order to provide simultaneous control. The following covariates were considered: age, gender, ethnicity, NYHA class, and anxiety and depression. We first tested the interaction term defining the continuous level variables for anxiety and depression, and the outcomes. We next tested the grouping variables identifying co-morbid depression and anxiety status. The assumptions of hierarchal Cox regression were tested and no violation occurred. A p-value of 0.05 was considered statistically significant.

Results

Demographic and clinical characteristics of patients (N = 1,260) are summarized in Table 2.1. The mean levels of anxiety and depression were 0.82 with a SD of 0.92, 7.48 with a SD of 6.22, respectively. Using the clinically defined cut points, 52.9 % of the participants were anxious and 32.5% were depressed. When the sample was divided into the four predefined groups, a total of 5.7% of the patients had depressive symptoms only, 26.1% had anxiety symptoms only, and 26.8% had co-morbid symptoms of anxiety and depression. Eighty-two (6.5%) of the participants died and 182 (14.4%) were hospitalized during the study.

Hierarchal Cox regression was run with anxiety and depression treated as continuous level variables and all-cause mortality as the outcome. In the first block in which demographic variables were entered, only older age was a significant predictor of all-cause mortality. In the second block, NYHA class was entered to the model. Age remained a significant predictor. Additionally, worse NYHA functional class was a significant predictor in this block. In the final block, age (HR 1.03; 95% CI: 1.01-1.05; p

= 0.009), worse NYHA class (HR 3.90; 95% CI: 2.39-6.36; p < 0.001), and higher levels of depression (HR 1.06; 95% CI: 1.01-1.11; p = 0.012) were significant predictors of all-cause mortality among HF patients. The interaction between anxiety and depression (HR 1.02; 95% CI: 1.01-1.03; p = 0.002) was also a significant predictor of all-cause mortality. However, anxiety (HR 1.07; 95% CI: 0.79-1.45; p = 0.652) was not a significant predictor of all-cause mortality (Table 2.2).

Another hierarchal Cox regression was run with anxiety and depression treated as continuous level variables and cardiac rehospitalization as the outcome. In the first block in which demographic variables were entered, older age, female gender, and ethnicity (African Americans compared to Caucasians, and Caucasians compared to other ethnicities) were significant predictors of cardiac rehospitalization. In the second block, NYHA class was entered to the model. All previous variables remained significant predictors. Additionally, worse NYHA functional class was a significant predictor in this block. In the final block, anxiety, depression, and the interaction between anxiety and depression were entered to the model. Age (HR 0.99; 95% CI: 0.97-1.00; p = 0.016), female gender (HR 1.40; 95% CI: 1.01-1.94; p = 0.042), African Americans ethnicity compared to Caucasians ethnicity (HR 2.43; 95% CI: 1.67-3.54; p < 0.001), and Caucasians ethnicity compared to other ethnicities (HR 0.30; 95% CI: 0.10 - 0.95; p = 0.040), and worse NYHA functional class (HR 2.62; 95% CI: 1.94-3.55; p < 0.001) were significant predictors of cardiac rehospitalization among HF patients. However, anxiety (HR 0.93; 95% CI: 0.75-1.15; p = 0.505), depression (HR 1.02; 95% CI: 0.99-1.05; p = 0.290), and the interaction between anxiety and depression (HR 1.00; 95% CI: 1.00-1.01; p = 0.648) were not significant predictor of cardiac rehospitalization (Table 2.3).

In the next analysis, anxiety and depression were treated as categorical variables and the four categories previously defined were entered in a hierarchical cox regression to predict all-cause mortality (Table 2.4). In the first block in which demographic variables were entered, only older age was a significant predictor of all-cause mortality. In the second block, NYHA class was entered to the model. Age remained a significant predictor. Additionally, worse NYHA functional class was a significant predictor in this block. In the final block, the four anxiety and depression groups were entered into the model. The final model demonstrated that that older age, worse NYHA class, and comorbid anxiety and depression were the significant predictors of all-cause mortality. In this analysis neither anxiety alone nor depression alone were significant predictors of all-cause mortality among HF patients (Figure 2.1). Based on these results, HF patients with comorbid anxiety and depression are 2.6 times more likely to die compared to those who are neither depressed nor anxious (Table 2.4 and Figure 2.1).

A final hierarchical Cox regression was used where anxiety and depression were treated as categorical variables to predict cardiac rehospitalization (Table 2.5). In the first block in which demographic variables were entered, older age, female gender, African American ethnicity compared to Caucasian, and Caucasian ethnicity compared to other ethnicities were significant predictors of cardiac rehospitalization. In the second block, NYHA class was entered to the model. Age, gender, and ethnicity remained significant predictors. Additionally, worse NYHA functional class was a significant predictor in this block. In the final block, the four anxiety and depression groups were entered into the model. The final model demonstrated that that older age, female gender, African American ethnicity compared to Caucasian, Caucasian ethnicity compared to other

ethnicities, and worse NYHA class were the significant predictors of cardiac rehospitalization. In this analysis neither anxiety alone, depression alone, or comorbid anxiety and depression were significant predictors of cardiac rehospitalization among HF patients (Table 2.5 and Figure 2.2).

Discussion

Several important findings are evident from this study. First, anxiety and depressive symptoms are common and are commonly comorbid in patients with HF. The majority of our sample experienced symptoms of depression or anxiety, or both. Second, we demonstrated that comorbid anxiety and depressive symptoms, when considered as a clinically relevant categorical variable, was predictive of all-cause mortality, while anxiety and depressive symptoms considered alone were not independent predictors of the same outcome. When treated as continuous level variables, both comorbid depression and anxiety, and depression alone were significant predictors of all-cause mortality. None of the psychological variables were predictive of the cardiac rehospitalization outcome, regardless of whether entered as continuous or categorical level variables. The findings of this study emphasize the hazardous effects of comorbid anxiety and depressive symptoms on the mortality rate of adults with HF.

More than 50% of HF patients suffer from significant symptoms of anxiety or depression. [11,31,32] HF patients' mortality rate is around 40% within the first year of diagnosis despite current medical and surgical advances. [7,8] Because anxiety and depression have been consistently associated with poorer health outcomes,[33,34] we wanted to examine whether they also explained the high rates of mortality among HF patients.

This study is one of few to investigate comorbid anxiety and depression and its effect on all-cause mortality and cardiac rehospitalization in patients with HF. Frasure-Smith and colleagues found that anxiety and depression were associated with cardiac mortality using a single instrument (the General Health Questionnaire-20) to assess psychological distress. However, these researchers did not control for disease severity, age, and other risk factors. In addition, the additive effect of anxiety and depression was not studied. [105] In another study by Doering and colleagues, [106] researchers focused on mortality and demonstrated that co-morbid anxiety and depression were predictive of all-cause mortality in patients with coronary artery disease, but did not study hospitalizations. Doering et al. also used the Multiple Adjective Affect Checklist (MAACL-D) to measure depression. [106] However, in the HF population, the PHQ-9 is considered one of the best instruments to measure depression. [100,101] In addition, Doering et al treated depression and anxiety as a categorical variables without consideration of these variables treated at the continuous level, which may mask expression of the phenomenon.

Our study is unique in its focus on comorbid anxiety and depression and its effect on cardiac rehospitalization and mortality for all causes in HF patients. Our strengths included the use of valid and reliable instruments to measure depression and anxiety symptoms in patients with HF, and a large sample size. Furthermore, we treated anxiety, depression, and both as continuous-level and categorical-level variables, and we controlled for multiple covariates such as age, gender, ethnicity, and NYHA class.

Our study showed that depression alone, and the interaction of depression and anxiety are the only significant psychological predictors of all-cause mortality among HF

patients when we included continuous measures of anxiety, depression, and the interaction between anxiety and depression in our model. When we conducted the analysis using categorical variables, we found that comorbid anxiety and depression was the only significant psychological predictor; neither anxiety nor depression alone was a significant predictor. For depression alone, the lack of significance may be explained by the low number of individuals who had depression alone (n=72). However, when we run the analysis again using an unadjusted model, depression alone (HR 2.53; 95% CI: 1.04-6.16; p = 0.042) was a significant predictor of all-cause mortality among HF patients. This finding suggests that sample size alone does not explain the failure of depression to independently predict the outcome, but rather, suggests that depression, in the company of other psychological, demographic and clinical predictors of outcomes, depression alone is not an independent predictor.

Our results that psychological factors are important mechanisms for the high mortality rate in HF. Anxiety and depression are strongly associated with unhealthy practices such as smoking, drinking, and unsatisfactory patient compliance [22,23]. They are also associated with physiological changes that can lead to hospitalization and death such as hypercortisolemia, impaired platelet function, reduced heart rate variability, cardiac arrhythmias, and sudden death [24-27,28-30]. Thus, these behavioral and physiological factors associated with anxiety and depression likely contribute to the continuing high morbidity and mortality in HF.

Study limitations

A potential limitation of our study was the use of self-reported measurement of symptoms of anxiety and depression, rather than diagnostic interviews. However, a strict

protocol was used to measure anxiety and depression, and we and others have previously demonstrated the reliability and validity of the self-report instruments used in patients with HF. [107-110] Another possible limitation was the absence of treatment, and failure to adjust for some covariate such as smoking and alcohol consumption that may contribute to the phenomena. However, the major covariates, age, gender, ethnicity, and NYHA class, were controlled for in this study. This, along with the large sample size, are strengths of the study.

Conclusion

Our findings have clinical and research implications. Comorbid anxiety and depression symptoms are a better predictor of death in HF patients than anxiety or depression alone. Thus, to improve outcomes in patients with HF, attention must be paid by healthcare providers to the assessment and management of co-morbid symptoms of depression and anxiety. Future studies should investigate and evaluate strategies or methods that able to screen and treat depression and anxiety symptoms in HF patients effectively.

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Table 2.1: Sample baseline characteristics (N = 1260)

Characteristic	N (%) OR MEAN ± SD
Age	63.57 ± 13
Anxiety score	0.82 ± 0.92
Depressive symptoms score	7.48 ± 6.22
Gender	
Male	804 (63.8)
Female	456 (36.2)
Ethnicity	
Caucasian	1017 (80.7)
African American	153 (12.1)
Other	90 (7.1)
New York Heart Association class	
I/II	664 (52.7)
III/IV	596 (47.3)
Anxiety and depression categories	
No Anxiety or Depression	521 (41.3)
Depression Only	72 (5.7)
Anxiety Only	329 (26.1)
Co-morbid Anxiety and Depression	338 (26.8)

Table 2.2: Cox proportional hazard regression of variables associated with all-cause mortality in patients with HF, and anxiety and depression treated as continuous level variables.

Predictor Variables	Exp.(B)	95% CI	P
Age	1.03	1.01 – 1.05	0.009
Female Gender	1.06	0.67 – 1.68	0.805
African American compared to Caucasian	0.30	0.07 – 1.23	0.095
Caucasian compared to ethnicity other than African American	0.55	0.17 – 1.76	0.315
NYHA class III/IV compared to I/II	3.90	2.39 – 6.36	< 0.001
Anxiety	1.07	0.79 – 1.45	0.652
Depression	1.06	1.01-1.11	0.012
Anxiety*Depression	1.02	1.01– 1.03	0.002

Overall Model (χ^2 = 60.08, df. = 6; p <0.001); NYHA = New York Heart Association

Table 2.3: Cox proportional hazard regression of variables associated with cardiac rehospitalization in patients with HF, and anxiety and depression treated as continuous level variables.

Predictor Variables	Exp.(B)	95% CI	P
Age	0.99	0.97 – 1.00	0.016
Female Gender	1.40	1.01 – 1.94	0.042
African American compared to Caucasian	2.43	1.67 – 3.54	< 0.001
Caucasian compared to ethnicity other than African American	0.30	0.10 – 0.95	0.040
NYHA class III/IV compared to I/II	2.62	1.94 – 3.55	< 0.001
Anxiety	0.93	0.75 – 1.15	0.505
Depression	1.02	0.99-1.05	0.290
Anxiety*Depression	1.00	1.00– 1.01	0.648
Overall Model (χ^2 = 87.37, df. = 6; p <0.001)			

Table 2.4: Cox proportional hazard regression of variables associated with all-cause mortality in patients with HF, and anxiety and depression treated as categorical variables.

