UNIFORMED SERVICES UNIVERSITY, SCHOOL OF MEDICINE GRADUATE PROGRAMS
Graduate Education Office (A 1045), 4301 Jones Bridge Road, Bethesda, MD 20814

9/7/2016

APPROVAL SHEET

Title of Dissertation: "State Anger and Short-Term Heart Failure Outcomes: Comparison with Perceived Stress"

Name of Candidate: Andrew J. Dimond, Master of Science in Medical and Clinical Psychology

BOR Meeting Date: November 1, 2016

THESIS AND ABSTRACT APPROVED:

DATE:

[redacted] 9-7-16

David S. Krantz, Ph.D.
Department of Medical and Clinical Psychology
Committee Chairperson and Thesis Advisor

[redacted] 9/14/16

Andrew J. Waters, Ph.D.
Department of Medical and Clinical Psychology
Committee Member

[redacted] 9/13/16

CAPT Jeffrey D. Quinlan, M.D., FAAFP, MC, USN
Department of Family Medicine
Committee Member

COPYRIGHT STATEMENT

The author hereby certifies that the use of any copyrighted material in the thesis manuscript entitled: *State Anger and Short-Term Heart Failure Outcomes: Comparison with Perceived Stress* is appropriately acknowledged and, beyond brief excerpts, is with the permission of the copyright owner.

[redacted]

Andrew J. Dimond

BOR Meeting Date: November 1, 2016

STATE ANGER AND SHORT-TERM HEART FAILURE OUTCOMES: COMPARISON WITH PERCEIVED STRESS

by

Andrew J. Dimond

Thesis submitted to the Faculty of the
Medical and Clinical Psychology Graduate Program
Uniformed Services University of the Health Sciences
In partial fulfillment of the requirements for the degree of
Masters of Science, 2016

[Dissertation approval form inserted here]

ACKNOWLEDGMENTS

I would like to thank Dr. David Krantz for all of his support and guidance throughout the process of completing my thesis. I am indebted to both Dr. Romano Endrighi for laying the research groundwork for this study and Dr. Andrew Waters for his significant statistical assistance and feedback on the project. I would also like to thank CAPT Jeffrey Quinlan, M.D. for his feedback as a member of my thesis committee. Finally, I wish to thank my family, my follow graduate school cohort members, and lab mates for the generous assistance and support that they have given me while I have been completing this work.

DEDICATION

This work is dedicated to all of the scientists, both giants and otherwise, upon whose shoulders I have stood.

COPYRIGHT STATEMENT

The author hereby certifies that the use of any copyrighted material in the thesis manuscript entitled: *State Anger and Short-Term Heart Failure Outcomes: Comparison with Perceived Stress* is appropriately acknowledged and, beyond brief excerpts, is with the permission of the copyright owner.

Andrew J. Dimond

BOR Meeting Date: November 1, 2016

ABSTRACT

Title of Thesis: State Anger and Short-Term Heart Failure Outcomes: Comparison with Perceived Stress

Andrew J. Dimond, Master of Science, 2016

Thesis directed by: David S. Krantz, Professor, Department of Medical and Clinical Psychology

Background: Evidence suggests that anger episodes may trigger adverse cardiac events, and we previously demonstrated that short-term stress appraisal levels were associated with heart failure (HF) exacerbations. This study investigates associations between anger and short-term exacerbations, including hospitalizations or death, functional status, symptoms, and B-type natriuretic peptide (BNP), in patients with congestive heart failure (CHF). Methods: In 144 systolic CHF patients (77% male; 57.5 ± 11.5 years old; left valve ejection fraction ≤ 40%), state anger (State Trait Anger Expression Inventory-2, STAXI-2), perceived stress (Perceived Stress Scale, PSS), and hospitalizations or death were prospectively assessed at baseline and at 2-week intervals for 3 months. Hospitalization for CV causes or death (adverse events; AE) were assessed every 2 weeks, and at 9-month follow-up. Functional status (Six-Minute Walk Test; 6MWT), symptom status (Kansas City Cardiomyopathy Questionnaire summary score; KCCQ-Summary), and BNP were also assessed biweekly for 3 months. Mixed model analyses were used with standard risk factors as covariates. Results: Average anger and PSS were strongly correlated (r=.51, p<.01). Acute increases in anger were associated with decreased functional status (*B*=-2.55, *p*=.035) and high average anger was associated with worsened symptom status (*B*=-1.23, *p*<0.0001). Anger was not associated with risk for AE. After controlling for PSS, associations between anger and functional status and symptom status were no longer significant. Conversely, when controlling for anger, high average PSS was significantly associated with AE (*B*=0.12, *p*=.001) and worsened symptom status (*B*=-1.57, *p*<.0001) and acute increases in PSS were associated with worsened symptom status (*B*=-0.24, *p*=.003) and decreased functional status (*B*=-2.94, *p*=.004). There were no effects of anger or stress on BNP. Conclusions: Perceived stress was more strongly associated with outcomes than state anger. State anger was associated with short-term fluctuations in decreased functional status and mean worsened symptom status in CHF patients, but psychological stress was more strongly associated with adverse events, functional status, and symptom status than state anger. After controlling for perceived stress, state anger was not associated with any CHF outcomes. Effects of state anger may operate through its associations with psychological stress.

TABLE OF CONTENTS

LIST OF TABLES x

LIST OF FIGURES xi

CHAPTER 1: Introduction 1

- Heart Failure 1
  - Biological Risk Factors 2
  - Psychosocial Risk Factors 2
- Anger and Cardiovascular Disease 4
  - Anger as a Trigger 5
- Stress 6
  - Stress and Cardiovascular Disease 7
  - Minor Life Events and CHF 8
  - Stress Appraisal and CHF 8
- Relationship between Stress and Anger 8
- Summary and Rationale 9
  - Specific Aim 1. 10
  - Specific Aim 2. 10
  - Specific Aim 3. 11

CHAPTER 2: Method 12

- Participants 12
- Procedure 12
- Measures 13
  - Psychosocial Questionnaires 14
    - Perceived Stress Scale (PSS) 14
    - State Trait Anger Expression Inventory-2 (STAXI-2) 14
  - Measures of Heart Failure Severity 14
    - Kansas City Cardiomyopathy Questionnaire (KCCQ) 15
    - Six-Minute Walk Test (6MWT) 15
    - B-type Natriuretic Peptide (BNP) 15
    - Adverse Events: Hospitalization for CV Causes and Death 16
- Statistical Analyses 16
  - Exposure and Outcomes 17
  - Covariates 17
  - Presentation of Results 17

CHAPTER 3: Results 19

- Descriptive Statistics 19
- Correlations between Psychosocial Variables 19
- Analyses of Individual Predictors 19

State Anger 19
Effects of state anger on adverse events (CV hospitalization or death) 19
Effect of state anger on CHF symptoms and reported health status (KCCQ-Summary) 20
Effects of state anger on functional status (6MWT) and B-type natriuretic peptide (BNP) 20
Trait Anger 20
Effect of trait anger on dependent variables 21
Stress Appraisal 21
Effects of stress on adverse events (CV hospitalization or death) 21
Effect of stress on CHF symptoms and reported health status (KCCQ-Summary) 21
Effects of stress on functional status (6MWT) and B-type natriuretic peptide (BNP) 22
Analyses of Independent Contributions of Stress and Anger 22
Tables 24
Figures 31
CHAPTER 4: Discussion 36
Summary of Results 36
Anger and Hospitalizations 37
Stress and Hospitalizations 39
Symptoms and Walk Test Results 40
BNP Results 41
Anger vs. Stress 42
Limitations 43
Clinical/Scientific Implications and Future Directions 43
Conclusion 44
REFERENCES 46

LIST OF TABLES

Table 1. Baseline Socio-demographic and Clinical Characteristics (N = 144) 24
Table 2. Summary Statistics of Exposure and Outcome Variables[a] 25
Table 3. Correlations between Subject Means at Baseline 26
Table 4. Associations between State Anger and Outcomes Variables 27
Table 5. Associations between Perceived Stress and Outcomes Variables 29

LIST OF FIGURES

Figure 1. Mean PSS & mean STAXI-2 scores aggregated across participants and time points. 31
Figure 2. Deviation of PSS & STAXI-2 scores at each time point from each participant's total mean across time points. 32
Figure 3. Correlations between Adverse Events and unadjusted mean PSS or mean STAXI-2 score across all time points. 33
Figure 4. Correlations between KCCQ score and unadjusted mean PSS or mean STAXI-2 score across all time points. 34
Figure 5. Correlations between KCCQ score and mean PSS (adjusted for STAXI-2) or mean STAXI-2 (adjusted for PSS) score across all time points. 35

CHAPTER 1: Introduction

HEART FAILURE

Congestive heart failure (CHF) is a chronic disease that produces high rates of recurrent hospitalizations, reduces quality of life, and leads to high mortality rates. Heart failure is a progressive disease that often begins with dysfunction of the endothelium (blood vessel lining) and atherosclerosis (arterial fatty plaque formation; 47). Other causes of CHF may include high blood pressure, smoking, alcohol use, and cocaine use. Systolic CHF is characterized by the heart being unable to pump sufficient blood to meet the needs of the rest of the body. Common symptoms of CHF include breathlessness, fatigue, and fluid overload (56). CHF produces a significant health impact on individuals' lives.

CHF produces a heavy burden both on individual patients and on healthcare systems. CHF is estimated to be present in approximately six million members of the U.S. population (64). A study by Cowie et al (12) found that in a cohort of newly diagnosed CHF patients that 62% died within 1 year of being first diagnosed. Up to 35% of CHF patients are re-hospitalized within 30 days of being released from the hospital (16), and up to 50% are re-hospitalized after 6 months (13). A study by Wexler et al (74) found that 44% percent of a population of 65 year old or younger patients diagnosed with CHF experienced re-hospitalizations within 6 months of hospital discharge. These frequent hospitalizations pose a major disruption in the lives of CHF patients and cost the U.S. healthcare system and Medicare billions of dollars each year (30). Wexler et al. estimated that each re-hospitalization of CHF patients on average incurred a cost of

$7,174. Wexler et al. concluded that interventions producing even slight reductions in re-hospitalizations rates would greatly reduce the financial impact CHF currently produces.

Biological Risk Factors

Considerable research has been conducted on the biological and behavioral risk factors for CHF deterioration and on the long-term predictors of CHF outcomes (17; 25; 27; 62). Any factor that weakens the heart or increases how hard the heart has to work to pump blood may increase an individual's risk for developing CHF. Currently known common risk factors include high blood pressure, a history of myocardial infarctions (heart attacks), coronary artery disease (CAD), obesity, smoking, alcohol use, and sleep apnea (52). The current approach to treating CHF often includes prescribing the patient a mix of various medications to reduce the patient's heart rate, improve heart muscle contractility, and reduce blood volume (53). Consequently, the patient's level of compliance with taking medications becomes another risk factor for heart failure worsening. Another behavioral risk factor is diet. A diet containing high amounts of fat can potentiate atherosclerosis and high salt content in a person's diet may lead to increased blood pressure.

Psychosocial Risk Factors

There are also a number of psychosocial risk factors that are associated with CAD. Some of the psychosocial elements that are related to heart disease include anger, hostility, anxiety, stress, a low level of social connectedness, and depressive symptomology (21; 38; 59; 61). It has been proposed that psychosocial factors contribute to the development of heart disease through four main mechanisms: activation of the autonomic nervous system and hypothalamic-pituitary-adrenal axis, serotonergic dysfunction, secretion of proinflammatory cytokines (cell signaling proteins), and blood platelet activation (21).

