ANGER, HOSTILITY, AND RE-HOSPITALIZATIONS IN PATIENTS WITH HEART FAILURE

by

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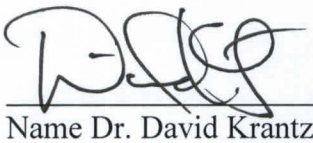

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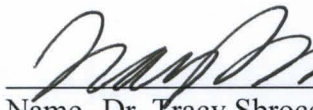

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DEDICATION

To my beautiful wife and our little zoo, without whom my life would be incomplete.

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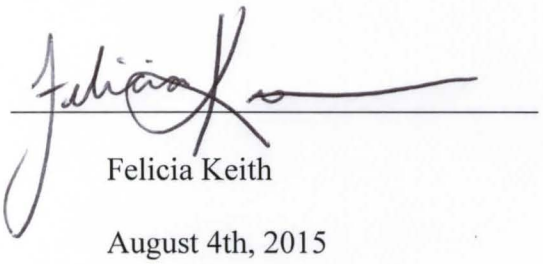

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ABSTRACT

Anger, Hostility, and Re-hospitalizations in Patients with Heart Failure

Felicia Keith, Masters of Science in Clinical Psychology, 2015

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Heart failure is a major health concern in the U.S., with billions of dollars spent annually on health care. The high number of re-hospitalizations significantly contributes to these rising health care costs. Traits of anger and hostility are psychological variables that have been associated with coronary heart disease morbidity and mortality. The present hypothesized that anger and hostility would show predictive utility for heart failure-related and all-cause hospitalizations in patients diagnosed with heart failure. Furthermore, it was hypothesized that depressive symptoms and cytokines will mediate the relationship between anger/hostility and hospitalizations. 150 heart failure patients were recruited from the Heart Failure Clinic at the University of Maryland Hospital in Baltimore, MD, at baseline participants were administered the STAXI, the Cook-Medley Hostility Scale, the Beck Depression Inventory, and cytokines levels were collected. Hospitalization data was then collected for every participant for up to 36-months. Results indicated that only the Cook-Medley Hostility Scale significantly predicted all-cause hospitalizations and not heart failure related hospitalizations. Furthermore, analyses did not support the cytokine hypothesis or a mediating role of depression. However, results revealed that perceived heart failure symptoms were a significant mediator in the relationship between hostility and all-cause hospitalizations. These results indicate that

hostility may predict hospitalizations, not by impacting heart failure directly, but instead by working to shape negative health behaviors that influence health in a global manner.

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CHAPTER 1: INTRODUCTION TO HEART FAILURE

Each year 670,000 Americans are diagnosed with heart failure and one in five cases are fatal (41). This costs over $39.2 billion a year in health care, medications and lost productivity (41). In the Framingham Heart Study conducted by the National Heart, Lung and Blood Institute, the risk of heart failure increases with age and approaches 10 per 1000 individuals after the age of 65 (45). Additionally, the Framingham Study found that at the age of 40 the lifetime risk for developing heart failure for both men and women is 1 in 5, with an increased risk for African American individuals. Mortality for those diagnosed with heart failure is improving, however 80% of men and 70% of women under the age 65 will die within 8 years of diagnosis. Additionally, men have a lower survival rate than women after diagnosis (45).

In light of heart failure's impact on mortality and overall health, this paper will investigate possible additional psychosocial risk factors for heart failure: anger and hostility. First we will review the definition, pathophysiology, development, and measurement of heart failure. Second we will present a look at the history of both anger and hostility as separate constructs and introduce the reader to subtypes of both anger and hostility. Next, we will explore the current state of the literature surrounding anger, hostility, heart failure and cardiovascular disease. Then, we will propose two possible mediating factors of anger, hostility and heart failure: pro-inflammatory cytokines and depression. Finally, we will offer a summary of the presented information and offer our aims and hypotheses.