Predictor Variables	Exp.(B)	95% CI	P
Block I			
Age	1.02	1.00-1.04	0.021
Female Gender	0.94	0.60-1.50	0.806
African American compared to Caucasian	0.30	0.07-1.23	0.094
Caucasian compared to ethnicity other than African American	0.59	0.19-1.88	0.374
Block II			
Age	1.02	1.00-1.04	0.048
Female Gender	0.98	0.62-1.55	0.929
African American compared to Caucasian	0.28	0.07-1.17	0.081
Caucasian compared to ethnicity other than African American	0.56	0.18-1.77	0.323
NYHA class III/IV compared to I/II	4.19	2.58-6.81	<0.001
Block III (Final Model)			
Age	1.03	1.01 – 1.05	0.006
Female Gender	0.92	0.58 – 1.45	0.717
African American compared to Caucasian	0.30	0.07 – 1.23	0.094
Caucasian compared to ethnicity other than African American	0.56	0.18 – 1.80	0.335
NYHA class III/IV compared to I/II	3.62	2.14 – 3.61	<0.001

Depression Only	1.67	0.68 – 4.12	0.263
Anxiety Only	1.35	0.74 – 2.46	0.332
Comorbid Anxiety and Depression	2.59	1.49 – 4.49	0.001

Overall Model (χ^2 = 62.78, df. = 8; p <0.001); NYHA = New York Heart Association

Table 2.5: Cox proportional hazard regression of variables associated with cardiac rehospitalization in patients with HF, and anxiety and depression treated as categorical variables.

Predictor Variables	Exp.(B)	95% CI	P
Block I			
Age	0.99	0.98-1.00	0.036
Female Gender	0.71	0.52-0.99	0.040
African American compared to Caucasian	2.49	1.71-3.61	<0.001
Caucasian compared to ethnicity other than African American	0.31	0.10-0.97	0.044
Block II			
Age	0.99	0.97-1.00	0.018
Female Gender	0.71	0.52-0.99	0.040
African American compared to Caucasian	2.44	1.69-3.56	<0.001
Caucasian compared to ethnicity other than African American	0.30	0.10-0.94	0.040
NYHA class III/IV compared to I/II	2.60	1.60-3.50	<0.001
Block III (Final Model)			
Age	0.99	0.97 – 0.99	0.035
Female Gender	0.70	0.51 – 1.97	0.034
African American compared to Caucasian	2.47	1.70 – 3.61	<0.001
	0.30	0.10 – 0.95	0.040

Caucasian compared to ethnicity other than			
African American	2.52	1.85 – 3.43	<0.001
NYHA class III/IV compared to I/II			
Depression Only	1.07	0.55 – 2.09	0.847
Anxiety Only	1.01	0.70 – 1.47	0.953
Comorbid Anxiety and Depression	1.18	0.81 – 1.71	0.391

Overall Model (χ^2 = 88.59, df. = 8; p <0.001); NYHA = New York Heart Association

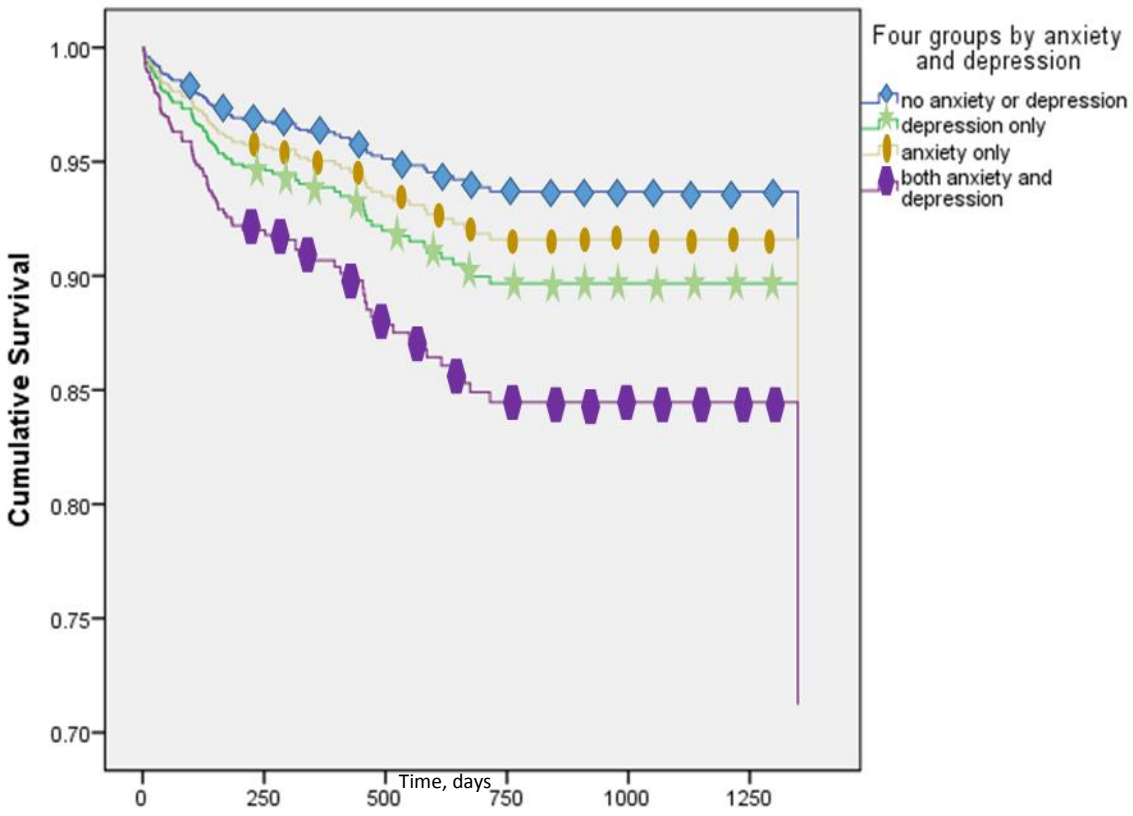

Figure 1. All-cause mortality according to co-morbid symptoms of depression and anxiety

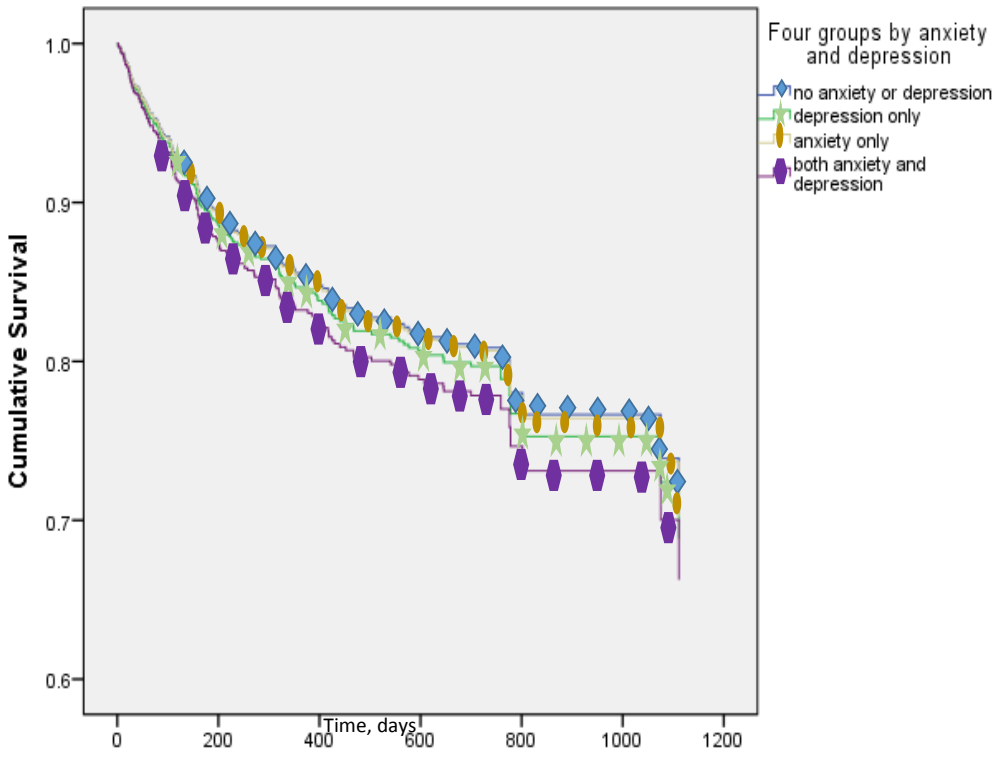

Figure 2. Cardiac rehospitalization according to co-morbid symptoms of depression and anxiety

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CHAPTER THREE

Examination of the Potential Association of Stress with Morbidity and Mortality Outcomes in Patient with Heart Failure

Introduction

Worldwide, heart failure (HF) is considered a major public health problem.[2,111-118] Although there have been significant therapeutic advances in pharmacological and surgical treatment of HF, hospital admission and readmission rates are extremely high for exacerbations of HF, and the one-year mortality rate of HF patients with progressive symptoms still approaches 40%.[7,8,119,120] The high mortality and morbidity rates associated with HF are not completely explained by biological mechanisms, [9] as psychological factors are important predictors of morbidity and mortality in HF. One psychological factor that might contribute to morbidity and mortality in patients with HF is stress. [9,11,121-125]

Stress is the condition that occurs when environmental demands exceed an individual's ability to adapt to the demands. [43] A prerequisite for stress to occur is the individual's perception that stressors are perceived as a persistent threat to their physical and/or psychological health or well-being.[42] Stress is an umbrella term that summarizes the effects of psychological and environmental stressors on an individual's physical and mental health.[44,45] Heart failure is commonly perceived by patients as a very stressful experience both physically and psychologically.[11,12]

There is limited information about the relationship between stress and HF. However, in patients with cardiovascular disease, psychological stress was associated with multiple adverse effects on patient health outcomes.[46-48,126,127] In patients with

cardiovascular disease, psychological stress has been associated with decreased coronary artery blood supply, greater severity of cardiac disease, worse prognosis, and poorer cardiac function.[49-53] Stress is also associated with multiple psychological factors such as anxiety and depression that have negative effects on health outcomes like mortality and morbidity in HF and cardiac disease.[121,128-130]

Given the likelihood that HF is a substantial stressor for many patients, the examination of the role of stress on health outcomes in patients with HF is important. The specific aims of this study were to (1) examine the association of stress with 6-month cardiac event-free survival, controlling for anxiety, depression, and New York Heart Association (NYHA) functional class; (2) examine the relationship of stress with salivary cortisol; and (3) examine the association of salivary cortisol level with 6-month cardiac event-free survival, controlling for age, gender, and NYHA class. We hypothesized that stress and salivary cortisol are predictors of event-free survival in HF patients. In addition, we hypothesized that stress is a predictor of salivary cortisol level in HF patients.

Method

Design, sample, and setting

A prospective design was used in which patients were followed for 6 months to determine occurrence of 6-month cardiac event-free survival, defined as time to the combined endpoint of cardiac rehospitalization or all-cause death. This study was a part of the Heart Outcomes Prevention Evaluation (HOPE) study at the University of Kentucky that investigated depression among hospitalized patients with HF. The parent study and the current study were approved by the Institutional Review Board at the

University of Kentucky. The sample consisted of 81 patients with confirmed HF who were hospitalized for cardiac reasons (i.e., hospitalization for HF, acute coronary syndrome, dysrhythmias) at the University of Kentucky Chandler Medical Center or Good Samaritan Hospital which are located in Lexington, Kentucky.

Patients with a diagnosis of chronic HF confirmed by echocardiogram and cardiologist were eligible for participation in the study if they met the following criteria: a) admitted to the hospital with a primary or secondary diagnosis of exacerbation of chronic HF or any other cardiac diagnosis, b) 21 years or older, c) able to read and speak English, and d) no obvious cognitive impairment. Patients with HF with either preserved or non-preserved ejection fraction were included. Patients were excluded from the study for the following reasons: a) co-existing terminal illness likely to be fatal within the next 6 months, b) presence of a left ventricular assist device, continuous inotropic infusion, or hospice care, c) active suicidality (defined as choosing option 2 or 3 on item 9 of the Beck Depression Inventory-II), d) history of the death of a spouse or child within the past month, e) history of psychotic illness or bipolar illness, f) current alcohol dependence or other substance abuse, and g) new-onset HF.