A more acute form of psychosocial factor associated with heart disease worsening has been termed "triggering." A growing body of research indicates that the sudden experience of intense emotions, such as stress, anger, or sadness, in vulnerable individuals may trigger acute cardiac events within a matter of hours (68). Kark et al (40) found that deaths due to cardiovascular causes spiked amid the first day of missile strikes on Israeli cities during the Persian Gulf War. Leor et al (51) examined Los Angeles County coroner reports for the week before, the day of, and six days after the 1994 Northridge earthquake. They found that the number of deaths due to acute cardiac causes increased from a daily average of 4.6 during the week before to 24 on the day of the earthquake. They further reported that 16 of the deceased individuals either exhibited premonitory symptoms or died during the first hour after the quake began. Wilbert-Lampen et al (75) studied the incidence rate of cardiac emergencies in the greater Munich area during the 2006 Fédération Internationale de Football Association World Cup. They observed that on days in which the German team played cardiac emergencies increased by 2.66 times compared to a control period. They also found that the highest rate of events occurred during the initial 2 hours following the start of a match.

The biological processes underlying emotional triggering may include a reduction in parasympathetic nervous system activity, sudden changes in heart rate and blood pressure, neuroendocrine activation, inflammatory responses involving cytokines, and increased blood platelet activity (68). Those processes then increase the likelihood of coronary plaque disruption, thrombus formation, cardiac dysrhythmia, and myocardial ischemia (68).

ANGER AND CARDIOVASCULAR DISEASE

Anger has long been associated with worsened cardiac health, both in folk wisdom and scientific research. Some of the first major research linking anger and cardiovascular disease came about in the 1970's as a result of growing interest in the Type A personality construct (70). Type A individuals were thought to be more likely to exhibit competitiveness, impatience, aggressiveness, intense work focus, and anger (22). Research conducted over ensuing decades did not bear out a strong or consistent link between the full Type A personality construct and cardiovascular illness, but the hostility and aggression subcomponents of the larger Type A construct were found to predict the development of cardiovascular diseases (70).

The discovery of anger's link to cardiac illnesses has led to the continued modern research interest in anger as a predictor of heart disease. Currently, researchers often use a three-factor model to understand anger-related experiences (70). The three-factors are anger, hostility, and anger expression. Anger is generally used to refer to the actual affective experience of being angry and is divided into a more acute form, state anger, and a more chronic dispositional form, trait anger. Hostility is the cognitive dimension of anger and is often characterized by cynicism and negative attributions regarding the behaviors of others. Finally, anger expression refers to verbal or physical behavior that is antagonistic in nature.

Numerous studies have explored the link between the three forms of anger experience and cardiovascular illness. Jenner et al (37) examined hospital readmissions amongst a sample of 175 CHF patients and found that trait anger significantly predicted length of stay in the hospital, but not number of readmissions. Newman et al (60) conducted a 10 year prospective study with 1,749 participants to elucidate the relationship between hostility and CAD. They found that the presence of any observed hostility (as measured via a structured interview) at baseline was associated with a doubled risk of developing CAD during the course of the study, when controlling for other cardiovascular and psychosocial risk factors. Newman et al. also used a self-report measure of hostility, but found that it did not significantly correlate with increased risk of developing CAD and it only had a .12 correlation with the observational hostility measure.

When examined across multiple meta-analyses, the three forms of anger experience generally provide a mixed level of risk prediction and are often reduced to non-significance when controlling for other risk factors (70). While some measures of anger have not produced highly consistent and significant results, state anger may still prove to be a useful measure in relation to predicting cardiovascular events.

Anger as a Trigger

There is a growing body of literature that indicates the importance of acute anger in triggering cardiac events. Mittleman et al (55) conducted a study using a case-crossover methodology to examine whether there is a link between acute experiences of anger and myocardial infarctions. They found that the relative risk of a myocardial infarction was 2.3 during the 2 hours following experiencing an episode of heightened anger. Tofler et al (72) completed a similar case-crossover study and found that patients had a 4.1 relative risk of myocardial infarction in the 2 hours following an episode of intense anger. A meta-analysis conducted by Mostofsky et al (58) found that the risk of cardiovascular events was heightened for 2 hours after experiencing an outburst of anger in a sample of nine case-crossover studies. The same meta-analysis also found that outbursts of anger increase individuals' risk of various cardiovascular events, including: cardiac arrhythmia, ischemic and hemorrhagic stroke, myocardial infarction, and acute coronary syndrome (any condition in which blood supply to the heart is suddenly obstructed; 58). A study of patients with implanted cardioverter-defibrillators (ICDs) found that heightened levels of anger were significantly associated with the 15 minute period prior to the development of a ventricular arrhythmia (48). Episodes of anger were also associated with a heightened risk of experiencing myocardial ischemia in a study of patients with CAD (26).

STRESS

The term stress has many different definitions and may encapsulate numerous levels of analysis. There are considered to be three main categories of stress research (10). The first of these categories defines stress as a physiological reaction to demanding situations. This approach derived from the works of Walter Cannon and Hans Selye, and is often concerned with the measurement of hormones and other biomarkers of physiological reactivity (10).

The second category of stress research is based around measuring objective external events that are frequently associated with adaptive demands (10). This research is based on the assumption that numerous and/or major life changes, including positive ones like marriage or a promotion, are inherently stressful. Part of the research in this area exclusively focuses on either just major life events or just minor daily events. Minor life events characterize daily hassles such as being cutoff in traffic or arguing with someone.

The final category of stress research was founded out of the work of Richard Lazarus and defines stress as occurring when organisms perceive that environmental demands will exceed their coping capacity and experience a negative emotional reaction (49). This category of stress is concerned with measuring one's appraised capacity to respond to situational demands (10). The Perceived Stress Scale is one measure that was designed to quantify individuals' experience of event appraisal and stress (9).

Stress and Cardiovascular Disease

Numerous studies have examined the relationship between cardiovascular disease and stress. Significant findings have been produced by various studies examining the relationship between laboratory mental stressors and cardiac ischemia (disruption in blood supply; 46). Mental stress tasks that have been used include activities such as public speaking (63) and mental arithmetic tasks (6). Stress, among other factors, may also trigger cardiac events (see Psychosocial Risk Factors above).

Psychological stress is known to indirectly affect CHF, by negatively influencing a number of the factors, such as alcohol use and triggering of inflammatory responses, which are predictive of CHF outcomes (69). Limited research has been conducted regarding the degree to which stress directly influences CHF outcomes and hospitalizations. Most research that has been conducted in this area has involved either retrospective designs, which have not been able to firmly establish causation, or short-term laboratory based experiments with high impact events, which lack ecological validity compared to the kinds of long-term stressors that most people face in their lives (54; 76).

Minor Life Events and CHF

Little is known about the direct relationship between minor events and CHF. At a very general level, there is evidence that health status and medical utilization rates are related to the degree to which one experiences daily hassles (4; 15). A longitudinal study of Dutch youths that collected data at ages 27 and 29 years old found that increases in daily hassles were related to increased CAD risk factors, such as increased lipoprotein levels, more smoking behavior, and less daily physical activity (73).

Stress Appraisal and CHF

The relationship between stress appraisal and CHF is another topic upon which limited research has been conducted. A correlational study of heart failure patients did find that those who had a greater sense of perceived control, a core element of stress appraisal, were more likely to exhibit less emotional distress and higher functional status (18). The only prospective study examining stress appraisal and CHF that this author is familiar with was conducted by Endrighi et al (19). It found that patients who repeatedly reported high levels of appraised stress had a higher likelihood of cardiovascular related hospitalizations and death, when compared to patients with lower stress scores.

Relationship between Stress and Anger

An important question for cardiovascular health research is to what degree do stress and anger overlap with each other? Unfortunately, this topic has rarely been directly addressed by researchers. Many studies treat stress and anger as wholly separate variables. They may, however, be connected in important ways when it comes to predicting cardiovascular illness development. Smith et al (65) conducted a set of studies on hostility and found that individuals who experience high hostility and anger are more likely to experience more severe and more frequent daily stressors, reduced social support satisfaction, and have fewer social supports. Each of those associated factors could lead to increased perceived stress and increased activity of the hypothalamic-pituitary-adrenocortical axis and sympathetic-adrenal-medullary system, which can promote the development of cardiovascular disease. A study of the psychometric properties of the Weekly Stress Inventory when used with a heart failure population found that minor events were significantly correlated with a measure of Type A personality (57). Finally, Girardi et al (28) found that increased interpersonal conflict in the workplace, which may lead to both stress and anger, was related to increased serum levels of pro-inflammatory cytokines (intercellular messaging proteins). A heightened inflammatory response may contribute to the development of atherosclerosis, which can lead to the development of CHF.

SUMMARY AND RATIONALE

CHF significantly reduces the quality and length of life of millions of individuals and cost patients and health care systems billions of dollars each year. Numerous studies have been conducted to better understand the biological and psychosocial risk factors for developing CHF and CHF worsening. Anger has previously been identified as likely playing a significant part in the progression and exacerbation of CHF, including triggering acute cardiac events. Stress in general has also been identified as probably contributing to the development and course of CHF. However, limited research has been conducted that specifically examines the degree to which stress appraisal may specifically contribute to CHF outcomes. Similarly, there appears to be a lack of research that assesses the potential overlap between stress and anger.

A previous study (19) produced from the same Behavioral Triggers of Heart Failure (BETRHEART) project as this study found that scores on the Perceived Stress Scale, a measure of stress appraisal, were related to adverse events (deaths and hospitalizations). This study seeks to extend those results and compare the relative importance of stress appraisal with anger experiences in predicting outcomes for CHF patients.

Specific Aim 1.

The first aim of this study will be to determine the effects of state anger on CHF hospitalizations, death, functional status, and symptoms. Outcomes assessed will consist of cardiac related hospitalizations and death, Kansas City Cardiomyopathy Questionnaire scores, six minute walk test distance, and blood levels of b-type natriuretic peptide. State anger will be measured with the State Trait Anger Expression Inventory-2.

Hypothesis 1: Patients with higher levels of state anger will exhibit higher rates of hospitalizations and death, reduced functional status, and greater CHF symptoms.

Specific Aim 2.

To determine the impact of stress appraisal, as measured by the Perceived Stress Scale, on acute CHF hospitalizations, deaths, functional status, and symptoms.

Hypothesis 2: Patients with higher stress appraisal will exhibit higher rates of hospitalizations and death, reduced functional status, and greater CHF symptoms.

Specific Aim 3.

To determine the independent contributions of (a) stress appraisal and (b) anger on measures of CHF worsening.

Hypothesis 3a: Patients with higher stress appraisal will exhibit, independent of state anger, higher rates of hospitalizations and death, reduced functional status, and greater CHF symptoms.

Hypothesis 3b: Patients with higher levels of state anger will exhibit, independent of stress appraisal, higher rates of hospitalizations and death, reduced functional status, and greater CHF symptoms.