Definition and Pathophysiology

Heart failure, also known as congestive heart failure (CHF), is an overarching term for a heart's inability to pump enough blood to meet the body's demands (36). Symptoms of heart failure include: shortness of breath, swelling in the feet or ankles, reduced ability to exercise, swelling of the abdomen, fatigue, and irregular or rapid heartbeat (36). This inability to provide sufficient blood to the heart can be cause by multiple underlying conditions, including but not limited to: coronary heart disease, hypertension, valvular disease, chronic pulmonary disease, cardiomyopathy, myocardial infarction, ischemic heart disease and coronary heart disease (42). Although these conditions are some of the underlying causes of heart failure, they do not, in and of themselves, constitute heart failure. Simply put, even if a patient is suffering from one of the aforementioned disease it does not mean they are currently experiencing heart failure.

Development

Research on risk factors for coronary heart disease has been plentiful and includes smoking, high fatty diet, elevated low-density lipoprotein, and elevated blood pressure. Heart failure is a progressive disease that can begin with the development of atherosclerosis, a disease in which cholesterol builds up within the artery walls and causes blood flow to be restricted (28). In addition to atherosclerosis, inflammation, vascular stiffening, endothelial dysfunction, and calcification have all been found to be intermediate markers of heart disease. Following the untreated presence of these markers, individuals will experience nonfatal events such as ischemia or angina, acute myocardial infarction (heart attack), and/or arrhythmia. These can then lead to death. However, research has found that coronary artery disease (one of the main intermediate markers of

heart disease) is more than simply the build up of fat and cholesterol, instead researchers now believe it is an inflammatory disorder (31).

Measurement

Given the severity and rapid progression of heart failure physicians and investigators rely on three major ways of measuring worsening heart failure: biomarkers, events (e.g., hospitalizations), and patient perceived symptoms. A biomarker is a quantifiable substance (such as enzymes, hormones, and biologic substances) within an organism that indicates a particular event such as an environmental exposure, disease or infection. Physicians have determined that a biomarker must met the following three criteria in order to deemed useful in the detection and treatment of heart failure: repeated, accurate and cost effective measurements of the biomarker must be available with a quick turnaround time, the biomarker must provide additional clinical information that is otherwise unavailable following a careful clinical assessment and the measured level should aid in medical decision making (39). In a review of the literature Braunwald (8) proposes that the identified biomarkers that meet (at least partially) the aforementioned criteria be broken into seven categories: inflammatory, oxidative stress, extracellular-matrix remodeling, neurohormones, myocyte injury, myocyte stress, and new biomarkers. This paper will focus primarily inflammatory biomarkers, which include C-reactive protein, tumor necrosis factor $\propto$, Fas (APO-1), and Interleukins 1, 6, and 18 (8).

One of the most basic measurements of heart failure progression is re-hospitalization. Logically it would follow that as an individual's heart failure worsened the more often they would need to be re-admitted. Individuals with heart failure seem to be particularly vulnerable to hospital readmission as Krumholz et al (29) found that out of

7596 heart failure patients on Medicare, 44% were readmitted to the hospital at least once. Furthermore, the amount of heart failure re-hospitalizations is on the rise, with an annual increase of 1.20% of men and 1.55% of women between 1980 and 2006, this is compared to coronary heart disease and cerebrovascular disease which have both decreased within this time period (32). Taking into consideration that heart failure patients are vulnerable to re-hospitalization, account for a growing number of readmissions and make a substantial economic impact with increasing admissions (34), re-hospitalization is a crucial outcome variable to not only capture the worsening of heart failure, but also to examine what variables may contribute or predict future hospitalizations.

More qualitative measures of heart failure includes assessments of quality of life (QoL) as heart failure is a chronic condition with no known "cure" and has an enormous impact on the life style of patients. Green et al (25) found that those with congestive heart failure who remained stable over a three month period only had minimal changes in their Kansas City Cardiomyopathy Questionnaire (KCCQ, a measure that assesses symptoms, physical symptoms, social interference, self-efficacy, and quality of life), while those with large changes in their KCCQ score showed improvement in their decompensated heart failure. This indicates that symptom measures such as the KCCQ can be used to detect and measure changes in heart failure.

CHAPTER TWO: Anger and Hostility as a Psychological Construct

TYPE-A PERSONALITY PATTERN.