Measures

Stress

Stress was measured using the brief version of the Perceived Stress Scale.[131] The brief version consists of a four-item scale which has been demonstrated to be reliable and valid.[131] The four items are: (1) how often have you felt that you were unable to control the important things in your life?, (2) how often have you felt confident about your ability to handle your personal problems?, (3) how often have you felt that things were going

your way?, and (4) how often have you felt difficulties were piling up so high that you could not overcome them? Each item is rated by respondents on a scale ranging from 0 (never) to 5 (very often). Higher scores indicate greater levels of stress. In this study, the Cronbach's alpha of the 4-items perceived stress scale was 0.70.

Event Free Survival

Event-free survival was defined as the combined endpoint of cardiac rehospitalization or all-cause death. Hospitalization data were determined through a combination of patient and family interviews and a review of medical records. Hospitalizations were verified by trained research assistants who reviewed medical records and clinic notes on a weekly basis. Given the possibility that patients could have been hospitalized at different facilities other than the three sites involved in the study, trained research assistants carefully questioned the patients or family members by phone to determine if hospitalization had occurred.

All-cause mortality was determined by interview with the patient's family, medical record review and review of county death records. At enrollment, the patient was asked for contact information for a close friend or family member in case the patient could not be contacted. At follow-up if a patient could not be reached by phone, hospital records were searched. When information regarding the patient was not available, family members or friends were contacted. If these contacts could not be reached, county death records were used to determine patient death.

Salivary Cortisol

Cortisol was measured from saliva obtained from patients at baseline through an unstimulated whole expectorated saliva collection protocol. Patients were provided a 20 mL vial containing freeze dried protease inhibitor. Patients were asked to swallow once and begin expectorating approximately every 20 to 30 seconds until 5 ml is collected. The specimen was kept on ice until returned to the lab. Salivary sample was obtained in the morning (9am) on the day of enrollment. The salivary samples were stored in a -80°C freezer until they were analyzed using a commercially available enzyme immunoassay kit designed for cortisol quantification in saliva (Salimetrics LLC, State College, PA, USA). This assay has a sensitivity of <0.007 ug/dL and is strongly correlated with serum cortisol measurement (0.91). Salivary cortisol is considered a more accurate and reliable measure for the clinical assessment of adrenocortical function than serum cortisol.[132,133]

Depressive Symptoms

The Patient Health Questionnaire-9 (PHQ-9)[98,99] was used to measure depressive symptoms. The PHQ-9 is a 9-item, self-reported measure of depressive symptom severity. Patients respond to each item on a Likert scale ranging from 0 (not at all) to 3 (nearly every day). The total summary score can range from 0 to 27; a higher score reflects more severe depressive symptoms. Good internal consistency, stability, construct and concurrent validity of the PHQ-9 have been supported. [98,101] The standard published cut point of 10 was selected in this study for PHQ-9 to identify those in the sample who had moderate to severe depressive symptoms.[28] This cut point was reported to have 88%

sensitivity and 88% specificity for diagnosing major depression.[100,101] In this study, the Cronbach's alpha of the PHQ-9 scale was 0.73.

Anxiety

The Brief Symptom Inventory (BSI) anxiety subscale was used to measure anxiety.[102,103] The subscale consists of 6 questions, each of which is scored by patients using a scale that ranges from 0 (not at all) to 4 (extremely). The total score is calculated as the mean of the 6 item scores. Thus, the possible range of scores for the anxiety scale is 0 to 4 with higher scores indicative of higher levels of anxiety. The BSI has demonstrated internal consistency, stability, construct and concurrent validity in other studies.[102,103] In this study, the Cronbach's alpha of the anxiety scale was 0.77. A standard published mean score of 0.35 was used to identify those in the sample who were anxious and those who were not anxious.[104]

Demographic and clinical variables

Data on demographic variables and clinical characteristics were collected by reviewing medical records and interviewing patients. These variables included age, gender, ethnicity, and NYHA class. The NYHA class indicates the level of functional impairment reported by patients as a result of symptoms and was rated by trained research nurses. These variables were selected because of their effects on the outcome variable as suggested in the literature.[97,100]

Procedure

Protocols for this study were approved by institutional review board of The University of Kentucky. All procedures were in accordance with institutional guidelines

for research using human subjects. Hospitalized patients were identified by clinicians and referred to research staff. The research staff determined the patient's eligibility. The study was thoroughly explained to each patient and signed consent was obtained after answering any questions about the study. The research staff met with the patient to administer study questionnaires via the web based Survey Monkey. The questionnaires took approximately 20 minutes to complete. A paper copy also was offered to the patient if they did not feel comfortable with the web based survey.

As a part of HOPE study, patient were contacted by phone to complete the follow up questionnaire at two weeks, three months, and six months from hospital discharge. At each telephone contact, the research staff asked the patient whether he or she has been hospitalized or visited the emergency unit. At the end of the study period and intermittently thereafter, hospital records were reviewed to confirm deaths, re-hospitalizations or emergency department visits.

Salivary samples were obtained for cortisol measurement in the morning at baseline at the time of questionnaires completion. All saliva samples were stored at -80^{o} C until analysis of samples at the University of Kentucky Dentistry Research laboratory.

Statistical Analysis

Data were analyzed using SPSS software, version 20.0 (SPSS Inc., Chicago, IL). Descriptive statistics, including mean, standard deviation and frequency distribution, were used to describe sample characteristics. To test Specific Aim 1, unadjusted, followed by adjusted, Cox regression analyses were used to determine whether stress, independently predicted event-free survival. The following covariates were considered in

the adjusted analysis and entered hierarchically: age, gender, NYHA class, and anxiety and depression. Demographic and clinical variables were entered first into the model. Then, anxiety and depressive symptoms were entered. Finally, stress as a continuous level variable was entered into the model. The same analysis was conducted using categorical level variables with the mean and median as cut-points.

To test Specific Aim 2, linear and multiple regressions were used to determine the association of stress with salivary cortisol. This analysis included a sample of 70 patients because not all of the patients were able to provide a salivary sample. Two groups, low and high salivary cortisol level, were created based on the median of salivary cortisol level and used in this analysis. This analysis was conducted using both categorical and continuous level variables of salivary cortisol. To test Specific Aim 3 using the same sample size (n=70), unadjusted Cox regression analysis was conducted to determine whether cortisol predicted event-free survival. Then, a hierarchal Cox regression analysis was used controlling to the following covariates: age, gender, and NYHA class. Again this analysis was conducted using both categorical and continuous level variables of salivary cortisol. The demographic and clinical variables were entered first and cortisol was entered second. The assumptions of all Cox regressions, and linear and multiple regressions were tested for violations and none were noted. A p-value of ≤ 0.05 was considered statistically significant.

Results

Demographic and clinical characteristics of patients (N = 81) are summarized in Table 3.1. The average stress score in this sample was 9.47 ± 3.86, with a range of 4 to

20. No cut point has been defined for this instrument to date; however, the mean stress score in this study was higher than has been reported in other studies for the same scale.[131,134,135] For example, in a study of college students the mean score was 5.6 ± 3.6,[131] and in a study of Chinese patients with cardiac conditions the mean was 6.0 ± 2.0 [135].

The average anxiety score was 0.58 ± 0.68. Using the published BSI average in the general population of 0.35,[104] 46.7% scored as anxious. The average depressive symptoms score was 8.00 ± 4.87, and using the standard published PHQ-9 cut point 10,[28] 29.6% of the sample was suffering from depressive symptoms. The average salivary cortisol level was 0.32 ± 0.23 ug/dL.

Specific aim 1: Stress and the prediction of event-free survival

A total of 28 (35%) patients had an event. Six (7.4%) died and 22 (27.2%) were hospitalized for cardiac reasons during the study. In the unadjusted model, stress (HR 1.04; 95% CI: 0.95-1.13; p = 0.46) was not a predictor of event-free survival. In the adjusted model with age, gender, NYHA, anxiety, and depressive symptoms as covariates, the overall model ($\chi 2 = 3.14$, df. = 6; p =0.79) was not significant (Table 3.2). None of the variables were significant in any step of the hierarchal Cox regression. In the final model, stress (HR 1.06; 95% CI: 0.95-1.81; p = 0.32) was not a predictor of event free survival. An additional exploratory Cox regression analysis was conducted using stress as a categorical variable. The results were similar in that stress did not predict the outcome.

Specific aim 2: Association of stress and salivary cortisol

The linear and multiple regressions (n = 70) showed that stress level was not a significant predictor of salivary cortisol (Tables 3.3 and 3.4). In addition, none of the covariate variables (age, gender, NYHA, and anxiety) in the multiple regression analysis was a significant predictor of salivary cortisol except age (HR 0.26; 95% CI: 0.00 – 0.01; p = 0.04) (Table 3.4). An additional exploratory Cox regression analyses was conducted using salivary cortisol as a categorical variable. The results were similar in that salivary cortisol did not predict the outcome.

Specific aim 3: Salivary cortisol and the prediction of event-free survival

In the Cox regression analysis, where salivary cortisol level was the independent variable (n=70), 24 patients (34.3%) had an event. Four (5.7%) of the participants died and 20 (28.6%) were hospitalized during the study. In an unadjusted model, salivary cortisol (HR 2.30; 95% CI: 0.99 – 5.93; p = 0.05) was a significant predictor of event free survival (Table 3.5 and figure 3.1). However, in the adjusted model with age, gender, and NYHA as covariates, the overall model ($\chi 2 = 5.34$, df. = 4; p =0.25) was not significant. None of the variables were significant in any step of the hierarchal Cox regression. In the final model, higher level of salivary cortisol (HR 2.03; 95% CI: 0.84 – 4.93; p = 0.12) was not a predictor of event-free survival (Table 3.6). An additional exploratory Cox regression analyses was conducted using salivary cortisol as a continuous variable. The results for both adjusted and unadjusted models were not significant.

Discussion

Psychosocial factors such as depression, anxiety and lack of social support are associated with poor health outcomes in adults with HF.[8,136] Clinicians and researchers commonly suggest that patients with HF have high levels of stress and that these levels of stress might contribute to poor outcomes.[137] To the best of our knowledge, this is the first study to investigate stress and associated cortisol level as predictors of cardiac morbidity and all-cause mortality in patients with HF. Based on our literature review and the scientific background related to HF, stress, and morbidity and mortality, we hypothesized that stress and salivary cortisol would be a predictor of 6-month cardiac event-free survival. We also hypothesized a significant association between stress level and salivary cortisol level. None of these hypotheses were supported expect that salivary cortisol was a significant predictor of 6-month cardiac event-free survival in the unadjusted model only. Our findings suggest that stress level was not associated with cardiac rehospitalization and mortality among HF patients.

Our hypotheses were based on the physiological mechanisms whereby stress may affect the progression of cardiovascular disease in general. Stress is thought to involve the hypothalamic–pituitary–adrenocortical (HPA). Much of the research on animals and humans suggests that psychological factors can influence the HPA axis, which controls the release of cortisol, a glucocorticoid that is secreted by the adrenal cortex to support and control physiological functions.[59] Over the past decades, many investigators have concluded that physical and psychological stressors are capable of activating the HPA axis and increasing cortisol level in the blood stream.[59] Through cortisol, the HPA supports physiological functions and regulates other systems. However, prolonged

elevation in cortisol due to frequent stress is associated with many negative biological effects such as suppression of the immune system, damage to hippocampal neurons, and development and progression of chronic diseases like diabetes and hypertension.[52,63] In HF, cortisol may contribute to the progression of cardiac damage by acting as a mineralocorticoid receptor (MR) agonist in the cardiac muscle where cortisol mimics the physiological and pathophysiological effects of aldosterone.[64-67] Given these data, it is crucial to determine whether the stressors that are associated with HF activate the cortisol system and contribute to the onset or exacerbation of certain health outcomes.