CHAPTER 2: Method

Participants

This study used a sample of 144 patients diagnosed with systolic CHF at the University of Maryland Medical Center (UMMC). Patients were eligible for inclusion in the study if they were 18 years of age or older, displayed a left ventricular ejection fraction equal to or less than 40%, and had exhibited a New York Heart Association Class II-IV functional status for at least three months. Patients that met any of the following criteria were excluded from the study: prior heart transplantation, clinically significant mitral valve disease, myocarditis in the past six months, thyroid dysfunction, implanted left ventricular assist device, alcohol abuse within the last six months, active cancer treatment, nursing home residency, and significant cognitive impairment. All participants were fully informed about the study and they provided written consent to participate. The study was approved by the IRBs of the Uniformed Services University of the Health Sciences and the UMMC.

Procedure

Potential participants were initially identified by treatment providers and referred to the study. Interested individuals then scheduled a baseline visit. During the baseline visit the potential participants were informed about the study and screened for participation eligibility. If they were determined to be eligible, they then completed a set of baseline psychosocial questionnaires; their functional status, symptoms, and subjective health were assessed; and CHF biomarkers were obtained.

After the baseline visit, participants were contacted once every two weeks over the course of a two and a half month time period for a total of five phone interviews.

Questionnaires were verbally administered during each phone interview and information about cardiovascular related hospitalizations ("adverse events") since the previous phone call was collected. Hospitalization information was then independently verified through medical chart review.

Participants scoring in the top or bottom 30 percent of the PSS distribution, approximately reflecting high (≥15) and low (≤9) stress scores, after a telephone interview were scheduled for a clinic assessment as soon as feasible (mean 4±3 days). Because the PSS is not a diagnostic tool with validated cutoffs (9), the scores were chosen a priori to ensure sampling of high and low tails of the PSS distribution and adequate numbers of participants at each assessment (8). Since participation in the two week clinic visits was based on previous phone interview PSS scores, participants differed in the number and timing of clinic assessments. During these clinic visits: self-report measures of symptoms and CHF health status were obtained, objective functional status assessments were completed, and biomarkers were sampled.

Three months following the baseline visit all participants repeated the same measures as at baseline, including psychosocial and health questionnaires, functional status assessment, and CHF biomarker sampling.

A telephone interview was scheduled six months after the last clinic visit (nine months after the baseline visit). Changes in clinical status, including hospitalizations or death were recorded and subsequently verified via medical record review. If the participant had died, the spouse or next of kin was interviewed regarding the date and cause of death. The present data are from the first nine months of the study.

Measures

Psychosocial Questionnaires

Perceived Stress Scale (PSS)

The 10-item PSS measures the generalized appraisal of stress over the past two weeks (9). This standardized instrument was developed to measure the extent to which an individual appraises events or situations in one's life as stressful or being out of one's control. The PSS has well-established reliability and validity, and has been used to measure stress in behavioral, epidemiological, and clinical research encompassing a wide range of samples and populations (2; 5; 8; 9; 29; 50). For example, in CAD patients, there is evidence that high stress appraisal measured with the PSS is an independent predictor of poor outcomes, including adverse events (2). Possible scores range from 0 to 40 with higher scores indicating a greater appraisal of psychosocial stress.

State Trait Anger Expression Inventory-2 (STAXI-2)

The STAXI-2 (67) is a 57-item questionnaire that measures state anger (15 items), trait anger (10 items), anger expression (16 items), and anger control (16 items). The state anger items ask how the respondent feels "right now" and the trait anger, anger expression, and anger control items ask how the respondent "generally" feels or reacts to things. The STAXI-2's validity and reliability have been established in general populations and, with a Portuguese adaptation, in medical patient populations (3; 67). Respondents endorse statements, such as "I feel angry," on a 4-point Likert scale that ranges from one ("almost never") to four ("almost always") for each item.

Measures of Heart Failure Severity

There are several ways that CHF severity can be assessed. These include measuring symptoms and self-reported health, objective assessment of functional status, CHF biomarkers, hospitalizations, and cardiac events. These elements of CHF severity will be measured as follows:

Kansas City Cardiomyopathy Questionnaire (KCCQ)

The KCCQ is a 23-item scale used to measure symptoms and CHF health status (31). It has been validated to predict CHF exacerbations and mortality (34; 66). Patients indicate to what degree they were limited by CHF over the past two weeks. The KCCQ includes domain measures of CHF symptoms, CHF induced physical and social limitations, and self-efficacy and quality of life. The present analyses utilized the KCCQ summary score (KCCQ-Summary), which is derived from the domain scores. Scores range from 0-100, with higher values indicating less symptom burden and better health status.

Six-Minute Walk Test (6MWT)

The 6MWT is an objective measure widely used to quantify physical functional limitations among CHF patients (32). 6MWT scores consist of the distance the patient is able to walk on a level course for six minutes, with longer distances reflecting better functional status. The distance patients are able to walk is predictive of hospitalizations and mortality, and is related to CHF severity (1; 36). In the present study, across all clinic visits and participants, there were 658 potential 6MWT assessments, with 108 (16.4%) not performed or terminated early due to severe physical limitations.

B-type Natriuretic Peptide (BNP)

BNP is a hormone released by the walls of the left ventricle that plays a role in the body's adaptive response to hemodynamic alterations, especially in CHF (11). BNP also functions as a measure of left ventricular wall stretch. Increases in BNP have been found to be a strong predictor of functional status decline and it has been proposed that BNP be used to stratify patient risk (44). A controlled trial found that providing treatment guided by BNP levels led to reduced hospitalizations and deaths in CHF patients (39). At each clinic visit circulating levels of BNP were measured as a biomarker of CHF severity. Concentrations were determined at the UMMC Clinical Chemistry Research Lab using a fluorescence standardized immunoassay (Beckman Coulter Access II, Fullerton CA) with a lower limit of detection of 1 pg/mL. Because BNP is not normally distributed, it was logarithmically transformed for use in statistical analyses.

Adverse Events: Hospitalization for CV Causes and Death

As noted earlier, hospitalizations were assessed by patient self-report and subsequently verified via hospital record review. Hospitalizations were categorized into CHF or CV-related causes vs. hospitalizations for non-CV causes. CHF hospitalizations were classified as hospitalizations with a primary diagnosis of CHF exacerbation, characterized by a diagnosis of pump failure or fluid overload. CV-related hospitalizations were primarily characterized by a diagnosis of angina, myocardial infarction, ischemia or arrhythmia. Classification of hospitalization categories was determined by the treating physician and the emergency medical team. An “adverse event” variable was computed by determining, at each assessment, the number of CHF or CV-related hospitalization events, or death, occurring between that assessment and the subsequent assessment. Each patient was then assigned a “0” (no adverse event) or “n” (number of adverse events) for each of the seven time points.

STATISTICAL ANALYSES

Exposure and Outcomes

The exposure variables were the PSS and STAXI-2 scores measured at seven time points (baseline, phone interviews 1-5, and three month). The outcome variables were adverse events (dichotomized as: 0=no adverse events before next assessment; 1=at least 1 adverse event before next assessment). Symptom status (KCCQ-Summary), functional status (6MWT), and the biomarker BNP were continuous outcomes measured at up to seven time points (baseline, clinic visits 1-5, and three month).

Covariates

Known predictors of CHF exacerbations (assessed at baseline) used in adjusted analyses were age, gender, BMI, income (as an index of socioeconomic status), New York Heart Association (NYHA) classification, ejection fraction, creatinine, and history of hypertension. Missing data for creatinine (n = 4) and income (n = 1) were imputed by using mean substitution for a small number of participants.

Presentation of Results

Data are presented as means and standard deviations, or N and percentages, as appropriate. BNP values were logarithmically transformed; untransformed values are presented to aid interpretation. Linear mixed models (LMM) using SAS PROC GLIMMIX (dichotomous outcomes) and PROC MIXED (continuous outcomes) were used for data analyses. LMM takes into account the dependence between participant observations and allows for different numbers of observations. We used a random (subject-specific) intercept and an autoregressive model of order 1 for the residuals within subjects (continuous outcomes). Time was entered as a continuous variable in all models.

We present “Baseline” analysis (association between the initial psychosocial measure at Baseline with outcome variables), followed by analysis of associations between psychosocial measures and outcomes using all available time points (referred to as “Assessment-level” analyses). In Assessment-level analyses, entered together in the models were: a Mean IV score computed by aggregating over all assessments for each subject (i.e., a subject-level variable), and a Deviation IV score (an assessment-level variable), computed as the difference between the IV score at each assessment and the patient’s own Mean IV score. An effect for Mean IV score would indicate a between-subject association, and for Deviation IV score a within-subject association (33).

Parameter estimates of associations between exposure and outcomes are reported as B (SE). Analyses were conducted both unadjusted and adjusted for medical covariates, i.e., age, sex, BMI, income, NYHA class, ejection fraction, creatinine, and hypertensive status. The exceptions to this were analyses for Hypothesis 3 (determining the independent contributions of stress appraisal and anger), for which medical covariates were not used.

CHAPTER 3: Results

Descriptive Statistics

Sample demographic and medical characteristics are presented in Table 1, and the descriptive statistics for the study measures are summarized in Table 2. The total means and deviations from individual means for each participant are presented for state anger and perceived stress in Figure 1 and Figure 2, respectively. State anger had a positive skew (skewness = 3.77), but the size of our sample and the robustness of LMMs mean that this was likely not a significant issue, while PSS had a visibly more normal distribution.

Between baseline and 9 months, 42 patients (29.2%) experienced at least 1 CV hospitalization (4 of these subsequently died), and 5 (3.5%) died without experiencing a prior CV hospitalization. Therefore, 47 patients experienced at least 1 adverse event.

Correlations between Psychosocial Variables

The correlations between the means of the psychosocial variables are summarized in Table 3. All three measures showed relatively strong intercorrelations. The lowest correlation was between state anger and trait anger. The highest correlation was between trait anger and PSS scores.

Analyses of Individual Predictors

State Anger

Effects of state anger on adverse events (CV hospitalization or death)

Using multiple assessments, the odds of an adverse event before the next assessment were not greater in patients with higher, compared to those with lower, mean state anger scores across assessments (unadjusted $p = 0.30$; adjusted $p = 0.18$; see Table 4 and Figure 3). Also, there was no within-subjects association between state anger and adverse events (unadjusted $p = 0.62$; adjusted $p = 0.63$). The (single) baseline state anger score was not associated with subsequent adverse events (unadjusted $p = 0.59$; adjusted $p = 0.51$).

Effect of state anger on CHF symptoms and reported health status (KCCQ-Summary)

Using multiple assessments, patients with higher, compared to lower, mean state anger scores had poorer CHF symptom status during the study (adjusted B = -1.23, SE = 0.30, $p < 0.001$; see Figure 4). There was no within-subject association (unadjusted $p = 0.31$; adjusted $p = 0.30$). Baseline state anger scores were associated with subsequent KCCQ scores (adjusted B = -0.45, SE = 0.18, $p = 0.01$).

Effects of state anger on functional status (6MWT) and B-type natriuretic peptide (BNP)

When using multiple assessments, there was no between-subject association (unadjusted $p = 0.99$; adjusted $p = 0.61$). There was, however, a within-subjects association (adjusted B = -2.41, SE = 1.21, $p = 0.046$) indicating that when a patient experienced higher than his/her average state anger level, the same patient demonstrated poorer functional status compared to when they reported lower than their average state anger level. Baseline state anger scores were not associated with subsequent 6MWT distances (unadjusted $p = 0.53$; adjusted $p = 0.32$).