Dissatisfied with the traditional risk factors of cardiovascular disease and their inability to predict coronary heart disease in younger individuals, Friedman and Roseman (23) formulated what is now know as Type-A personality pattern. An individual, who has a Type-A personality pattern, aggressively pursues doing more and more with less time. This struggle manifests in ways such as: egoism, impatience, multi-tasking, need for external rewards, competitiveness, hostility, anger and aggressiveness (35). Researchers have found the Type-A personality pattern to be an individual predictor of coronary heart disease (14; 16). However Matthews (35) makes the case that both reviews, and most research done on Type-A, is flawed due to the lack of comprehensive conceptualization. Additionally, a recent meta-analysis (40) that showed no association between Type-A and coronary heart disease. The incomplete conceptualization and lack of relationship between Type-A and coronary heart disease, led researchers to investigate individual components of Type-A including anger and hostility.

Cook-Medley Hostility Scale.

The Cook-Medley hostility scale was originally developed to measure rapport among teachers and students (13). However, Williams et al (60) found that hostility was a stronger predictor of atherosclerosis than Type-A. This finding sparked additional research in the role of hostility in coronary artery disease. This additional research included breaking down the Cook-Medley hostility scale into subcomponents including: cynicism, hostile attributions, hostile affect, aggressive responding, social avoidance, and other (4). Following the development and exploration of hostility and its subcomponents,

researchers then turned their attention to the individual role of anger in coronary heart disease. However, research on anger and its subcomponents is lacking.

Sub-components of anger and hostility.

Anger, hostility and aggression are three separate constructs that research often intertwines as one. Anger is an emotional state that varies in severity anywhere from minor annoyance to rage (53). In contrast, hostility is usually tied to a complex set of attitudes that inform and propel aggressive behaviors toward unwanted or undesirable objects or people, while aggression is the act of violence or destructive/punitive behavior that is directed toward the source of displeasure (53). Within the construct of anger lies several sub-constructs that comprise the State-Trait Anger Expression Inventory (STAXI), one sub-construct is "anger-expression out" and "anger-expression in." According to Spielberger et al (54) "anger-expression out" typifies an individual that express their anger towards their environment, while "anger-expression in" is representative of an individual that turns their anger inwards towards their sense of self which may result in depression and/or feelings of guilt. State anger and trait anger are two additional sub-constructs; state anger measures the anger an individual feels during a particular incident, while trait anger measures dispositional differences towards anger (20). Finally, the STAXI also captures "anger control-in" and "anger control-out"; an individual high in "anger control-in" will spend a great amount of time and energy calming down and focusing on reducing their anger as soon as possible, while an individual high in "anger control-out" will concentrate on preventing their outward expression of anger (56).

The most recent meta-analysis on anger, hostility and coronary heart disease was conducted by Chida and Steptoe (11). They established the following inclusion criteria: published in a peer reviewed English language journal, and a longitudinal prospective examination of the association of anger, hostility and the development or prognosis of CHD. If studies included overlapping cohorts, the studies with smaller sample sizes, shorter follow-ups and poorer study quality were excluded. Additionally, articles looking at acute anger episodes as CHD triggers were excluded. Finally, if women and men were examined separately within one study, the studies were included as separate studies. Overall, 25 studies were selected resulting in 21 initially healthy cohorts and 18 diseased cohorts with participants from all over the world, the studies dated from 1983 to 2006. The meta-analysis contained 71,606 healthy participants and 8,120 participants that were already diagnosed with CHD.

Findings of the study revealed that combined hazard ratios (HR) for the healthy population studies were 1.19 (95% CI: 1.05 to 1.35, $p = .008$) and 1.23 (95% CI: 1.08 to 1.42, $p = .002$) for the populations that were previously diagnosed with CHD. These HRs indicate that there is a positive association between hostility and anger and CHD. Authors noted that studies with longer follow-up periods exhibited higher HRs in both the healthy and diseased populations. However, researchers also found that when studies fully controlled for behavioral covariates, such as smoking, body mass index, physical activity and socioeconomic status, the negative effect of anger and hostility on CHD was no longer significant. Authors contend that other unmeasured factors may have confounded these associations. Overall, this meta-analysis illustrated that anger and hostility are both significantly associated with CHD in both healthy populations and already unhealthy

populations with CHD. The effects of hostility and anger were slightly greater in patients with CHD than healthy populations, indicating that anger and hostility may play a role in accelerating the effects of CHD.