Although there is evidence suggesting a relationship between stress and poor outcomes in cardiac patients without HF, the overall picture presented by the literature is one of conflicting findings.[138] Stress, variably defined as psychological, psychosocial and mental stress, has been shown to predict mortality and morbidity in patients with cardiovascular diseases.[139-141] Others, with large sample sizes, have found no association between stress level and increased admission rates related to cardiovascular disease.[142] In fact, some of these investigators demonstrated an inverse relationship between stress and all-cause mortality, as well as cardiac mortality.[142] Other investigators have demonstrated a difference between men and women in the prediction of mortality by stress in hospitalized medical patients.[50, 51] Stress in male patients predicted all-cause mortality; however, no association was found between stress and mortality among women.[143,144] Investigators explained those results by stating that men are more vulnerable to stress than women. In addition, they expressed concerns that use of the two-question short version of the perceived stress scale did not capture some aspects of the stress phenomena.[143,144]

Our neutral finding about the relationship between stress and outcomes may be related to our small sample size, yet other investigators with very large sample sizes have similarly failed to find an association.[142] Although patients in our sample had a higher stress level compared to other populations,[131,135] the average score on the stress instrument was only moderately high. Thus, it may be that patients in this sample did not experience a stress level high enough to demonstrate the hypothesized relationship. Another potential explanation for our finding is that the instrument did not adequately capture stress. We used the 4-item perceived stress scale, which has been demonstrated to be valid and reliable; nonetheless, the full instrument may have provided more complete information about stress level than the short version.[131,135,145] The 6 month follow up period may have been too short to capture the effect of stress on the health outcomes in patients with HF. Another possible explanation is that there is no relationship between stress level and outcomes in patients with HF. This explanation is supported by the number of investigations in which no relationship has been found in patients with a variety of health conditions.[142,146,147] A final possible explanation is that there is an indirect association of stress with outcomes that is mediated through another construct such as coping.

We found no association between stress level and salivary cortisol level. Our findings are consistent with a study of breast cancer patients that showed no significant relationship between stress and salivary cortisol level.[148] Our study was similar to this study of breast cancer patients in that medically ill individuals with conditions that may be stressful were studied. In a literature review [149] designed to evaluate salivary cortisol as a biomarker of self-reported mental stress in field studies of healthy adults, the authors

examined 14 studies published in medium or high quality journals. Results from eight studies demonstrated no association between self-reported mental stress and cortisol response, in 4 studies there was a positive association, and in 2 studies a negative association.[149] They concluded that in healthy adults, there were insufficient data to support a relationship and postulated that the association, if present, might only be evident in those with extremely high levels of stress. There are no other reviews more relevant to our sample of HF patients, but the suggestion that patients may need to experience very high levels of stress for the association to become evident is valid to our sample.

Our finding showed an association between salivary cortisol level and all-cause mortality in patients with HF in the unadjusted model which is consistent with those of Yamaji and colleagues [150] who found that serum cortisol levels were a predictor of cardiac events patients with chronic HF. However, in the adjusted model that association was no longer significant. Similarly, others have found no such relationship between cortisol and acute coronary events among patients with acute coronary syndrome.[151] The investigators relate their negative results to the interruption in cortisol rhythms during hospitalization, and this explanation may be relevant to our sample.

Study strengths and limitations

Strengths of our study include use of valid and reliable instruments to measure stress, salivary cortisol, and other covariates. Furthermore, we investigated multiple associations in this study that will form a foundation for future research in the field who are interested in stress and its effect on health outcomes in patients with HF.

The sample size of our study was a limitation that may have hindered our ability to demonstrate potential associations. As previously noted, however, a failure to find these associations has been noted in several studies with much larger sample sizes. The use of the 4-item perceived stress scale may limit the amount of information that we are able to collect related to stress; however, we used strict protocols and reliable and valid instruments for patients with HF.[107-110]

Conclusion

Our findings suggest that there is no relationship between stress level, as measured using the 4-item Perceived Stress Scale, and cardiac rehospitalization and all-cause death in patients with HF. Our findings also suggest that in the setting of HF, a condition that produces high levels of background physiological stress, there is no association between self-reported stress and salivary cortisol. Before these findings can be accepted, future studies among HF patients with higher levels of stress and in larger sample sizes must be conducted.

Table 3.1: Sample Characteristics (N = 81)

Characteristic	N (%) OR MEAN ± SD
Age, years	58.07 ± 13.07
Anxiety score	0.58 ± 0.63
Depressive symptoms score	8.00 ± 4.87
Stress Score	9.47 ± 3.86
Cortisol level, ug/dL **(N = 70)**	0.32 ± 0.23
Gender	
Male	43 (53.1)
Female	46 (46.9)
Ethnicity	
Caucasian	62 (76.5)
African American	19 (23.5)
NYHA class	
I/II	39 (48.1)
III/IV	42 (51.9)
Stress	
Not Stressed	42 (51.9)
Stressed	39 (48.1)
Anxiety	
Not Anxious	44 (54.3)
Anxious	37 (45.7)
Depression	
None/ Mild Depression	57 (70.4)
Moderate/ Severe	24 (29.6)

Note: CI = confidence interval, HF = heart failure, NYHA = New York Heart Association.

Table 3.2: Adjusted Cox Proportional Hazards Regression Model of Variables Associated with Cardiac Event-free Survival (Stress Model)

Predictor Variables	Hazard Ratio	95% CI	P
Age	1.01	0.98 – 1.04	0.57
Female Gender	0.92	0.43 – 1.98	0.84
NYHA class III/IV compared to I/II	0.70	0.29 – 1.47	0.30
Anxiety	0.70	0.30 – 1.52	0.68
Depression	1.07	0.97 – 1.18	0.19
Stress	1.06	0.95 – 1.18	0.32
Final Model Overall Model (χ^2 = 3.14, df. = 6; p =0.79)			

Note: CI = confidence interval, HF = heart failure, NYHA = New York Heart Association.

Table 3.3: Linear Regression of Stress Level Associated with Salivary Cortisol of Patients with Heart Failure

Predictor Variable	β	95% CI	P
Stress	-0.06	-0.02 – 0.01	0.60

Overall Model (Adjusted R2 = -0.01, F=0.28; P= 0.60)

Note: CI = confidence interval, β = adjusted regression slope coefficient, NYHA = New York Heart Association.

Table 3.4: Multiple Linear Regression of Variables Associated with Salivary Cortisol of Patients with Heart Failure

Predictor Variables	β	95% CI	P
Age	0.26	0.00 – 0.01	0.04
Female Gender	-0.20	-0.25 – 0.03	0.11
NYHA class III/IV compared to I/II	0.15	-0.07 – 0.23	0.27
Anxiety	-0.002	-0.12 – 0.12	0.99
Stress	-0.09	-0.03 – 0.01	0.55
Overall Model (Adjusted R^2 = 0.056, F=1.769; P= 0.133)			

Note: CI = confidence interval, β = adjusted regression slope coefficient, NYHA = New York Heart Association.

Table 3.5: Unadjusted Cox Proportional Hazards Regression Model of Variables Associated with Cardiac Event-free Survival (Salivary Cortisol Model)

Predictor Variables	Hazard Ratio	95% CI	P
High Cortisol Level compared to Low level	2.30	0.99 – 5.927	0.05
Overall Model ($\chi 2 = 4.00$, df. = 1; p =0.45)			

Note: CI = confidence interval, NYHA = New York Heart Association.

Table 3.6: Adjusted Cox Proportional Hazards Regression Model of Variables Associated with Cardiac Event-free Survival (Salivary Cortisol Model)

Predictor Variables	Hazard Ratio	95% CI	P
Age	1.01	0.97 – 1.04	0.69
Female Gender	0.64	0.27 – 1.52	0.31
NYHA class III/IV compared to I/II	0.74	0.33 – 1.65	0.50
High Cortisol Level compared to Low level	2.03	0.84 – 4.927	0.12
Overall Model ($\chi 2 = 5.34$, df = 4; p =0.25)			

Note: CI = confidence interval, NYHA = New York Heart Association.

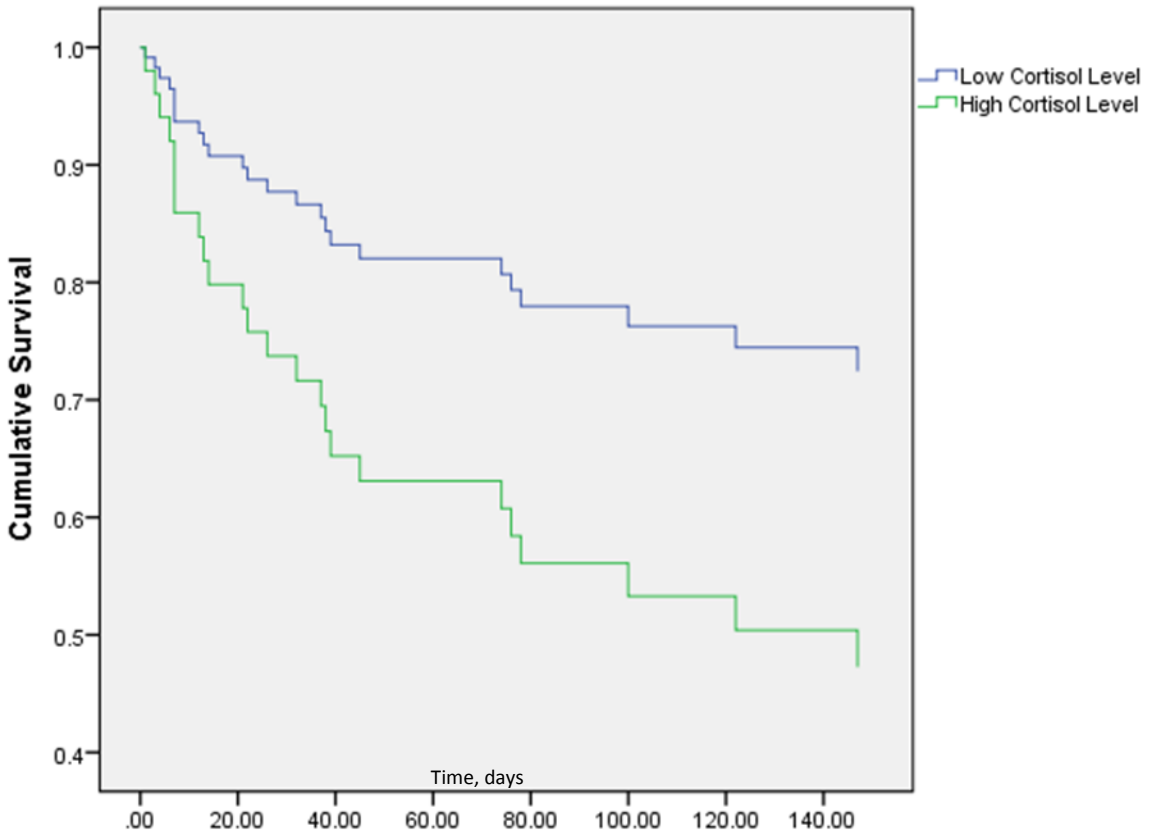

Figure 1. Event Free Survival According to Salivary Cortisol Level

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CHAPTER FOUR

Introduction

Heart failure (HF) is costly condition with high mortality and morbidity rates.[5,152] In 2012, the total costs for HF were around $31 billion, and this amount will rise to around $70 billion by 2030.[6] Although biological factors contribute to the high morbidity and mortality in HF, there are many unexplored psychosocial factors that also likely contribute to the poor prognosis.[9,10]

Heart failure is commonly perceived as stressful and thus associated with considerable psychological distress.[11-15] Based on the literature to date, [10-15,44,45,70-72,77-80,94, 81,82] a model of HF patients' response to stressors is proposed (see Figure 1). Stressors have been defined as environmental circumstances or chronic conditions that are perceived by an individual as a threat to their physical and/or psychological health or well-being.[42] Stressors may lead to a state in which an individual perceives that environmental demands exceed his or her ability to adapt to the situation[43], this state is called stress. Stress is an umbrella term that is used to summarize the effect of unpredictable and seemingly uncontrollable events that may affect an individual's physical and mental health. [44,45]

Chronic stress can stimulate the sympathetic nervous system and the hypothalamic–pituitary–adrenocortical axis (HPA) which may lead to negative biological effects such as suppression of the immune system, damage to hippocampal neurons, and development and progression of chronic diseases like diabetes and hypertension.[52,63,153]

Some researchers suggest that mental or psychological stress is associated with coronary artery diseases and sudden death,[10,94] while others argue the connection between stress and these outcomes is less certain.[138]