There were no associations between state anger scores and BNP levels in either between-subject (unadjusted $p = 0.90$; adjusted $p = 0.36$) or within-subject analyses (unadjusted $p = 0.26$; adjusted $p = 0.27$).

Trait Anger

Effect of trait anger on dependent variables

Baseline trait anger was not associated with subsequent adverse events (unadjusted $p = 0.98$; adjusted $p = 0.94$), baseline KCCQ scores (unadjusted $p = 0.10$; adjusted $p = 0.09$), baseline functional status (unadjusted $p = 0.53$; adjusted $p = 0.55$), or baseline BNP (unadjusted $p = 0.31$; adjusted $p = 0.47$).

Stress Appraisal

Effects of stress on adverse events (CV hospitalization or death)

Using multiple assessments, the odds of an adverse event before the next assessment were greater in patients with higher, compared to those with lower, mean PSS scores across assessments (unadjusted: B = 0.10, SE = 0.03, $p = 0.001$, OR = 1.11, 95% CI = 1.04, 1.18; adjusted: B = 0.10, SE = 0.03, $p = 0.001$, OR = 1.11, 95% CI = 1.05, 1.18; see Table 5 and Figure 3). The baseline PSS score was not associated with subsequent adverse events (unadjusted $p = 0.09$; adjusted $p = 0.17$).

In contrast, there was no within-subjects association between stress and adverse events (unadjusted $p = 0.95$; adjusted $p = 0.89$). This indicates that at any assessment (baseline, phone interviews 1-5, or 3 month), when a patient reported higher stress level compared to his/her average, there was no change in the likelihood of experiencing an imminent adverse event. (See Table 2 for a summary of associations between exposure and study outcomes).

Effect of stress on CHF symptoms and reported health status (KCCQ-Summary)

Using multiple assessments, patients with higher, compared to lower, mean PSS scores had poorer CHF symptom status during the study (adjusted B = -1.61, SE = 0.17, $p < 0.001$; see Figure 4). There was also a robust within-subject association (adjusted B = -

0.26, SE = 0.08, p = 0.001), indicating that when a patient experienced higher, compared to lower, than his/her average stress level the same patient experienced worsened CHF symptom status. Baseline PSS scores were associated with subsequent KCCQ scores (adjusted B = -0.45, SE = 0.15, p = 0.004).

Effects of stress on functional status (6MWT) and B-type natriuretic peptide (BNP)

When using multiple assessments, there was no between-subject association between PSS scores and functional status (unadjusted p = 0.38; adjusted p = 0.07). There was, however, a robust within-subjects association (adjusted B = -3.30, SE = 1.00, p = 0.001) indicating that when a patient experienced higher than his/her average stress level, the same patient demonstrated poorer functional status compared to when they reported lower than their average stress level. Baseline PSS scores were not associated with subsequent 6MWT distances (unadjusted p = 0.17; adjusted p = 0.40).

There were no associations between PSS scores and BNP levels in between-subject (unadjusted p = 0.96; adjusted p = 0.74), within-subject (unadjusted p = 0.59; adjusted p = 0.56), or baseline analyses (unadjusted p = 0.77; adjusted p = 0.48).

ANALYSES OF INDEPENDENT CONTRIBUTIONS OF STRESS AND ANGER

In order to determine the independent contributions of state anger and stress appraisal, multivariable analyses were conducted by controlling for state anger by matching it with each level (e.g. baseline, mean, and deviation) of PSS, and vice versa.

When controlling for state anger, PSS scores were still significantly associated with between-subject adverse events (B = 0.12, SE = 0.03, p = 0.001), between-subject KCCQ (B = -1.57, SE = 0.20, p < 0.001; see Figure 5), within-subject KCCQ (B = -0.24, SE = 0.08, p = 0.003), baseline KCCQ (B = -0.30, SE = 0.15, p = 0.04), and within-subject 6MWT (B = -2.94, SE = 1.02, p = 0.004; see Table 5).

When controlling for PSS, state anger's associations with between-subject KCCQ (p = 0.81; see Figure 5), baseline KCCQ (p = 0.09), and within-subject 6MWT (p = 0.14) became non-significant (see Table 4).

Tables

Table 1. Baseline Socio-demographic and Clinical Characteristics (N = 144)

Variable	Mean ± SD or %
Age (yrs)	57.51± 11.52
Male sex (%)	77.0
Race	
Caucasian (%)	29.2
African American (%)	70.1
American Indian (%)	0.7
BMI (kg/m^2)	30.87 ± 7.50
Ejection fraction (%)	23.10 ± 7.48
Smoking	
yes (%)	27.2
no (%)	72.8
Systolic BP (mm/Hg)	121.05 ± 19.32
Creatinine (mg/dL)	1.38 ± 0.71
Hypertension	
yes (%)	79.2
no (%)	20.8
NYHA class	
II (%)	54.9
III (%)	43.1
IV (%)	2.1
Income $	
<15k (%)	34.3
15-30k (%)	26.6
30-70k (%)	30.1
>70k (%)	9.1
Employment status	
full time (%)	14.6
part time (%)	7.6
disabled (%)	51.4
unemployed (%)	4.9
retired (%)	21.5

Note. BMI = body mass index; BP = blood pressure; NYHA = New York Heart Association.

Table 2. Summary Statistics of Exposure and Outcome Variables[a]

Time Measure[b]	Base N=144	PA1 N=137	PA2 N=129	PA3 N=125	PA4 N=125	PA5 N=126	3 mo. N=126
PSS	13.16 (8.36)	12.00 (8.22)	12.29 (8.13)	10.94 (7.35)	11.62 (7.91)	10.08 (7.71)	10.04 (7.91)
State Anger	16.78 (5.39)	18.02 (6.59)	18.02 (6.28)	16.47 (4.32)	17.16 (6.37)	17.18 (6.59)	16.70 (5.40)
Likelihood[c] of Adverse Event (%)	5.00	2.96	5.56	1.61	4.80	2.46	27.97

Note. PSS = Perceived Stress Scale; State Anger = STAXI-2 State Anger Score; Base = Baseline; PA = phone assessment interview. Possible range of scores for PSS are 0 – 40, for State Anger are 15-60, and for KCCQ are 0 - 100. Lower KCCQ scores indicate less HF symptom burden and better health status.
[a]Data for PSS and State Anger are Means (SD).
[b]N's reflect number of participants attending each visit and providing PSS data (total of 912 assessments). Since different numbers of participants were asked to attend each clinic visits, N's for KCCQ, 6MWT, and BNP differ following PA1 through PA5; N's for KCCQ range from 72-143; N's for 6MWT range from 60-130; N's for BNP range from 64-140; N's for events range from 118-140.
[c]Likelihood of adverse events is reported as percentage of participants that experienced at least one adverse event (CV hospitalization or death) before the subsequent assessment.

Table 3. Correlations between Subject Means at Baseline

	PSS	**State Anger**
State Anger	.51	-
Trait Anger	.57	.39

Note. PSS = Perceived Stress Scale; State Anger = STAXI-2 State Anger Score; Trait Anger = STAXI-2 Trait Anger Score.

Table 4. Associations between State Anger and Outcomes Variables

Table Analysis Type	Covariates	Exposure[b]	Outcomes[a]			
			Adverse Event	KCCQ	6MWT	BNP
Baseline[c]	Unadjusted	Baseline State Anger	0.019	**-0.42***	1.32	-0.01
			(0.036)	(0.17)	(2.09)	(0.01)
	Adjusted[e]	Baseline State Anger	0.022	**-0.45***	2.07	-0.01
			(0.033)	(0.18)	(2.08)	(0.01)
	Adjusted PSS[g]	Baseline State Anger	0.001	-0.31	0.42	-0.01
			(0.030)	(0.18)	(2.21)	(0.01)
Assessment-Level[d]	Unadjusted	Mean State Anger[f]	0.044	**-1.23*****	-0.06	0.003
			(0.042)	(0.30)	(5.42)	(0.02)
	Adjusted	Mean State Anger	0.054	**-1.30*****	-2.42	0.017
			(0.041)	(0.29)	(4.69)	(0.018)
	Adjusted PSS	Mean State Anger	0.037	-0.07	3.29	0.003
			(0.05)	(0.29)	(6.57)	(0.03)
	Unadjusted	Deviation State Anger[f]	-0.022	-0.10	**-2.55***	0.006
			(0.044)	(0.10)	(1.21)	(0.006)

Adjusted	Deviation State Anger	-0.022	-0.10	**-2.41***	0.006
		(0.045)	(0.10)	(1.21)	(0.006)
Adjusted PSS	Deviation State Anger	0.035	-0.05	-1.83	0.006
		(0.05)	(0.10)	(1.22)	(0.006)

Note. State Anger = STAXI-2 State Anger Score, KCCQ = Kansas City Cardiomyopathy Questionnaire-summary score, 6MWT = Six-Minute Walk Test, BNP = B-type natriuretic peptide (natural log values used), PSS = Perceived Stress Scale.

[a]Outcomes are cardiovascular hospitalization or death (adverse events) occurring after each assessment (baseline, phone interview 1-5 and 3 month), and KCCQ summary score, 6MWT distance walked and BNP level at each assessment (baseline, clinic visit 1-5, and 3 month) (see text for details). Values are parameter estimates B (SE) from linear mixed models.

[b]Exposure refers to the Baseline State Anger score, Mean State Anger score, and Deviation State Anger score for their respective analyses. (See text for details).

[c]For the Baseline analyses, the baseline score of respective outcomes (except adverse event) were included in models.

[d]Assessment-Level refers to linear mixed model analyses using all available data.

[e]Adjusted analyses include the following covariates: age, sex, BMI, income, NYHA class, ejection fraction, creatinine and hypertensive status (parameter estimates for time or covariates not shown).

[f]Mean State Anger scores and Deviation State Anger scores are entered concurrently (see text). All models include time as a within-subject variable.

[g]Analysis included only PSS as a covariate.

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

Table 5. Associations between Perceived Stress and Outcomes Variables

Table Analysis Type	Covariates	Exposure[b]	Outcomes[a]			
			Adverse Event	KCCQ	6MWT	BNP
Baseline[c]	Unadjusted	Baseline PSS	0.03	**-0.37***	2.06	0.002
			(0.03)	(0.14)	(1.46)	(0.006)
	Adjusted[e]	Baseline PSS	0.02	**-0.45****	1.24	0.003
			(0.03)	(0.15)	(1.49)	(0.006)
	Adjusted State Anger[g]	Baseline PSS	0.03	**-0.30***	1.91	0.004
			(0.22)	(0.15)	(1.54)	(0.006)
Assessment-Level[d]	Unadjusted	Mean PSS[f]	**0.10****	**-1.59*****	-2.75	0.000
			(0.03)	(0.17)	(3.16)	(0.015)
	Adjusted	Mean PSS	**0.10****	**-1.61*****	-5.01	0.004
			(0.03)	(0.17)	(2.77)	(0.013)
	Adjusted State Anger	Mean PSS	**0.12****	**-1.57*****	-3.79	0.000
			(0.03)	(0.20)	3.82	(0.02)
	Unadjusted	Deviation PSS[f]	0.00	**-0.25*****	**-3.26****	0.003
			(0.03)	(0.08)	(1.00)	(0.005)

Adjusted	Deviation PSS	0.00	**-0.26*** **	**-3.30*** **	0.003
		(0.03)	(0.08)	(1.00)	(0.005)
Adjusted State Anger	Deviation PSS	0.1	**-0.24** **	**-2.94** **	0.001
		(0.03)	(0.08)	(1.02)	(0.005)

Note. PSS = Perceived Stress Scale, KCCQ = Kansas City Cardiomyopathy Questionnaire-summary score, 6MWT = Six-Minute Walk Test, BNP = B-type natriuretic peptide (natural log values used), State Anger = STAXI-2 State Anger Score.