Considered in the context of HF, cognitive appraisal is a patient's perception of an event or situation and their assessment of the degree to which the event is stressful. Cognitive appraisal also involves the patient's assessment of the impact of the event on their personal goals and resources to manage stressor. [68,69] People have considerable differences in their appraisal of and response to stressors.[154] Thus, cognitive appraisal is a core component of many stress models.[59,68] Stressors can be apprised as: (1) irrelevant when the situation has no effect on the individual, (2) benign positive when the situation is evaluated as positive, or (3) or stressful.[68] When appraised as stressful, the stressor can be further appraised as: (1) harm/loss resulting in damage to self or social esteem; (2) threat, which refers to suspected harm; or (3) challenge, which allows for the opportunity for gain and growth. [68] Cognitive appraisal has been shown to play an important role in determining the impact of the stress response. [70] Specifically, appraisal of a stressor in the harm/loss or threat categories resulted in poor health outcomes, impaired performance and lower quality of life. [71,72] In contrast, appraisal as a challenge has been associated with positive effects on cardiovascular reactivity and task engagement.[71,72]

A patient's cognitive appraisal of HF can predict their psychological and physical coping responses. [73] Lazarus and Folkman[68] defined coping as "Constantly changing cognitive and behavioral efforts to manage specific external and/or internal demands that are appraised as taxing or exceeding the resources of the person." Coping also includes cognitive or behavioral attempts to manage, master, or alter the stressful situation by

reducing it or by tolerating it.[74,75] Two major types of coping have been suggested. [68] One type is emotion-focused coping, which describes the patient's attempt to control his or her emotional response to the stressful situation. [68] It is used when the individual believes they cannot change the situation. [68,76] Examples of emotion focused coping include denial of the stressful situation, using drugs or alcohol to suppress anxiety about the stressful situation or seeking emotional support from others. The other type is problem-focused coping, which occurs when the patient attempts to manage the stressful situation. [68,76]

Emotion-focused coping includes a range of strategies that patients use to reduce or manage the emotional distress relating to stressful events. These strategies can be divided into active emotional coping and avoidant emotional coping.[77,78] Active emotional coping includes venting, positive reframing, humor, acceptance, and emotional support strategies. Avoidant emotional coping includes self-distraction, denial, behavioral disengagement, self-blame, and substance use.[79,80] The predominant view of emotion-focused coping is that it is a maladaptive form of coping associated with impaired health outcomes.[81,82] In contrast, problem-focused coping contains cognitive and behavioral strategies aimed to alter or manage the stressor, such as planning, reaching out for instrumental support, and religion.[79,80] Problem-focused coping is positively associated with better adjustment and health outcomes.[82] According to Folkman, emotion-focused coping strategies are used in situations with high levels of uncertainty, in which the individual perceives few possibilities for effective beneficial change. In contrast, problem-focused coping strategies are used in situations in which the individual feels a sense of personal efficacy and perceives the possibility for making positive change.[75]

Among patients with HF, problem focused coping is associated with positive health-related quality of life and lower levels of depression. [82-85,88] In contrast, emotion focused is associated with a negative effect on health-related quality of life and a higher prevalence of depression.[83-85] Avoidant emotional coping is also significantly associated with anxiety and poorer health patients with HF.[86] Furthermore, avoidant emotional coping is associated with lower health-related quality of life in patient with head and neck cancer disease.[87]

In a study conducted by Ransom et al.[88], cancer patients, who focused on managing symptoms and seeking out information about their cancer, experienced more positive changes in their physical health and quality of life than those who focus on their emotions. [88] In another study on job stress, employees who used problem-focused coping experienced better job performance as compared with other employees who used emotion- focused coping.[58] Moreover, when the stressful situation is perceived as a challenge versus a threat, problem-focused coping ensued, which led to better health outcomes. In contrast, threat, harm and loss cognitive appraisals are significantly correlated with emotional-focused coping, which leads to unsatisfactory health outcomes.[71,89-93]

The purposes of this study were to describe self-reported stress level, cognitive appraisal and coping among patients with HF, and to examine the association of cognitive appraisal and coping strategies with event-free survival.

Method

Design, sample, and setting

A prospective design was used in which patients were followed for 6 months to determine occurrence of the combined endpoint of rehospitalization for cardiac causes or all-cause death. The study was a part of the Heart Outcomes Prevention Evaluation (HOPE) study at the University of Kentucky that investigated depression among hospitalized patients with HF. The parent study and the current study were approved by the Institutional Review Board at the University of Kentucky. The sample consisted of 88 patients with HF who were hospitalized for cardiac reasons at the University of Kentucky Chandler Medical Center or Good Samaritan Hospital located in Lexington, Kentucky. These same data were used to study the association of stress with morbidity and mortality in patients with HF.[155]

Patients with a diagnosis of chronic HF were eligible for participation in the study if they were: a) admitted to the hospital with a primary or secondary diagnosis of exacerbation of chronic HF or any other cardiac diagnosis, b) 21 years or older, c) able to read and speak English, and d) not obviously cognitively impairment. Patients were excluded from the study for: a) co-existing terminal illness likely to be fatal within the next 6 months, b) presence of a left ventricular assist device, continuous inotropic infusion, or hospice care, c) active suicidality (defined as choosing option 2 or 3 on item 9 of the Beck Depression Inventory-II), d) history of the death of a spouse or child within the past month, e) history of psychotic illness or bipolar illness, and f) current alcohol dependence or other substance abuse.

Measures

Stress

Stress was measured using the brief version of the Perceived Stress Scale.[131] The original, longer version of the scale consists of 14-items that measure the degree to which patients appraised situations as stressful in the last month.[131] The brief version consists of a four-item scale that has been demonstrated to be reliable and valid.[131] Each item is rated by patients on a scale ranging from 0 (never) to 5 (very often). The four items are: (1) how often have you felt that you were unable to control the important things in your life?, (2) how often have you felt confident about your ability to handle your personal problems?, (3) how often have you felt that things were going your way?, and (4) how often have you felt difficulties were piling up so high that you could not overcome them? Higher scores indicate greater levels of stress.

Coping

Coping was measured using the Brief COPE scale.[156] This 28-item scale is an abbreviated version of the COPE Inventory. It was modified from the full instrument because of the length and redundancy of the full instrument and because of the associated time burden.[156] The scale's author has demonstrated the reliability and validity of the brief version in health related research through factor analysis and reliability testing.[156] The responses in this scale range from 1 (I haven't been doing this at all) to 4 (I have been doing this a lot). This instrument has 14-subscales of two items each that reflects a variety of different coping methods (e.g., praying or meditating, receiving emotional support from others, criticizing oneself) with reliable psychometric properties.[156] Based

on conceptual and empirical literature the 14- subscales were grouped in three coping strategies which are active emotional coping, avoidant emotional coping, and problem focused coping.[45,68,157] Higher scores indicate that the patient used that coping strategy commonly.

Cognitive Appraisal

Cognitive appraisal was measured using the brief version of the Cognitive Appraisal Health Scale.[158,159] This brief version contains 13 items derived from Kessler's scale, which is one of the major measures of cognitive appraisal of stressful and non-stressful events.[69] Validity was supported by component factor analysis and reliability has been shown in previous studies.[158,159] The responses in this scale range from 0 (strongly agree) to 5 (strongly disagree). Higher scores indicate that the patient does not commonly use that type of appraisal.

Event-free survival

Event-free survival was defined as the combined endpoint of cardiac rehospitalization or all-cause death. Hospitalization data were determined through a combination of patient and family interviews and a review of medical records. Hospitalizations were verified and documented by trained research assistants who reviewed medical records and clinic notes on a weekly basis. Given the possibility that patients could have been hospitalized at different facilities, trained research assistants carefully questioned the patients or family members by phone to determine if hospitalization had occurred elsewhere.

All-cause mortality was determined by interview with the patient's family, medical record review and review of county death records. At enrollment, the patient was asked for contact information for a close friend or family member in case the patient could not be contacted. At follow-up if a patient could not be reached by phone, hospital records were searched. When information regarding the patient was not available, family members or friends were contacted. If these contacts could not be reached, county death records were used to determine patient death.

Demographic and clinical variables

Data on demographic variables and clinical characteristics were collected by reviewing medical records and interviewing patients. These variables included age, gender, ethnicity, and New York Heart Association (NYHA) class. NYHA class indicated the level of functional impairment reported by patients as a result of symptoms and was determined by trained research nurses using a structured interview. These variables were selected because of their effects on the outcome variables as suggested in the literature.[97,100]

Procedure

Hospitalized patients were identified by clinicians and referred to research staff who determined each patient's eligibility. The study was thoroughly explained to each patient and signed consent was obtained after answering any questions patients had about the study. Research staff discussed the voluntary nature of the study. The research staff met with the patient to administer study questionnaires via the web based Survey

Monkey. The questionnaires took approximately 20 minutes to complete. A paper copy was offered to the patient if they did not feel comfortable with the web based survey.

As a part of HOPE study, patients were contacted by phone to complete the follow up questionnaires at two weeks, three months, and six months from hospital discharge. At each telephone contact, the research staff asked the patient whether he or she has been hospitalized or visited the emergency unit. At the end of the study period, hospital records were reviewed to confirm deaths, re-hospitalizations or emergency department visits.

Statistical Analysis

Data were analyzed using SPSS software, version 20.0 (SPSS Inc., Chicago, IL). Descriptive statistics, including means, standard deviations and frequency distributions, were used to describe sample characteristics. Two tailed Pearson correlation coefficients were used to determine bivariate relationship among the variables. Linear and multiple regressions were used to determine the association between stress and cognitive appraisal type, stress and coping style, and cognitive appraisal and coping style. Two groups, low and high perceived stress level, were created based on the mean of perceived stress level and used in this analysis. To examine the association of cognitive appraisal and coping strategies with event-free survival, unadjusted, followed by adjusted, Cox regression analyses were used to determine whether different types of cognitive appraisal and coping styles, independently predicted event-free survival. Each type of cognitive appraisal and each style of coping was entered in separate Cox regression analyses. The following covariates were considered in the adjusted analyses: age, gender, and NYHA

class. The assumptions of all Cox regressions, and linear and multiple regressions were tested for violations and none were noted. A p-value of ≤ 0.05 was considered statistically significant.

Results

Sample Characteristics

Demographic and clinical characteristics of patients (N = 88) are summarized in Table 4.1. The average stress score in this sample was 9.44 ± 3.86, with a range of 4 to 20. This mean is higher than reported in studies of college students the mean score was 5.6 ± 3.6,[131] and in Chinese cardiac patients the mean was 6.0 ± 2.0).[131,134,135] The average cognitive appraisals scores were as following: threat appraisal 2.46 ± 0.87, challenge appraisal 2.47 ± 0.77, and harm/loss appraisal 2.65 ± 0.88. The possible range of cognitive appraisal score is between 0 and 5 and a higher score indicates less use of that type of cognitive appaisal. [158,159] The average coping styles scores were as follows: problem focused coping 2.82 ± 0.66, active emotional coping 2.57± 0.56, and avoidant emotional coping 1.56 ± 0.38. The range of coping style score is between 1 and 4, and a higher score indicate greater use of that coping style. [156] A total of 29 (32.9%) patients had an event: seven (7.9%) died and 23 (25%) were hospitalized for cardiac reasons.

Bivariate Correlations Among the Variables

The two tailed Pearson correlations (Table 4.2) showed that harm/loss cognitive appraisal was significantly correlated with stress level ($r= -0.342$, $p = 0.005$). Specifically, higher levels of stress were associated with more common use of harm/loss appraisal. Stress level was also significantly correlated with avoidant emotional coping ($r= 0.429$, $p < 0.001$). Avoidant emotional coping style was associated with higher levels

of stress. In addition, threat cognitive appraisal was significantly correlated with harm/loss cognitive appraisal (r= 0.325, p = 0.008) and avoidant emotional coping (r= -0.372, p = 0.002). Appraisal of HF as a threat was associated with avoidant emotional coping style, and appraisal of the condition as harm/loss. Furthermore, harm/loss cognitive appraisal was significantly correlated with challenge cognitive appraisal (r= -0.324, p = 0.008) and avoidant emotional coping (r= -0.433, p < 0.001). When HF patients appraise their condition as harm/loss, they tend to use avoidant emotional coping style and are less likely to appraise their condition as a challenge.

Prediction of Cognitive Appraisal

In unadjusted analyses, and with regard to prediction of cognitive appraisal type using stress level, stress was not a significant predictor of challenge (β -0.10; 95% CI: -0.23 – 0.54; p = 0.43) or threat (β -0.14; 95% CI: -0.69 – 0.19; p = 0.26) cognitive appraisals. However, stress was a significant predictor of harm/loss cognitive appraisal (β -0.3; 595% CI: -1.03 – -0.20; p = 0.01). High level of stress was associated with greater use of harm/loss cognitive appraisal.

In adjusted analyses, and with regard to prediction of cognitive appraisal, multiple linear regressions showed that none of the demographic, clinical, or stress variables was a significant predictor of challenge (Table 4.3). The only significant predictors of cognitive appraisal as threat were age (β 0.39; 95% CI: 0.01 – 0.04; p = 0.01) and gender (β -0.23; 95% CI: -0.81– 0.01; p = 0.05; Table 3). Specifically, older age and female gender were associated with cognitive appraisal as threat. Finally, age (β 0.06; 95% CI: -0.01 – 0.02; p = 0.05) and stress (β -0.37; 95% CI: -1.11 – -0.23; p < 0.001) were the only significant

predictors of cognitive appraisal as harm/loss (Table 4.3). Specifically, older age and higher stress level were associated with harm/loss cognitive appraisal.

Prediction of Coping Style

In unadjusted analyses, and with regard to prediction of coping style, none of the cognitive appraisal styles was a significant predictor of problem focused coping style which was as follows: challenge cognitive appraisal (β -0.09; 95% CI: -0.31 – 0.17; p = 0.55), threat cognitive appraisal (β -0.14; 95% CI: -0.32 –0.11; p = 0.32), and harm/loss cognitive appraisal (β -0.01; 95% CI: -0.23 – 0.21; p = 0.94). In addition, none of the cognitive appraisal styles was a significant predictor of active emotional coping style which was as follows: challenge cognitive appraisal (β 0.08; 95% CI: -0.15 – 0.26; p = 0.59), threat cognitive appraisal (β -0.11; 95% CI: -0.26 – 0.12; p = 0.45), and harm/loss cognitive appraisal (β 0.04; 95% CI: -0.16 – 0.21; p = 0.80). Finally, harm/loss cognitive appraisal (β -0.35; 95% CI: -0.25 – -0.03; p = 0.01) was a significant predictor of avoidant emotional coping style. However, challenge (β -0.20; 95% CI: -0.12 – 0.11; p = 0.88) and threat cognitive (β -0.23; 95% CI: -0.20 – 0.10; p = 0.08) appraisals were not significant predictors of avoidant emotional coping.

In adjusted analyses, and with regard to prediction of coping style, harm/loss cognitive appraisal (β -0.28; 95% CI: -0.21 – -0.02; p = 0.02) and stress level (β 0.29; 95% CI: 0.04– 0.38; p = 0.02) were significant predictors of avoidant emotional coping controlling for age, gender, and NYHA class (Table 4.4). Higher levels of stress and greater use of harm/loss cognitive appraisal were associated with avoidant emotional coping style. Neither challenge (β -0.05; 95% CI: -0.14 – 0.09; p = 0.72) nor threat (β -

0.15; 95% CI: -0.18– 0.06; p = 0.30) cognitive appraisals were significant predictors of avoidant emotional coping (Table 4.4). None of the demographic, clinical, stress, or cognitive appraisal variables was associated with active emotional coping style or problem focused coping style in adjusted regression analyses (Tables 4.5 and 4.6).

Prediction of Event-Free Survival

Using Cox regression to predict death and cardiac rehospitalization from cognitive appraisal, and in unadjusted analyses, only harm/loss cognitive appraisal was associated with event-free survival (HR 0.51; 95% CI: 0.22 – 0.89; p = 0.02). Specifically, greater use of harm/loss cognitive appraisal predicted shorter event-free survival. Using Cox regression to predict death and cardiac rehospitalization from coping style, and in unadjusted analyses, the only significant coping style associated with event-free survival was avoidant emotional coping style (HR 2.53; 95% CI: 1.07 – 6.00; p = 0.04). Specifically, greater use of avoidant emotional coping style was associated with shorter event-free survival.

In analyses adjusted for age, gender and NYHA class, where cognitive appraisal types were the independent variables, none of the demographics, clinical characteristics, or cognitive appraisal variables was significant predictors of event-free survival (Table 4.7). Where coping styles were the independent variables, none of the demographics, clinical characteristics or coping styles were significant predictors (Table 4.8).

Discussion

Despite the medical and surgical advances in HF treatment, mortality and morbidity rates are still substantial even in comparison to some aggressive types of

cancer. [3,4,7,8] Biological factors explain some of this high morbidity and mortality.[160-164] There are, however, many psychosocial factors that may contribute to high morbidity and mortality rates and that remain relatively unexplored in patients with HF, including stress, cognitive appraisal, and coping style. [9,10] We hypothesized the relationships among the study variables (stress, cognitive appraisal, and coping) depicted in the model (Figure 1) that was developed based on the literature to date. [10-15,44,45,70-72,77-80,94, 81,82]

Based on the model, we hypothesized that stress level would be a predictor of type of cognitive appraisal. The only type of cognitive appraisal that was predicted by stress level was harm/loss cognitive appraisal. Higher stress levels were associated with greater use of harm/loss cognitive appraisal. This finding suggests that patients with HF respond negatively to higher stress levels with an appraisal type that is associated with negative health outcomes, and are unable to marshal a positive coping response to stress. In some populations, patients have demonstrated the ability to respond to the stress imposed by their condition with a healthier type of cognitive appraisal, challenge, which is associated with better adherence and outcomes. [70-72]

We further hypothesized that cognitive appraisal type would be a predictor of coping style. Only stress and harm/loss cognitive appraisal were predictors of avoidant emotional coping style. Our findings suggest that higher levels of stress and greater use of harm/loss cognitive appraisal were associated with avoidant emotional coping style. Thus, the dominant type of cognitive appraisal in our sample of patients with HF is associated with a coping style that has negative health outcomes and a negative impact on emotional well-being.

Furthermore, we hypothesized that coping style would predict 6-month event-free survival. In the unadjusted model, avoidant emotional coping was a significant predictor of 6-month event-free survival, but it was not an independent predictor. This finding suggests that in the company of other variables, coping style is a less important predictor of outcomes. We also investigated whether cognitive appraisal type predicted 6-month event-free survival. Our findings suggest that greater use of harm/loss cognitive appraisal predicted shorter event-free survival in HF. None of the other cognitive appraisal types were significant predictors. Taken together, our findings suggest that the usual type of appraisal and coping used by patients with HF in response to stress, which is common among them, should be avoided. Healthcare providers must assist patients to learn and use more positive types of appraisal and coping in response to stress. Cognitive behavioral therapy is effective in assisting patients assume healthier appraisal and coping strategies, which are associated with better health outcomes, greater self-efficacy, and less depression and anxiety.[165,166]

In a study conducted among patients with the human immunodeficiency virus, psychological stress was associated with threat cognitive appraisal.[167] Our findings suggest that HF patients may have different appraisal for the stressful situation since higher level of stress was associated with harm/loss cognitive appraisal. However, these findings demonstrate that cognitive appraisal plays a role in the stress response.[70]

In addition, cognitive appraisal plays a significant role determining the coping style used by HF patients. In an Israeli's study conducted among immigrants from the Soviet Union, threat and harm/loss cognitive appraisal were associated with avoidant emotional coping that was negatively related to the adaptation to the immigration

situation. On the other hand, challenge cognitive appraisal was associated with problem focused coping that was positively related to the adaptation to new immigration situation.[168] Our findings suggest that HF patients, who appraise their condition as harm/loss, tend to use avoidant emotional coping style that is associated with negative health outcomes across literature. [83-87] Unfortunately HF patients in our sample, seem unable to respond with the more positive appraisal and coping styles.

In a study conducted among chronic pain patients, threat and harm/loss cognitive appraisals were associated with passive coping styles such as avoidant coping. In addition, passive coping styles were associated with higher levels of pain.[91] On the other hand, challenge cognitive appraisal was associated with problem focused coping that was associated with lower levels of pain.[91] Our findings were similar to those findings as threat and harm/loss cognitive appraisal was associated with avoidant emotional coping style that predicted all-cause mortality and cardiac rehospitalization among HF patients in the unadjusted model. Another study conducted on melanoma survivors showed that cognitive appraisals such as threat and harm/loss were associated with poor adjustment, high distress, and reduction of well-being in melanoma patients. However, challenge cognitive appraisal, which is considered a healthier appraisal type was associated with ability to adjust, reduce distress, higher well-being of melanoma patients.[169]

Our study was the first to investigate stress, cognitive appraisal, coping, and event-free survival in HF patients. Many of our findings were consistent with other investigations conducted on different groups of healthy and ill subjects. [91,167-169] However, we did not find hypothesized associations in our model from the literature. These findings may be related to small sample size. Another potential explanation is that

the instruments did not adequately capture stress and coping styles. We used brief stress and coping scales that contains 4 and 28 items respectively. Both shortened measures have been demonstrated to be valid and reliable; nonetheless, the full instruments may have provided more complete information about stress level, and coping styles than the shorter versions. [131,135,145,156]. Another potential explanation is that the 6 month follow up period may have been too short to capture the effect of coping styles on the health outcomes in patients with HF. A final possible explanation is that there is no relationship between the variables and outcomes in patients with HF.

Study Strengths and Limitations

Strengths of our study include the use of valid and reliable instruments to measure stress, cognitive appraisal, coping, and other covariates. Furthermore, we investigated multiple associations among the variables of this study and our findings form a foundation for future studies of stress, cognitive appraisal, coping, and health outcomes in HF patients.

The small sample size is one of the limitation of this study that may affect our ability to find significant association similar to those that been presented in the literature. In addition, the use of brief versions of stress and coping scales may affect our ability to capture the proper stress level and coping styles in a way that allow us to find significant associations; however, we used strict protocols and reliable and valid instruments for patients with HF.[107-110]

Conclusion

Our findings suggest that there is an association between stress level and harm/loss cognitive appraisal that is associated with shorter event free survival among HF patients. In addition, harm /loss cognitive appraisal is associated with avoidant emotional coping that is associated with negative health outcomes and shorter event-free survival. Thus, to improve health outcomes in patients with HF, interventions are needed to the reduce stress of HF and change how HF patients appraise their condition and cope with it. Cognitive restructuring may be useful among patients with HF who negatively appraise the stress of HF as such appraisal leads to negative coping strategies that are associated with worse event-free survival.

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Table 4.1: Sample Characteristics (N = 88)

Characteristic	N (%) OR MEAN ± SD
Age, years	58.13 ± 12.64
Stress Score	9.44 ± 3.86
Cognitive appraisal	
Threat Score	2.46 ± 0.87
Challenge Score	2.47 ± 0.77
Harm/Loss Score	2.65 ± 0.88
Coping Style	
Problem Focused Coping Score	2.82 ± 0.66
Active Emotional Coping Score	2.57± 0.56
Avoidant Emotional Coping Score	1.56 ± 0.38
Gender	
Male	47 (53.4)
Female	41 (46.6)
Ethnicity	
White	68 (77.3)
African American	20 (22.7)
NYHA class	
I/II	40 (45.5)
III/IV	48 (54.5)
Stress	
Not Stressed	47 (53.4)
Stressed	41 (46.6)

Note: CI = confidence interval, HF = heart failure, NYHA = New York Heart Association.

Table 4.2. Bivariate Correlations Among Stress, Coping, and Cognitive Appraisal Variables

Variables	Stress	Threat Appraisal	Harm/Loss Appraisal	Challenge Appraisal	Active Emotional Coping	Avoidant Emotional Coping	Problem-Focused Coping
Stress							
Threat Appraisal	r= -0.131 P= 0.296						
Harm/Loss Appraisal	r= -0.342 p=0.005	r= 0.325 P= 0.008					
Challenge Appraisal	r=0.096 P=0.443	r= 0.110 P= 0.383	r= -0.324 P= 0.008				
Active Emotional Coping	r=0.042 P=0.739	r= -0.115 P= 0.360	r= -0.045 P= 0.724	r= 0.035 P= 0.779			
Avoidant Emotional Coping	r= 0.429 P <0.001	r= -0.372 P= 0.002	r= -0.433 P <0.001	r= 0.054 P= 0.674	r= 0.125 P= 0.321		
Problem-Focused Coping	r= 0.061 P=0.628	r= -0.152 P= 0.235	r= -0.027 P= 0.836	r= -0.141 P= 0.272	r= 0.536 P< 0.001	r= 0.021 P= 0.873	

Note: r = two tailed Pearson correlation, p = two tailed significance level

Table 4.3: Multiple Linear Regression of Variables Associated with Cognitive Appraisal Type.