[a]Outcomes are cardiovascular hospitalization or death (adverse events) occurring after each assessment (baseline, phone interview 1-5 and 3 month), and KCCQ summary score, 6MWT distance walked and BNP level at each assessment (baseline, clinic visit 1-5, and 3 month) (see text for details). Values are parameter estimates B (SE) from linear mixed models.

[b]Exposure refers to the Baseline PSS score, Mean PSS score, and Deviation PSS score for their respective analyses. (See text for details).

[c]For the Baseline analyses, the baseline score of respective outcomes (except adverse event) were included in models.

[d]Assessment-Level refers to linear mixed model analyses using all available data.

[e]Adjusted analyses include the following covariates: age, sex, BMI, income, NYHA class, ejection fraction, creatinine and hypertensive status (parameter estimates for time or covariates not shown).

[f]Mean PSS scores and Deviation PSS scores are entered concurrently (see text). All models include time as a within-subject variable.

[g]Analysis included only State Anger as a covariate.

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

FIGURES

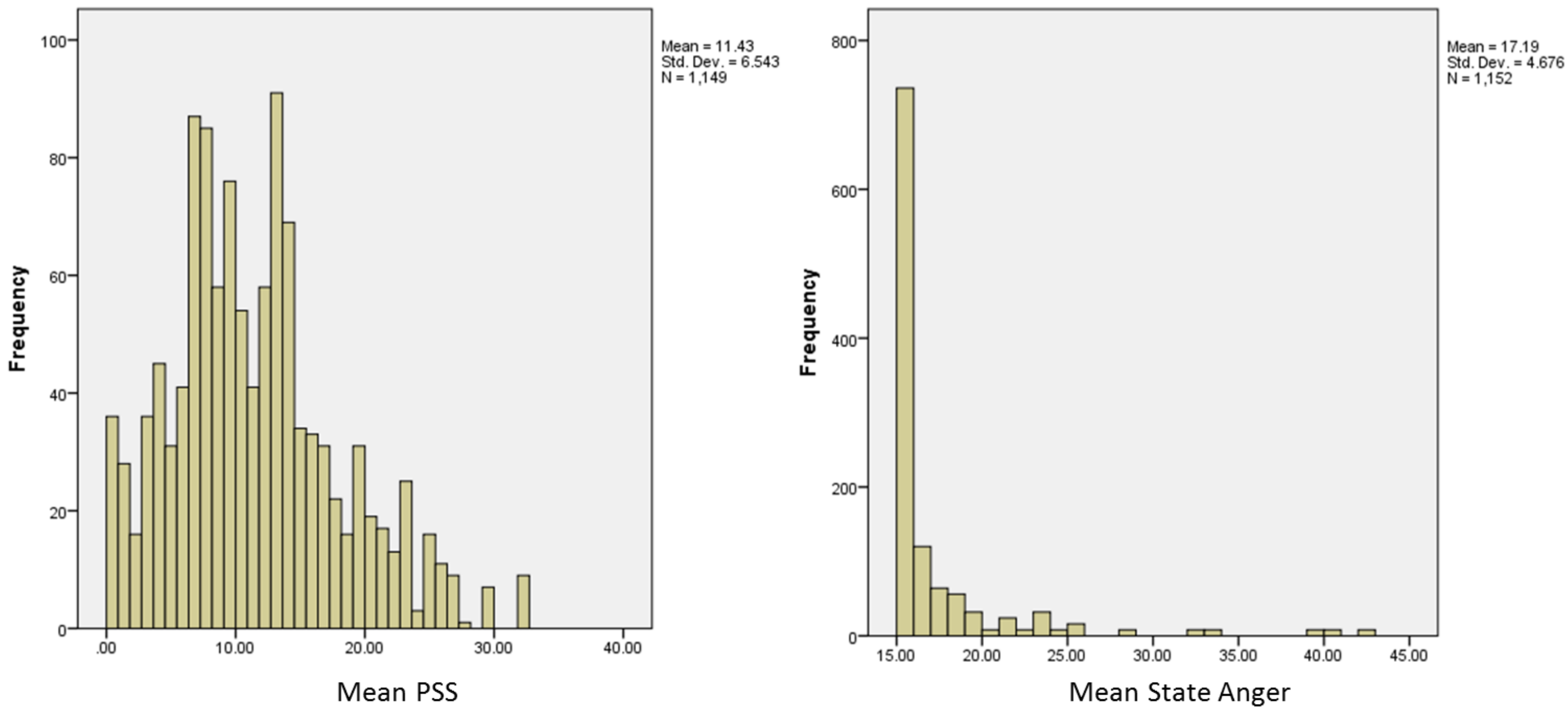


Figure 1. Mean PSS & mean STAXI-2 scores aggregated across participants and time points.

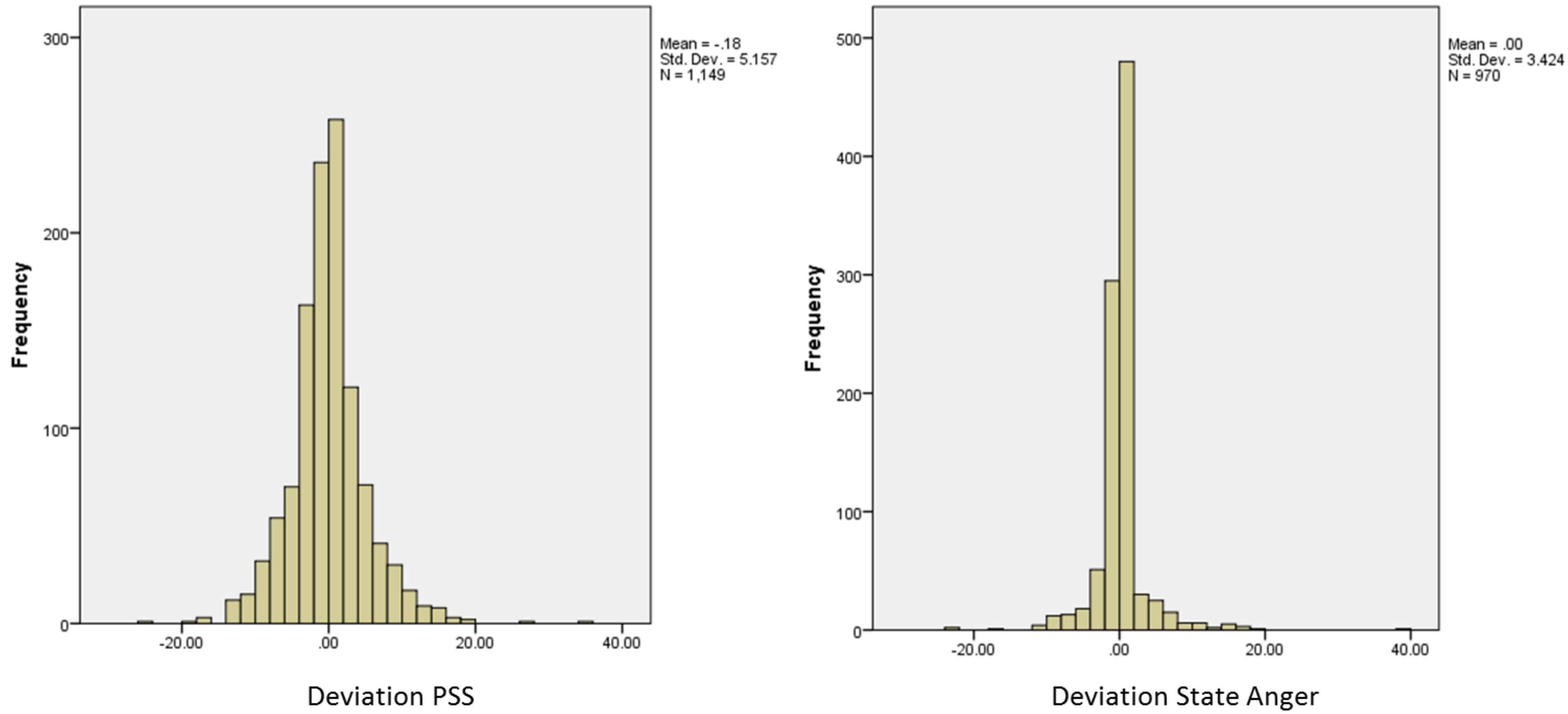


Figure 2. Deviation of PSS & STAXI-2 scores at each time point from each participant's total mean across time points.

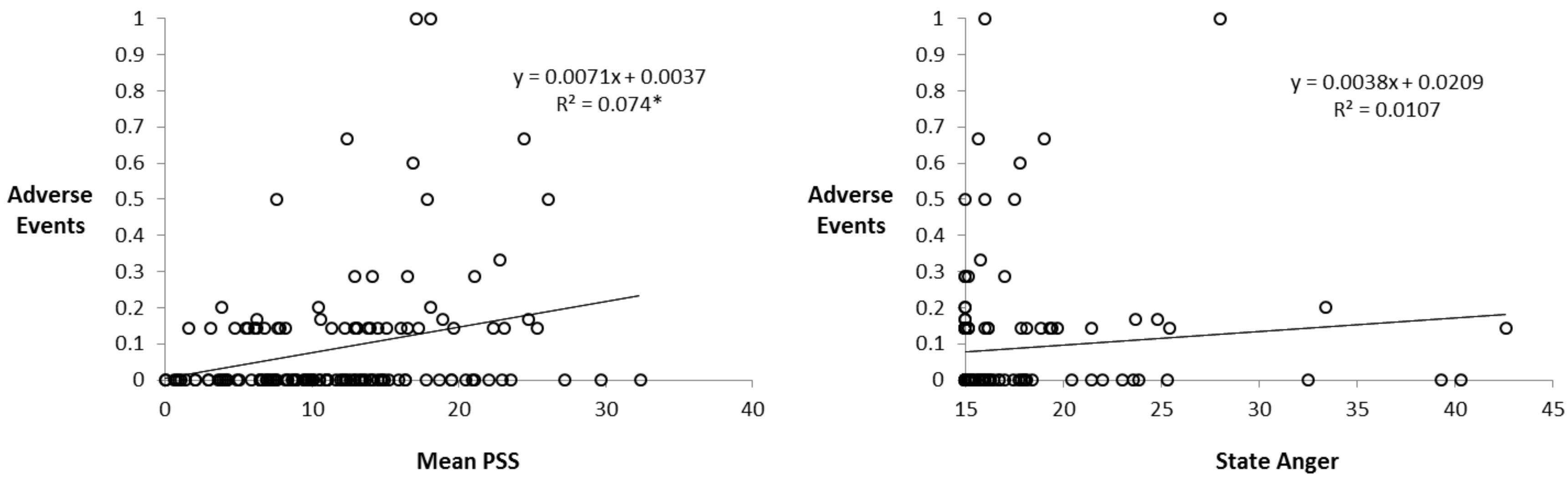


Figure 3. Correlations between Adverse Events and unadjusted mean PSS or mean STAXI-2 score across all time points. *p < .01.