Predictor Variables	β	95% CI	P
Challenge Cognitive Appraisal			
Age	0.06	-0.01 – 0.02	0.68
Female Gender	0.08	-0.29 – 0.52	0.57
NYHA class III/IV compared to I/II	-0.18	-0.70 – 0.13	0.18
High stress level compared to low stress level	0.13	-0.21 – 0.62	0.32
Overall Model (Adjusted R2 = -0.02, F=0.665; P= 0.619)			
Threat Cognitive Appraisal			
Age	0.39	0.01 – 0.04	0.01
Female Gender	-0.23	-0.81– 0.01	0.05
NYHA class III/IV compared to I/II	0.24	0.01– 0.83	0.46
High stress level compared to low stress level	-0.06	-0.52– 0.31	0.61
Overall Model (Adjusted R2 = 0.215, F=5.173; P= 0.001)			
Harm/loss Cognitive Appraisal			
Age	0.06	-0.01 – 0.02	0.05
Female Gender	0.01	-0.42 – 0.46	0.91
NYHA class III/IV compared to I/II	0.20	-0.09 – 0.81	0.12
High stress level compared to low stress level	-0.37	-1.11 – -0.23	<0.001
Overall Model (Adjusted R2 = 0.126, F=3.190; P= 0.020)			

Note: CI = confidence interval, β = adjusted regression slope coefficient, NYHA = New York Heart Association

Table 4.4: Multiple Linear Regression of Variables Associated with Avoidant Emotional Coping of Patients with Heart Failure

Predictor Variables	β	95% CI	P
Age	-0.15	-0.01 – 0.00	0.20
Female Gender	0.13	-0.10 – 0.25	0.25
NYHA class III/IV compared to I/II	-0.15	-0.27 – 0.06	0.19
High stress level compared to low stress level	0.30	0.04 – 0.38	0.02
Harm/loss cognitive appraisal	-0.28	-0.21 – 0.02	0.02
Threat cognitive appraisal	-0.15	-0.12– 0.06	0.30
Challenge cognitive appraisal	-0.05	-0.14– 0.10	0.72
Overall Model (Adjusted $R^2 = 0.26$, $F=5.425$; $P< 0.001$)			

Note: CI = confidence interval, β = adjusted regression slope coefficient, NYHA = New York Heart Association

Table 4.5: Multiple Linear Regression of Variables Associated with Active Emotional Coping of Patients with Heart Failure

Predictor Variables	β	95% CI	P
Age	0.07	-0.01 – 0.01	0.66
Female Gender	0.12	-0.18 – 0.45	0.85
NYHA class III/IV compared to I/II	-0.13	-0.47 – 0.18	0.38
High stress level compared to low stress level	0.05	-0.26 – 0.38	0.72
Harm/loss cognitive appraisal	0.04	-0.18 – 0.23	0.82
Threat cognitive appraisal	-0.06	-0.25– 0.17	0.70
Challenge cognitive appraisal	0.05	-0.18– 0.25	0.72
Overall Model (Adjusted R^2 = 0.04, F=0.34; P= 0.932)			

Note: CI = confidence interval, β = adjusted regression slope coefficient, NYHA = New York Heart Association

Table 4.6: Multiple Linear Regression of Variables Associated with Problem-Focused Coping of Patients with Heart Failure

Predictor Variables	β	95% CI	P
Age	0.14	-0.01 – 0.02	0.35
Female Gender	0.07	-0.27 – 0.46	0.61
NYHA class III/IV compared to I/II	-0.07	-0.46 – 0.28	0.63
High stress level compared to low stress level	0.06	-0.30 – 0.46	0.67
Harm/loss cognitive appraisal	-0.00	-0.24 – 0.24	0.99
Threat cognitive appraisal	-0.15	-0.36– 0.13	0.35
Challenge cognitive appraisal	-0.10	-0.34– 0.16	0.49
Overall Model (Adjusted R^2 = 0.06, F=0.483; P= 0.842)			

Note: CI = confidence interval, β = adjusted regression slope coefficient, NYHA = New York Heart Association

Table 4.7: Adjusted Cox Proportional Hazards Regression Model of Variables Associated with Cardiac Event-free Survival (Cognitive Appraisal Model)

Predictor Variables	Hazard Ratio	95% CI	P
Age	1.02	0.98 – 1.06	0.35
Female Gender	0.84	0.32 – 2.24	0.73
NYHA class III/IV compared to I/II	0.86	0.33 – 2.23	0.76
Harm/loss cognitive appraisal	0.53	0.28 – 1.02	0.05
Threat cognitive appraisal	0.89	0.49 – 1.60	0.69
Challenge cognitive appraisal	1.14	0.59 – 2.18	0.70
Overall Model ($\chi 2 = 7.56$, df = 7; p =0.48)			

Note: CI = confidence interval, NYHA = New York Heart Association

Table 4.8: Adjusted Cox Proportional Hazards Regression Model of Variables Associated with Cardiac Event-free Survival (Coping Styles Model)

Predictor Variables	Hazard Ratio	95% CI	P
Age	1.02	0.98 – 1.07	0.37
Female Gender	0.76	0.31 – 1.83	0.54
NYHA class III/IV compared to I/II	0.74	0.29 – 1.87	0.52
Problem Focused Coping	1.98	0.92 – 4.25	0.08
Active Emotional Coping	0.91	0.39 – 2.11	0.83
Avoidant Emotional Coping	3.23	1.14 – 9.16	0.03
Overall Model ($\chi 2 = 7.97$, df = 6; p =0.24)			

Note: CI = confidence interval, NYHA = New York Heart Association

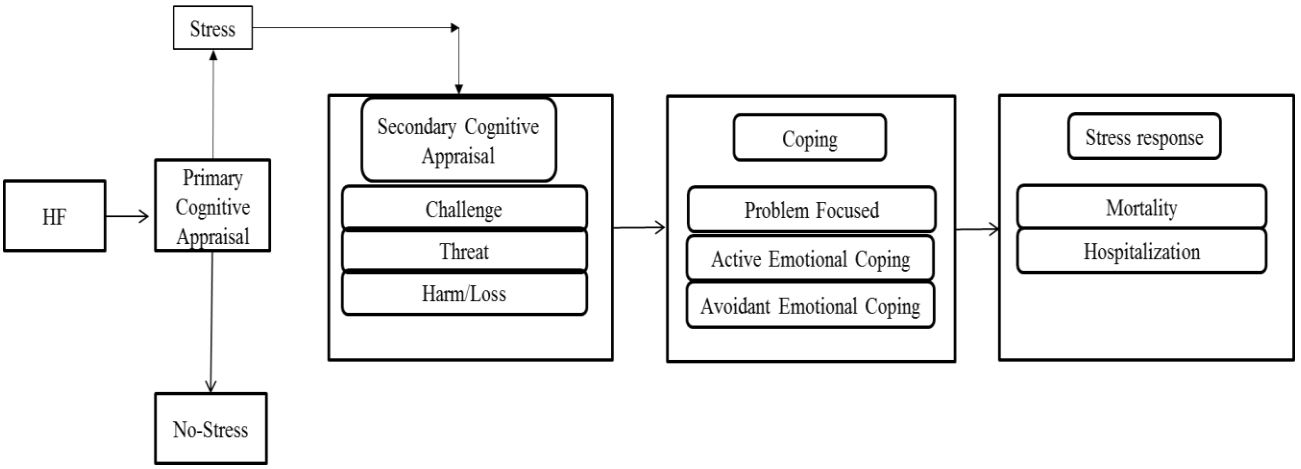

Figure 4.1. Proposed model of heart failure patients' response to stressors based on literature to date.

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CHAPTER FIVE

Conclusions and Discussion

Heart failure is a major health problem that is responsible for some of the highest mortality and hospitalization rates in the world.[2,111-118] Patients with HF experience multiple changes in their heart structure and function that affect the ability of cardiac ventricles to fill with, or eject, blood. [1] In addition, patients with HF experience many psychological symptoms that may contribute to additional physiological changes and affect survival. [9-16,20-23] In the United States, HF and sudden death combined are accountable for the largest number of deaths. [4,5] Furthermore, HF is the leading cause of hospitalization and discharge among adults patient older than 65, with substantial increases in hospitalization and discharge rates seen every year. [2,6] The total estimated cost of HF in the United States is $37 billion with an expected increase of $2 billion each year. [2,6] Although there have been significant medical and surgical advancements in HF treatment, mortality and hospitalizations rates continued to increase every year. [3,4] The pathophysiology of HF explains a major part of these high rates, however, there are many unexplored psychosocial factors that also likely contribute to poor prognosis such as comorbid depression and anxiety, stress, cognitive appraisal, and coping.

Depression is a major mood disorder that is highly prevalent in HF and is associated with multiple unhealthy behaviors. [16,17,20,12,22,23]Anxiety is a negative emotion state that is associated with adverse cardiac events and progression of disease. [10,16] Anxiety also is highly prevalent in patients with HF.[12] Depression and anxiety are independently associated with survival among HF patients. [10,16,21]

Whether co-morbid symptoms of anxiety and depression are associated with outcomes in patients with HF is unknown. The purpose of chapter two was to examine whether co-morbid symptoms of depression and anxiety are associated with all-cause mortality or rehospitalization for cardiac causes in patients with HF. We found that comorbid depression and anxiety predicted all–cause mortality when treated at both the categorical and continuous levels. However, comorbid depression and anxiety was not a significant predictor of cardiac rehospitalization when treated as categorical or continuous level. The study presented in chapter two continued the work of other investigators such as Frasure-Smith and colleagues,[105] and Doering and colleagues[106] who examined the comorbid effect of depressive and anxiety symptoms in patients with heart disease, but without HF. IN addition to being the first investigation of this type in patients with HF, our findings filled some of the gaps in previous work by using valid and reliable measures to assess depressive and anxiety symptoms, controlling for age and disease severity, addressing rehospitalization, and considering the impact of variables treated at both the categorical and continuous levels. Our findings highlighted the hazardous effect of comorbid depressive and anxiety symptoms on the mortality rate of adults with HF. In addition, our findings suggest that psychological factor plays an important role in the mechanism of high mortality rate in HF patients.

Because depressive and anxiety symptoms usually develop after stressful life events that are not cognitively processed in a healthy way[35] and because HF is considered a substantial stressor for many patients, [11,12] examination of the role of stress on health outcomes in patients with HF is important. Thus, chapter three of this dissertation aimed to (1) examine the association of stress with 6-month cardiac event-free survival,

controlling for anxiety, depression, and New York Heart Association (NYHA) functional class; (2) examine the relationship of stress with salivary cortisol; and (3) examine the association of salivary cortisol level with 6-month cardiac event-free survival, controlling for age, gender, and NYHA class.

Stress can be defined as a condition where the environmental demands exceed the individual's ability to adapt to these demands. [43] This definition can be applied to HF as a stressor that may lead to a stress state if patients' abilities are unable to meet the environmental demands associated with HF. We hypothesized that stress and salivary cortisol would be predictors of event-free survival in HF patients. In addition, we hypothesized that stress would be a predictor of salivary cortisol level in HF patients.

Our findings showed that none of these hypotheses were supported expect that salivary cortisol was a significant predictor of 6-month cardiac event-free survival in the unadjusted model only. Our only result consistent with our hypotheses was the association between salivary cortisol level and all-cause mortality in patients with HF in the unadjusted model which been presented in other studies such as Yamaji and colleagues.[150] However, this relationship was no longer significant in the adjusted model.

Our results regarding the relationship between stress and event-free survival and between stress and salivary cortisol were consistent with other investigators' findings who conducted their study with larger samples in different populations. [142,148] However, the short follow up period and the abbreviated stress scale we used may have contributed to inability to capture the possible effect of stress on health outcomes in HF patients. Another possible explanation is that the relationship between stress and health outcomes

in HF patients may present but in indirect way through other variables such as cognitive appraisal and coping.

Therefore, in another study presented in chapter four we examined the relationships of stress, cognitive appraisal, coping style, with health outcomes presented in Figure 1, which is a proposed model of HF patients' response to stressors based on the literature to date. [10-15,44,45,70-72,77-80,94, 81,82]

Cognitive appraisal can be defined as patients' perceptions of an event or a situation and to degree to which this event or situation is viewed as stressful to the patient. [68,69] Any event or situation can be appraised as (1) irrelevant when the situation has no effect on the individual, (2) benign positive when the situation is evaluated as positive, or (3) or stressful.[68] When appraised as stressful, the stressor can be further appraised as: (1) harm/loss resulting in damage to self or social esteem; (2) threat, which refers to suspected harm; or (3) challenge, which allows for the opportunity for gain and growth. [68] The cognitive appraisal process plays a major role in the stress response and coping process. [70] Coping can be defined as "Constantly changing cognitive and behavioral efforts to manage specific external and/or internal demands that are appraised as taxing or exceeding the resources of the person." [68] Coping strategies can be divided in three categories: active emotional coping, avoidant emotional coping, and problem-focused coping. [68,77,78] The major view of emotion-focused coping is that it is a maladaptive form of coping associated with impaired health outcomes.[81,82] Problem-focused coping is usually associated with better adjustment and health outcomes.[82]

The purpose of the study presented in chapter four was to describe self-reported stress level, cognitive appraisal and coping among patients with HF, and to examine the association of cognitive appraisal and coping strategies with event-free survival.

Our findings demonstrated that higher stress levels were associated with greater use of harm/loss cognitive appraisal which is considered a negative response associated with negative health outcomes. [70-72] In addition, we found that higher levels of stress and greater use of harm/loss cognitive appraisal were associated with avoidant emotional coping style, considered a negative coping style. [86] Furthermore, our findings suggest that avoidant emotional coping was a significant predictor of 6-month event-free survival in the unadjusted model, but it was not an independent predictor in the company of other variables. Also, we found that greater use of harm/loss cognitive appraisal predicted shorter event-free survival in HF. We conclude that the usual type of appraisal and coping used by patients with HF in response to stress should be avoided. Our findings demonstrated that cognitive appraisal and selected coping style plays a role in the stress response and health outcomes.[70,83-87] Our findings where consistent with other studies that investigated stress, cognitive appraisals, coping styles, and health outcomes in HF population and other populations. [91,167-169]

Implication

Psychosocial factors are associated with many hazardous effects on mortality and morbidity rates of adults with HF. Until now, many of the health care providers do not pay much attention to those factors during delivering care and focus primarily on the pathophysiological aspect of HF. Thus, psychosocial factors remain an important problem that associated with HF and may contribute to the high comorbidity and mortality rates. The studies in this dissertation described and examine several of psychosocial factors that associated with HF.

We found that comorbid anxiety and depression symptoms are a better predictor of death in HF patients than anxiety or depression alone controlling for disease severity, age, gender, and ethnicity. Our recommendation to improve health outcomes in patient with HF is to increase the awareness of health care providers to the importance of assessing and managing co-morbid symptoms of depression and anxiety. Furthermore, we recommend future studies that investigate and evaluate strategies regarding depression and anxiety symptoms screening and treatment in HF patients.

Our findings also suggest no relationship between stress level and event-free survival or between stress level and salivary cortisol level in HF patients. However, our findings showed some indictors of a possible association between salivary cortisol level and event-free survival. We recommend before accepting any of these findings, future studies should be conducted with sample that have higher stress levels and larger size. Health care providers should also include cortisol level in their ordered lab studies when they provide care for HF patients. Cortisol level may be used as indicator for future

cardiac events. Thus, cortisol level needs to be monitored with developing strategies to control it in HF patients.

Finally, we found that stress level is associated with harm/loss cognitive appraisal that associated with shorter event free survival in HF patients. In addition we found that harm/loss cognitive appraisal is associated with avoidant emotional coping that is associated with negative health outcomes and shorter event-free survival. Our recommendation to improve health outcomes in HF patients is to develop interventions to reduce stress levels among HF patients and to change their perception about their health condition. Furthermore, offering strategies to cope with HF that depend on cognitive restructuring especially for those who negatively appraise the stress of HF. This cognitive restructuring may lead them to a positive coping strategy that associated with better event-free survival. Thus, it is important for future studies in HF felid to address these psychosocial factors and try to develop management strategies to limits their possible hazardous effects.

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Curriculum Vitae

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Education

Institution	Degree	Date Conferred	Field of Study
University of Kentucky	PhD	March,2016	Nursing
University of Kentucky	PhD/Minor	December, 2012	Applied Statistics
Sullivan University	MBA	June, 2016	Healthcare
University of Jordan	MSN	February, 2008	Clinical Nursing
University of Jordan	BSN	February, 2006	Nursing

Certifications and Licensure

Kentucky RN License # 1133408

Basic Life Support – present

Advanced Life Support – present

Basic Life Support Instructor # 05140248908

Advanced Life Support Instructor # 05140248908

Trauma Nursing Core Course (TNCC) – present

Professional Experience

Dates	Institution and Location	Academic Positions Held
August, 2014 – Present	Kentucky State University	Assistant Professor
August, 2010 – Present	University of Kentucky, Lexington, KY	Graduate Research Assistant
January, 2012 – January, 2015	Bluegrass Community College Lexington, KY	Faculty
February, 2006 – August, 2009	University of Jordan, Amman, Jordan	Research and Teaching Assistant

Dates	Institution and Location	Clinical Positions Held
June, 2015 – April,2016	Frankfort Regional Medical Center Frankfort, KY	Staff Nurse ICU/CCU
January, 2013 – present	Central Baptist Hospital Lexington, KY	Charge Nurse/Telemetry Unit
February, 2009 – August, 2009	Specialty Hospital Amman, Jordan	Medication nurse
March, 2006 – June, 2008	Jordan University Hospital Amman- Jordan	ICU- Registered Nurse

Awards and Honors

Year	Award
2016	Delta Psi Chapter of Sigma Theta Tau Research Award
2015	American Heart Association Travel Award
2015	Spring 2015 UK CON New Opportunity Fund Graduate Scholarship
2014	Fall 2014 UK CON New Opportunity Fund Graduate Scholarship
2014	Spring 2014 UK CON New Opportunity Fund Graduate Scholarship

Publications

Alhurani, A. S., Dekker, R., Tovar, E., Bailey, A., Lennie, T. A., Randall, D. C., & Moser, D. K. (2014). Examination of the potential association of stress with morbidity and mortality outcomes in patient with heart failure. SAGE Open Med, 2. doi: 10.1177/2050312114552093

Alhurani, A. S., Dekker, R. L., Abed, M. A., Khalil, A., Al Zaghal, M. H., Lee, K. S., . . . Moser, D. K. (2015). The association of co-morbid symptoms of depression and anxiety with all-cause mortality and cardiac rehospitalization in patients with heart failure. Psychosomatics, 56(4), 371-380. doi: 10.1016/j.psym.2014.05.022

Reeves, G. C., Alhurani, A. S., Frazier, S. K., Watkins, J. F., Lennie, T. A., & Moser, D. K. (2015). The association of comorbid diabetes mellitus and symptoms of depression with all-cause mortality and cardiac rehospitalization in patients with heart failure. BMJ Open Diabetes Res Care, 3(1), e000077. doi: 10.1136/bmjdrc-2014-000077

Publications: (In process)

Stress, Cognitive Appraisal, Coping, and Event Free Survival in Heart Failure Patients, Clinical Nursing Research Journal.

Predisposing factors of persistent symptoms of depression and anxiety among patients with acute coronary syndrome.

The association of persistent symptoms of depression and anxiety with recurrent acute coronary syndrome

Presentations:

Date	Program Title	Sponsor
Spring, 2016	The association of persistent symptoms of depression and anxiety with recurrent acute coronary syndrome	Top Ten Student Posters: Southern Nursing Research Society, VA
Spring, 2016	Predisposing factors of persistent symptoms of depression and anxiety among patients with acute coronary syndrome.	Southern Nursing Research Society, VA
Fall 2015	Predisposing factors of persistent symptoms of depression and anxiety among patients with acute coronary syndrome.	American Heart Association, FL
Fall 2015	Trajectories of Anxiety and Depression are Predictive of Physical Health-Related Quality of Life, Mortality, and Hospital Admission at 1-Year among Patients with Heart Failure.	American Heart Association, FL
Spring 2015	The Association of Comorbid Diabetes Mellitus and Symptoms of Depression with All-Cause Mortality and Cardiac Rehospitalization in Patients with Heart Failure.	Southern Nursing Research Society, FL
Spring 2015	Stress, Cognitive Appraisal, Coping, and Event Free Survival in Heart Failure Patients.	Southern Nursing Research Society, FL
Fall 2014	The Association of Co-morbid Symptoms of Depression and Anxiety with All-Cause Mortality in Patients with Heart failure.	American Heart Association, IL
Spring 2012	The Association of Co-morbid Symptoms of Depression and Anxiety with Event-Free Survival in Patients with Heart failure, Poster presentation.	Southern Nursing Research Society, AR
Spring 2012	The Effect of Psychological Distress Factors on the Perceived Health Status, Emergency Department Visits, Re-hospitalization, and Mortality in Adults with Heart Failure.	The 8th (2012) Annual University of Kentucky Scholarship Showcase, KY

Spring 2011	The 7th (2011) Annual University of Kentucky Scholarship Showcase	The 7th (2011) Annual University of Kentucky Scholarship Showcase, KY

Professional Memberships

Date	Organization
2014 – Present	Sigma Theta Tau, Nursing Honor Society, University of Kentucky Chapter.
2014 – Present	Delta Epsilon Iota Academic Honor Society, University of Kentucky Chapter.
	American Association of critical Care Nurses.
2014 – Present	American Heart Association
2014 – Present	Southern Nursing Research Society.
2012 – Present	

Academic Service
Teaching

Semester	Course Title and Number, Credit Hours	
Spring 2016	NUR 212 Advanced Medical Surgical Nursing Kentucky State University	10 credit hours (classroom)
Spring 2016	Nursing Clinical NUR 212 Advanced Medical Surgical Nursing Kentucky State University	
Fall 2015	NUR 322 Nursing Assessment Kentucky State University	RN to BSN (online) 3 credit hours
Fall 2015	NUR 321 Professional Role Transition Kentucky State University	RN to BSN (online) 3 credit hours
Fall 2015	NUR 325 Teaching and Learning in Nursing Kentucky State University	RN to BSN (online) 2 credit hours
Fall 2015	NUR 326 Community Support Systems Kentucky State University	RN to BSN (online) 4 credit hours
Spring 2015	NUR 212 Advanced Medical Surgical Nursing Kentucky State University	10 credit hours (classroom)
Spring 2015	Nursing Clinical NUR 212 Advanced Medical Surgical Nursing Kentucky State University	
Fall 2014	NUR 111 Fundamentals of Nursing Kentucky State University	7 credit hours
Fall 2014	Nursing Clinical NUR 111 Fundamentals of Nursing Kentucky State University	
Spring 2014	NSG 215 Pharmacology I Blue Grass Community College	Associate Degree (online) 1 credit hour
Spring 2014	NSG 225 Pharmacology II Blue Grass Community College	Associate Degree (online) 1 credit hour
Spring 2014	NSG 230 Medical Surgical Nursing III Blue Grass Community College	Associate Degree (classroom) 6 credit hour
Fall 2013	NSG 220 Medical Surgical Nursing II Blue Grass Community College	Associate Degree (classroom) 6 credit hour
Fall 2013	NSG 101 Nursing practice Blue Grass Community College	Associate Degree (classroom) 9 credit hour

Spring 2013	NSG 210 Medical Surgical Nursing I Blue Grass Community College	Associate Degree (classroom) 6 credit hour
Spring 2013	NSG 230 Medical Surgical Nursing III Blue Grass Community College Nursing Clinical	Associate Degree (classroom) 6 credit hour
Fall 2012	NSG 220 Medical Surgical Nursing II Blue Grass Community College	Associate Degree (classroom) 6 credit hour
Fall 2012	NSG 101 Nursing practice Blue Grass Community College	Associate Degree (classroom) 9 credit hour