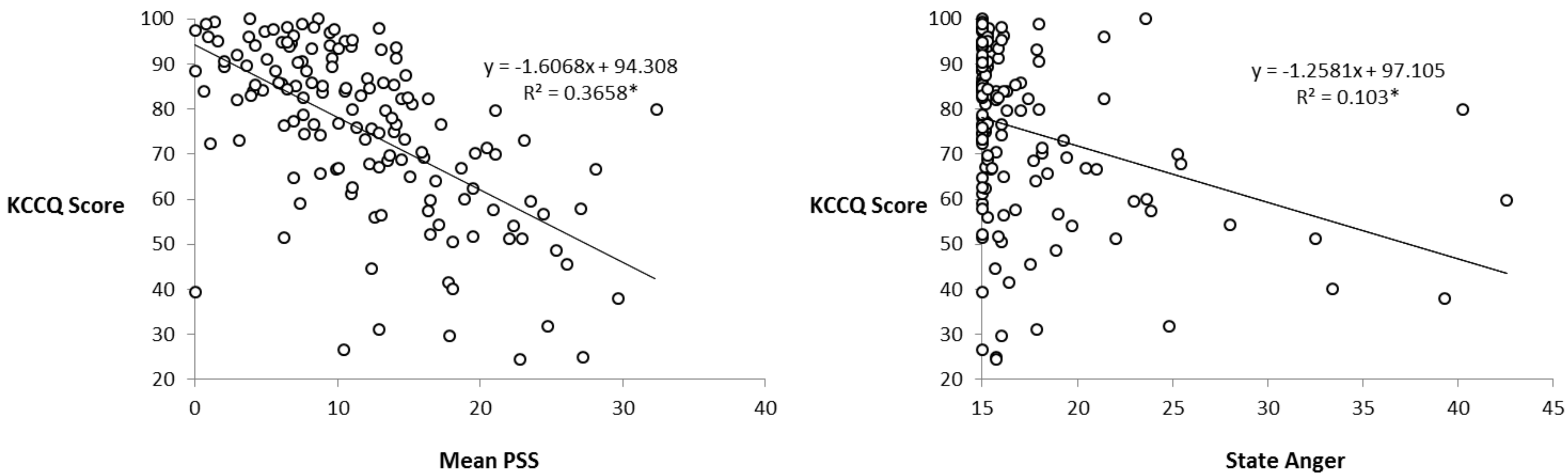
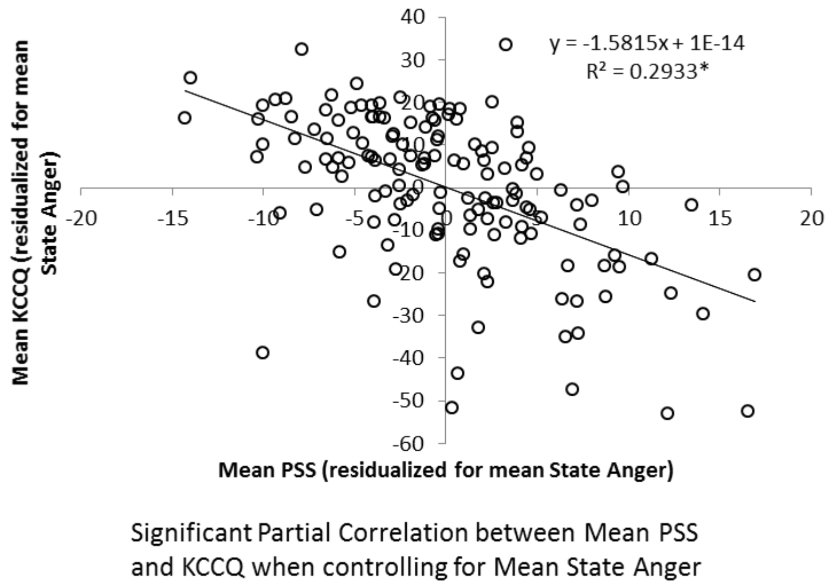


Figure 4. Correlations between KCCQ score and unadjusted mean PSS or mean STAXI-2 score across all time points.
*p < .01.



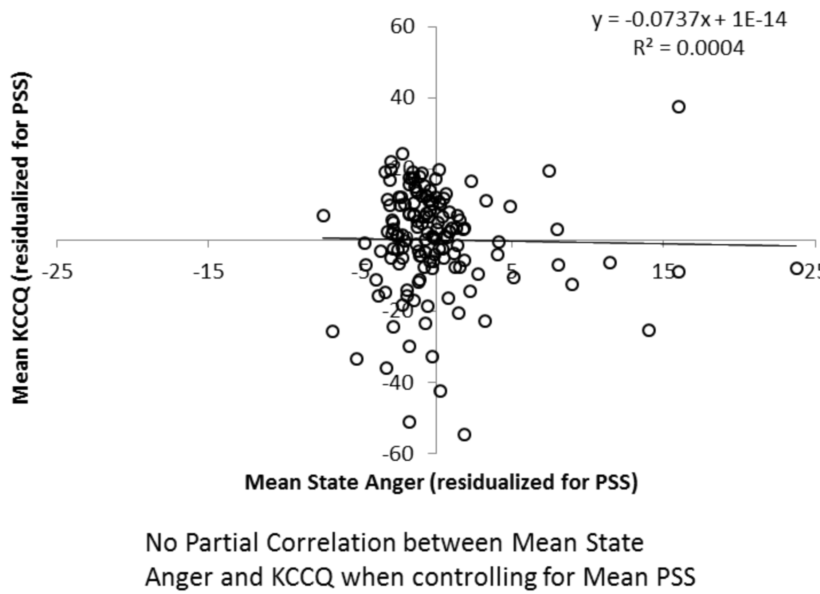


Figure 5. Correlations between KCCQ score and mean PSS (adjusted for STAXI-2) or mean STAXI-2 (adjusted for PSS) score across all time points.
*p < .01.

CHAPTER 4: Discussion

SUMMARY OF RESULTS

The results of the present study indicate that state anger was independently associated with functional status, but not adverse events or BNP. PSS was associated with adverse events, in addition to functional status, but not BNP. When PSS was adjusted for in analyses with state anger, state anger became non-significant. Conversely, when state anger was adjusted for in the analysis of PSS, PSS retained its significance.

The results of this study are partially consistent with the proposed hypotheses. Hypothesis 1 was that patients with higher levels of state anger would exhibit higher rates of hospitalizations and death, reduced functional status, and greater CHF symptoms. This hypothesis was partially supported, since patients with higher anger did exhibit reduced functional status and higher symptoms. Hypothesis 2 was that patients with higher stress appraisal would exhibit higher rates of hospitalizations and death, reduced functional status, and greater CHF symptoms. This hypothesis was fully supported by the analysis results. Hypothesis 3a was that patients with higher stress appraisal would exhibit, independent of state anger, higher rates of hospitalizations and death, reduced functional status, and greater CHF symptoms. This hypothesis was fully supported by the analysis results. Hypothesis 3b was that patients with higher levels of state anger would exhibit, independent of stress appraisal, higher rates of hospitalizations and death, reduced functional status, and greater CHF symptoms. This hypothesis was not support by the analysis results.

Anger and Hospitalizations

Our finding that state anger does not predict short-term cardiac hospitalizations or death is not consistent with other studies indicating a relationship between short-term anger episodes and various manifestations of coronary heart disease. A study by Ironson et al (35) found that anger acted as a significant stressor that led to reduced left ventricular ejection fraction, indicative of ischemia. A case-crossover study by Mittleman et al (55) found that participants had an increased risk of experience a myocardial infarction in the two hours following an outburst of anger. A study by Lampert et al (48) found that heightened anger was significantly associated with the 0-15 minute period before receiving a shock in a sample of patients with implantable cardioverter-defibrillators. A meta-analysis of studies examining the association between outbursts of anger and cardiovascular events produced evidence that incidence of acute coronary syndrome and myocardial infarction increased 2.4-7.3 fold within two hours after an anger outburst (58).

There are some notable differences between this study and previous ones examining cardiovascular disease and short-term anger. Many of the extant studies looked at only specific cardiac events, such myocardial infarction, compared to our wider analysis of hospitalization and death events, which gives a better sense of healthcare system impact. We are not aware of any other studies examining state anger and hospitalizations, so a direct comparison of results cannot be made. Previous studies have also often relied on retrospective self-report of anger prior to a cardiovascular event. The accuracy of those self-reports may be confounded by the general public commonly accepting the link between anger and cardiac events. Thus, a patient may have been experiencing a more mild level of anger before a cardiac event, but subsequently believes that it must have been a severe level of anger, since it led to the cardiac event, and will report it as such. Our study avoided this potential confound by using a measure of state anger that has no retrospective element.

As a further contrast, studies looking at anger as a trait and examining longer-term consequences suggest that there is a complex relationship between trait forms of anger and heart disease outcomes. For example, Jenner et al (37) found that trait anger was not associated with the number of hospital readmissions among a sample of CHF patients, but it was associated with the length of their hospital stays. A study conducted using the same Project BETRHEART dataset by Keith et al (43) found that trait measures of outward anger expression, trait anger, and the latent construct of hostility were all predictive of all cause hospitalizations. Kawachi et al (41) found that men with greater difficulty controlling their anger were more likely to experience adverse coronary events. Additionally, a meta-analysis by Chida and Steptoe (7) found that greater anger was associated with adverse events in both healthy and CHD populations. Conversely, Eng et al (20) found that men exhibiting moderate levels of anger expression were less likely to experience a myocardial infarction than men exhibiting low levels of anger expression. Also, when using clinical interviews to identify patients as exhibiting a destructive or constructive anger style, Davidson and Mostofsky (14) found that highs levels of destructive anger were associated with increased risk of developing CHD, while high levels of constructive anger were associated with reduced risk of developing CHD, in men only. Therefore, our own findings and previous mixed findings regarding anger and adverse outcomes may be due in part to self-report measures lacking sufficient metrics for constructive and destructive anger.

Our study differed from these studies in significant ways. Our selection of measures and analyses emphasized short-term state anger and time point to time point fluctuations in experience of anger. In contrast, many of these previous studies looked at more stable tendencies toward experiencing anger and had longer-term outcomes. Previous trait anger studies have also often emphasized the risk of developing a disease, while our study examined CHF patients and risk of hospitalization or death. Finally, it is noteworthy that our finding of no association between hospitalizations and state anger matches the finding for trait anger from the study by Jenner et al (37). They also found that trait anger was associated with length of hospital stays. We did not test for an association between state anger and length of hospital stay, which could be one future direction for this research.

Stress and Hospitalizations

In contrast to anger, perceived stress was related to hospitalizations and death, even when controlling for state anger. There are limited studies to which this result can be compared. There is evidence that major stressful events, such as earthquakes and missile attacks, may lead to increased incidence of cardiac events (40; 51). Psychological stress is also known to be able to indirectly affect CHF, by negatively influencing a number of the factors that are predictive of CHF prognosis and hospitalizations (69). However, very few studies have evaluated whether psychological stress is a direct predictor of adverse clinical outcomes in CHF (23). Much of the existing research on stress and CHF is limited to retrospective studies of emergency room admissions for CHF or to laboratory acute stress studies. Some of those studies do, however, point to stress having a deleterious impact on CHF, which is in-line with the present findings (54; 76).

Finally, some may wonder about the directionality of the relationship between stress and hospitalizations, such as whether hospitalizations cause increased stress, as opposed to increased stress causing more hospitalizations. The study by Endrighi et al (19), which used the same dataset as this study, addressed that question and found evidence for both increases in stress being related to subsequent hospitalizations and hospitalizations being related to subsequent increases in stress.

Symptoms and Walk Test Results

This study's results indicated that, with respect to the symptom and functional status measures, anger was associated with symptoms at the between subject level and functional status at the within subject level. However, when controlling for perceived stress, these relationships disappeared, indicating that there is an overlap between state anger and perceived stress in regards to their influence on these measures. An element of this relationship that should be considered is that an individual can clearly feel psychological stress, but not feel angry. On the other hand, it is possible that one cannot feel angry without experiencing some degree of concomitant stress. State anger having some contribution to these measures may indicate that they are more behavioral and are more susceptible to being impacted by a patient's present mood state. Previous research has provided evidence that depression is associated with worsened 6MWT performance in CHF patients (45). It is interesting that anger, which is usually thought of as an activating emotion, would be associated with worsened physical performance. The mechanisms for this association are unclear, but it could potentially be due to factors like distraction, lack of motivation, or intentional poor performance during the walk test. For example, individuals who are angrier may be less willing to exert effort on the walk test.

Hospitalizations and death, on the other hand, were only associated with perceived stress, which may indicate that perceived stress captures a more biological component of the mechanisms of CHF. A possible explanation for this connection is that the PSS captures a longer time span than the state anger component of the STAXI-2, which could better encapsulate how activated an individual's physiological systems have needed to be in response to psychological stressors. It is also possible that, with respect to short term heart failure hospitalizations, perceived stress simply has a more deleterious effect on this outcome than state anger.

Another BETRHEART dataset study conducted by Keith (42) found no association between hospitalizations or symptoms and the higher order construct of Negative Affect, which was composed of state and trait anger, total stress, hostility, state and trait anxiety, and total depression. The difference in results between the present study and Keith's could indicate that there are important differences between the more short-term outcomes of this study (9 months) and the longer-term outcomes of their study (39 months). It could also be that the heavier loading of trait measures in Keith's construct of Negative Affect could have different predictive characteristics than this study's emphasis on state measures. Finally, the difference of using linear mixed models versus structural equation modeling may in part account for the divergent results.

BNP Results

Across all analyses state anger and perceived stress had non-significant associations with plasma BNP, which acts as an indicator of left ventricular wall stretch. These results may indicate that experiencing stress or state anger did not consistent lead to sustained, intense hemodynamic effects in our sample. Consequently, the relationships that were significant between our IVs and DVs can likely not be explained as occurring purely due to the hemodynamic consequences of stress and anger.

Anger vs. Stress

There is currently a surprising lack of research regarding the possible relationship between state anger and perceived stress. Consequently, it is difficult to develop an empirically informed theory regarding how state anger and perceived stress interact. Some studies have found that anger was a significant predictor of cardiovascular worsening, which contrasts with our finding that state anger became non-significant when controlling for stress. Given that all of the significant associations between state anger and CHF status became non-significant when controlling for perceived stress, it appears possible that the effects of state anger may operate in some way through state anger's associations with perceived stress.

There are several possible mechanisms that may explain these relationships. One possible explanation for other studies finding anger to be significant is that many of those studies do not sufficiently differentiate between stress and anger or they lack comparative analyses like those that we conducted. It is also important to note that our measure of stress looked more at appraisal of events. Whereas, our measure of state anger capture more of an individual's response to events. It is possible that a person's appraisal versus response tendencies in reaction to events play a more significant role in our findings than just the difference between stress and anger. It is also possible that the observed CHF outcomes could be due primarily to physiological responses, such as HPA-axis activity. Consequently, perceived stress could have a stronger association simply due to the fact that it was measured over a longer time span (two weeks) than state anger, which was based on how the respondent felt at the time of the assessment. The physiological, psychological, or behavioral changes that may be co-occurring with perceived stress and state anger that could explain the pattern of results this study produced remain to be determined.

Limitations

The limitations of this study should also be factored into considerations of its results. Only individuals who reported perceived stress scores that were in the top or bottom third of the sample completed the six-minute walk test and KCCQ during the bi-weekly assessment period. Therefore, it is possible that the effects of perceived stress do not apply across the entire range of PSS scores. Additionally, the two week timeframe between phone assessments may have been too long a period to fully capture participants' experiences of state anger during the assessment phase of the study. This study also obtained a sample of participants that were somewhat different from those used for most studies in this research area. Our participants were primarily African-American and of lower SES. They were also of a somewhat younger average age and had a higher prevalence of non-ischemic heart failure than most other CHF study samples. It is notable that there is evidence to suggest that the prognosis of patients with non-ischemic CHF is often better than for patients with ischemic CHF (24). Due to the above stated reasons, the results from our sample may not generalize to all populations.

Clinical/Scientific Implications and Future Directions

Based on these results, it is possible that treatments targeting stress, as opposed to anger, may provide greater benefit in heart failure patients for reducing short-term hospitalizations and symptoms and improving functional status. Treating anger in combination with treating stress may also increase the benefit for reducing symptoms and improving functional status, especially in patients who report experiencing frequent high levels of anger.

In addition, since the present study examined only cardiac hospitalizations and not short-term hospitalizations, it would be important to determine whether stress and anger are predictive of all-cause hospitalizations in the short-term.

These results also raise issues with the approach of looking at a single psychosocial risk factor used in many previous studies. Other studies may miss the overlap that can occur between psychosocial risk factors, such as that found between perceived stress and state anger in this study. This issue in the literature has been raised before by Suls and Bunde (71). Consequently, more research should be done that simultaneously examines multiple psychosocial risk factors, such as anger, depression, anxiety, and stress, each of which has been extensively studied in relation to cardiovascular disease. A specific future direction for this research could be exploring what unique and combined contributions anger, stress, anxiety, and depression have to CHF outcomes.

CONCLUSION

CHF is a chronic disease that produces high rates of recurrent hospitalizations, reduces quality of life, and leads to high mortality rates. It produces a heavy burden both on the individual patients and on healthcare systems. Significant research has been conducted on the biological and psychological risk factors for cardiovascular disease. However, there have been few prospective studies in patients with CHF examining the relationship of state anger and perceived stress to short-term outcomes. We found that state anger was independently associated with functional status, but not adverse events. PSS was associated with adverse events, in addition to functional status. When PSS was adjusted for in analyses with state anger, state anger became non-significant. Conversely, when state anger was adjusted for in the analysis of PSS, PSS retained its significance. A tentative conclusion from this study is that you can take the anger out of being stressed, but you can’t take the stress out of being angry.

REFERENCES

1. Alahdab MT, Mansour IN, Napan S, Stamos TD. 2009. Six Minute Walk Test Predicts Long-Term All-Cause Mortality and Heart Failure Rehospitalization in African-American Patients Hospitalized With Acute Decompensated Heart Failure. *Journal of Cardiac Failure* 15:130-5

2. Arnold SV, Smolderen KG, Buchanan DM, Li Y, Spertus JA. 2012. Perceived stress in myocardial infarction: long-term mortality and health status outcomes. *Journal of the American College of Cardiology* 60:1756-63

3. Azevedo FBd, Wang Y-P, Goulart AC, Lotufo PA, Benseñor IM. 2010. Application of the Spielberger's State-Trait Anger Expression Inventory in clinical patients. *Arquivos de Neuro-Psiquiatria* 68:231-4

4. Brantley PJ, Dutton GR, Grothe KB, Bodenlos JS, Howe J, Jones GN. 2005. Minor life events as predictors of medical utilization in low income African American family practice patients. *Journal of Behavioral Medicine* 28:395-401

5. Brotman DJ, Golden SH, Wittstein IS. The cardiovascular toll of stress. *The Lancet* 370:1089-100

6. Burg MM, Vashist A, Soufer R. 2005. Mental stress ischemia: Present status and future goals. *Journal of Nuclear Cardiology* 12:523-9

7. Chida Y, Steptoe A. 2009. The association of anger and hostility with future coronary heart disease: A meta-analytic review of prospective evidence. *Journal of the American College of Cardiology* 53:936-46

8. Cohen S, Janicki-Deverts D. 2012. Who's Stressed? Distributions of Psychological Stress in the United States in Probability Samples from 1983, 2006, and 20091. *Journal of Applied Social Psychology* 42:1320-34

9. Cohen S, Kamarck T, Mermelstein R. 1983. A global measure of perceived stress. *Journal of Health and Social Behavior*:385-96

10. Cohen S, Kessler RC, Gordon LU. 1995. Strategies for measuring stress in studies of psychiatric and physical disorders. In *Measuring stress: A guide for health and social scientists*, ed. S Cohen, RC Kessler, LU Gordon. New York, NY: Oxford University Press. Number of.

11. Cowie MR, Mendez GF. 2002. BNP and congestive heart failure. *Progress in Cardiovascular Diseases* 44:293-321

12. Cowie MR, Wood DA, Coats AJ, Thompson SG, Suresh V, et al. 2000. Survival of patients with a new diagnosis of heart failure: A population based study. *Heart* 83:505-10

13. Curtis LH, Greiner MA, Hammill BG, Kramer JM, Whellan DJ, et al. 2008. Early and long-term outcomes of heart failure in elderly persons, 2001-2005. *Archives of Internal Medicine* 168:2481-8

14. Davidson KW, Mostofsky E. 2010. Anger expression and risk of coronary heart disease: Evidence from the Nova Scotia Health Survey. *American heart journal* 159:199-206

15. DeLongis A, Coyne JC, Dakof G, Folkman S, Lazarus RS. 1982. Relationship of daily hassles, uplifts, and major life events to health status. *Health Psychology* 1:119-36

16. Dharmarajan K, Hsieh AF, Lin Z, Bueno H, Ross JS, et al. 2013. Diagnoses and timing of 30-day readmissions after hospitalization for heart failure, acute myocardial infarction, or pneumonia. *The Journal of the American Medical Association* 309:355-63

17. Djousse L, Driver JA, Gaziano JM. 2009. Relation between modifiable lifestyle factors and lifetime risk of heart failure. *The Journal of the American Medical Association* 302:394-400

18. Dracup K, Westlake C, Erickson VS, Moser DK, Caldwell ML, Hamilton MA. 2003. Perceived control reduces emotional stress in patients with heart failure. *JOURNAL OF HEART AND LUNG TRANSPLANTATION* 22:90-3

19. Endrighi R, Waters AJ, Gottlieb SS, Harris KM, Wawrzyniak AJ, et al. 2016. Psychological stress and short-term hospitalisations or death in patients with heart failure. *Heart*

20. Eng PM, Fitzmaurice G, Kubzansky LD, Rimm EB, Kawachi I. 2003. Anger expression and risk of stroke and coronary heart disease among male health professionals. *Psychosomatic Medicine* 65:100-10

21. Everson-Rose SA, Lewis TT. 2005. Psychosocial factors and cardiovascular diseases. *Annu. Rev. Public Health* 26:469-500

22. Eysenck H, Fulker D. 1983. The components of type A behaviour and its genetic determinants. *Personality and Individual Differences* 4:499-505

23. Feenstra J, Grobbee D, Jonkman F, Hoes A, Stricker B. 1998. Prevention of relapse in patients with congestive heart failure: The role of precipitating factors. *Heart* 80:432-6

24. Follath F. 2001. Ischemic versus non-ischemic heart failure: Should the etiology be determined? *Heart Failure Monitor* 1:122

25. Fonarow GC, Abraham WT, Albert NM, Stough WG, Gheorghiade M, et al. 2008. Factors identified as precipitating hospital admissions for heart failure and clinical outcomes. *Archives of Internal Medicine* 168:847-54

26. Gabbay FH, Krantz DS, Kop WJ, Hedges SM, Klein J, et al. 1996. Triggers of myocardial ischemia during daily life in patients with coronary artery disease: Physical and mental activities, anger and smoking. *Journal of the American College of Cardiology* 27:585-92

27. Giamouzis G, Kalogeropoulos A, Georgiopoulou V, Laskar S, Smith AL, et al. 2011. Hospitalization epidemic in patients with heart failure: risk factors, risk prediction, knowledge gaps, and future directions. *Journal of Cardiac Failure* 17:54-75

28. Girardi D, Falco A, De Carlo A, Benevene P, Comar M, et al. 2015. The mediating role of interpersonal conflict at work in the relationship between negative affectivity and biomarkers of stress. *Journal of Behavioral Medicine*:1-10

29. Glaser R, Kiecolt-Glaser JK, Marucha PT, MacCallum RC, Laskowski BF, Malarkey WB. 1999. Stress-related changes in proinflammatory cytokine production in wounds. *Archives of General Psychiatry* 56:450-6

30. Go AS, Mozaffarian D, Roger VL, Benjamin EJ, Berry JD, et al. 2013. Executive summary: Heart disease and stroke statistics--2013 update: A report from the American Heart Association. *Circulation* 127:143-52

31. Green CP, Porter CB, Bresnahan DR, Spertus JA. 2000. Development and evaluation of the Kansas City Cardiomyopathy Questionnaire: a new health status measure for heart failure. *Journal of the American College of Cardiology* 35:1245-55

32. Guyatt GH, Sullivan MJ, Thompson PJ, Fallen EL, Pugsley SO, et al. 1985. The 6-minute walk: a new measure of exercise capacity in patients with chronic heart failure. *Canadian Medical Association Journal* 132:919-23

33. Hedeker D, Mermelstein RJ, Berbaum ML, Campbell RT. 2009. Modeling mood variation associated with smoking: An application of a heterogeneous mixed‐effects model for analysis of ecological momentary assessment (EMA) data. *Addiction* 104:297-307

34. Heidenreich PA, Spertus JA, Jones PG, Weintraub WS, Rumsfeld JS, et al. 2006. Health Status Identifies Heart Failure Outpatients at Risk for Hospitalization or Death. *Journal of the American College of Cardiology* 47:752-6

35. Ironson G, Taylor CB, Boltwood M, Bartzokis T, Dennis C, et al. 1992. Effects of anger on left ventricular ejection fraction in coronary artery disease. *The American Journal of Cardiology* 70:281-5

36. Jehn M, Schmidt-Trucksäss A, Schuster T, Weis M, Hanssen H, et al. 2009. Daily walking performance as an independent predictor of advanced heart failure: Prediction of exercise capacity in chronic heart failure. *American heart journal* 157:292-8

37. Jenner RC, Strodl ES, Schweitzer RD. 2009. Anger and depression predict hospital use among chronic heart failure patients. *Australian Health Review* 33:541-8

38. Jiang W, Alexander J, Christopher E, Kuchibhatla M, Gaulden LH, et al. 2001. Relationship of depression to increased risk of mortality and rehospitalization in patients with congestive heart failure. *Archives of Internal Medicine* 161:1849-56

39. Jourdain P, Jondeau G, Funck F, Gueffet P, Le Helloco A, et al. 2007. Plasma Brain Natriuretic Peptide-Guided Therapy to Improve Outcome in Heart Failure: The STARS-BNP Multicenter Study. *Journal of the American College of Cardiology* 49:1733-9

40. Kark JD, Goldman S, Epstein L. 1995. Iraqi missile attacks on israel: The association of mortality with a life-threatening stressor. *JAMA* 273:1208-10

41. Kawachi I, Sparrow D, Spiro A, Vokonas P, Weiss ST. 1996. A prospective study of anger and coronary heart disease - The normative aging study. *Circulation* 94:2090-5

42. Keith F. 2016. *Behaviors and cognitions as mediators of psychosocial variables and re-hospitalizations in patients with heart failure: A structural equation modeling approach*. Uniformed Services University of the Health Sciences, Bethesda, MD

43. Keith F, Krantz DS, Chen R, Harris KM, Ware CM, et al. 2016. Title. Volume:In press

44. Koglin J, Pehlivanli S, Schwaiblmair M, Vogeser M, Cremer P, vonScheidt W. 2001. Role of brain natriuretic peptide in risk stratification of patients with congestive heart failure. *Journal of the American College of Cardiology* 38:1934-41

45. Kop WJ, Synowski SJ, Gottlieb SS. 2011. Depression in heart failure: Biobehavioral mechanisms. *Heart Failure Clinics* 7:23-38

46. Krantz DS, Burg MM. 2014. Current perspective on mental stress-induced myocardial ischemia. *Psychosomatic Medicine* 76:168-70

47. Krantz DS, Whittaker KS, Sheps DS. 2012. Psychosocial risk factors for coronary heart disease: Pathophysiological mechanisms. In *Heart and Mind: The practice of cardiac psychology*, ed. R Allan, JA Fisher:91-114. Washington D.C.: American Psychological Association. Number of 91-114 pp.

48. Lampert R, Joska T, Burg MM, Batsford WP, McPherson CA, Jain D. 2002. Emotional and physical precipitants of ventricular arrhythmia. *Circulation* 106:1800-5

49. Lazarus RS. 1993. From psychological stress to the emotions: A history of changing outlooks. *Annual Review of Psychology* 44:1-21

50. Lee E-H. 2012. Review of the psychometric evidence of the Perceived Stress Scale. *Asian Nursing Research* 6:121-7

51. Leor J, Poole WK, Kloner RA. 1996. Sudden Cardiac Death Triggered by an Earthquake. *New England Journal of Medicine* 334:413-9

52. Mayo Clinic. 2015. *Heat failure: Risk factors*. http://www.mayoclinic.org/diseases-conditions/heart-failure/basics/risk-factors/con-20029801

53. Mayo Clinic. 2015. *Heat failure: Treatments and drugs*. http://www.mayoclinic.org/diseases-conditions/heart-failure/basics/risk-factors/con-20029801

54. Middlekauff HR, Nguyen AH, Negrao CE, Nitzsche EU, Hoh CK, et al. 1997. Impact of acute mental stress on sympathetic nerve activity and regional blood flow advanced heart failure: Implications for 'triggering' adverse cardiac events. *Circulation* 96:1835-42

55. Mittleman MA, Maclure M, Sherwood JB, Mulry RP, Tofler GH, et al. 1995. Triggering of acute myocardial infarction onset by episodes of anger. *Circulation* 92:1720

56. Mondoa C. 2005. Chronic heart failure. *Practice Nurse* 30:50

57. Mosley TH, Payne TJ, Plaud JJ, Johnson CA, Wittrock DA, et al. 1996. Psychometric properties of the weekly stress inventory (WSI): Extension to a patient sample with coronary heart disease. *Journal of Behavioral Medicine* 19:273-87

58. Mostofsky E, Penner EA, Mittleman MA. 2014. Outbursts of anger as a trigger of acute cardiovascular events: a systematic review and meta-analysis. *European heart journal* 35:1404-10

59. Moudgil R, Haddad H. 2013. Depression in heart failure. *Current Opinion in Cardiology* 28:249-58

60. Newman JD, Davidson KW, Shaffer JA, Schwartz JE, Chaplin W, et al. 2011. Observed Hostility and the Risk of Incident Ischemic Heart Disease: A Prospective Population Study From the 1995 Canadian Nova Scotia Health Survey. *Journal of the American College of Cardiology* 58:1222-8

61. Perlman LV, Ferguson S, Bergum KAY, Isenberg EL, Hammarsten JF. 1971. Precipitation of congestive heart failure: Social and emotional factors. *Annals of Internal Medicine* 75:1-7

62. Pocock SJ, Wang D, Pfeffer MA, Yusuf S, McMurray JJV, et al. 2006. Predictors of mortality and morbidity in patients with chronic heart failure. *European Heart Journal* 27:65-75

63. Ramachandruni S, Fillingim RB, McGorray SP, Schmalfuss CM, Cooper GR, et al. 2006. Mental stress provokes ischemia in coronary artery disease subjects without exercise- or adenosine-induced ischemia. *Journal of the American College of Cardiology* 47:987-91

64. Redfield MM, Jacobsen SJ, Burnett JC, Jr., Mahoney DW, Bailey KR, Rodeheffer RJ. 2003. Burden of systolic and diastolic ventricular dysfunction in the community: Appreciating the scope of the heart failure epidemic. *The Journal of the American Medical Association* 289:194-202

65. Smith TW, Smith TW, Frohm KD. 1985. What's so unhealthy about hostility? Construct validity and psychosocial correlates of the Cook and Medley Ho scale. *Health Psychology* 4:503-20

66. Spertus J, Peterson E, Conard MW, Heidenreich PA, Krumholz HM, et al. 2005. Monitoring clinical changes in patients with heart failure: A comparison of methods. *American heart journal* 150:707-15

67. Spielberger CD, Johnson EH, Russell SF, Crane RJ, Jacobs GA, Worden TJ. 1985. The experience and expression of anger: Construction and validation of an anger expression scale. *Anger and hostility in cardiovascular and behavioral disorders*:5-30

68. Steptoe A, Brydon L. 2009. Emotional triggering of cardiac events. *Neuroscience and biobehavioral reviews* 33:63-70

69. Steptoe A, Kivimaki M. 2012. Stress and cardiovascular disease. *Nature Reviews Cardiology* 9:360-70

70. Suls J. 2013. Anger and the Heart: Perspectives on Cardiac Risk, Mechanisms and Interventions. *Progress in Cardiovascular Diseases* 55:538-47

71. Suls J, Bunde J. 2005. Anger, anxiety, and depression as risk factors for cardiovascular disease: The problems and implications of overlapping affective dispositions. *Psychological Bulletin* 131:260-300

72. Tofler G, Hoo SYS, Buckley T, O'Farrell A, Shaw E, et al. 2009. Triggers of Acute Myocardial Infarction: Role of Heavy Physical Exertion, Anger and Respiratory Infection. *Heart, Lung and Circulation* 18, Supplement 3:S127-S8

73. Twisk JWR, Snel J, Kemper HCG, van Mechelen W. 1999. Changes in daily hassles and life events and the relationship with coronary heart disease risk factors: A 2-year longitudinal study in 27-29-year-old males and females. *Journal of Psychosomatic Research* 46:229-40

74. Wexler DJ, Chen J, Smith GL, Radford MJ, Yaari S, et al. 2001. Predictors of costs of caring for elderly patients discharged with heart failure. *American heart journal* 142:350-7

75. Wilbert-Lampen U, Leistner D, Greven S, Pohl T, Sper S, et al. 2008. Cardiovascular Events during World Cup Soccer. *New England Journal of Medicine* 358:475-83

76. Wirtz PH, Redwine LS, Hong S, Rutledge T, Dimsdale JE, et al. 2010. Increases in B-type natriuretic peptide after acute mental stress in heart failure patients are associated with alcohol consumption. *Journal of Studies on Alcohol and Drugs* 71:786-94