To our knowledge only one study has investigated the effect of anger on adverse outcomes in patients currently experiencing heart failure. In a study by Jenner et al (26) researchers found that anger (as measured by the State-Trait Anger Expression Inventory, STAXI) significantly predicted length of stay in the hospital but not readmissions. Due to the lack of literature looking specifically at patients with heart failure, more research is warranted to continue to work to understand the role that anger and hostility play in heart failure.

CHAPTER 3: Possible Mediating Factors between Anger and Heart Failure

DEPRESSION

Research has shown that the constructs of anger and depression overlap significantly (59) so it is important to understand the extent of the relationship and overlap that anger and depression share. Baeg et al (3) found individuals who report severe depression symptoms also report higher anger experience and anger expression. While this study showed that anger and depressive symptoms are positively correlated, Stewart et al (57) found that both hostility and anger may precede and subsequently predict depressive symptoms. Taking these findings into consideration, it is important to understand the extent to which anger and depression co-exist within a heart failure patient. A better understanding of this relationship will provide health care professionals an insight into heart failure patients that present with depressive symptoms, and connect them with the appropriate anger management and therapy.

Research has found a strong link between depression and cardiovascular disease. Frasure-Smith et al (22) found that depression was an independent risk factor for coronary artery disease, similar to smoking, cholesterol, and hypertension. In a review of the literature, Dimos et al (18) note that the relationship between heart failure and depression is multifaceted. Specifically heart failure can lead to the development of depression and some pathophysiological mechanisms underlie both (i.e., similar genetic predisposition, increased levels of cytokines and disturbances in platelet function). Additionally, the literature indicates that the psychosocial factors that impact heart failure such as stress, medication non-compliance, non-adherence to strict diet guidelines, and lack of exercise, also exacerbate depression. In their meta-analysis, which included 36

studies of patients with heart failure and depression, Rutledge et al (46) found that those patients with clinical levels of depression were at twice the risk for any adverse cardiac event and cardiac death. Furthermore, those with clinical levels of depression had higher rates of hospitalization and ER visits than those without depression. Additionally, Gottlieb et al (24) found that 48% of heart failure patients also suffered from depression, depressed patients were more likely to be younger, women were more likely to be depressed than men, and depressed patients had worse quality of life than those patients who are not depressed. Overall, depression and heart failure seem explicitly linked, and due to the overlap of anger and depression it is imperative that we understand the role of anger in heart failure.

Cytokine Hypothesis

The cytokine hypothesis posits that the mechanism behind the progressive nature of heart failure is the cascade of cytokines that are activated following a myocardial injury (49). In other words, cytokines (IL-10, IL-6, TNF-alpha) are activated when an individual experiences an adverse myocardial event, such as a rupture of an unstable plaque. The biologic properties of cytokines are then sufficient to contribute to the progression of heart failure through inciting premature cell death and progressive myocardial fibrosis (50). The hypothesis holds that cytokines may not be the cause of heart failure but rather they are responsible for the progression of the disease (50). However it is unclear whether cytokines are responsible for the progression or merely the markers of the progression. There are two major classes of cytokines that have been recognized to be present during the progression of heart failure: vasoconstrictor cytokines and vasodepressor or pro-inflammatory cytokines.

Along this line of research, Askevold et al (1) found that when IL-6 is elevated it is associated with cardiovascular mortality and death from deteriorating heart failure. In a review of the literature, Braunwald (8) proposes seven categories of biomarkers that play a role in heart failure: inflammatory (i.e., c-reactive protein, tumor necrosis factor α, interleukins 1, 6, and 18), oxidative stress (i.e., oxidized low-density lipoproteins), extracellular-matrix remodeling (i.e., collagen propeptides), neurohormones (i.e., renin, aldosterone), myocyte injury (i.e., myosin light-chain kinase), myocyte stress (i.e., brain natriuretic peptide), and new biomarkers (i.e., chromogranin). Currently, research has established a positive association between anger/hostility and inflammatory markers such as interleukin (IL)-6 (10; 38) and tumor necrosis factor-alpha (TNF-alpha) (38; 58). Alternations in TNF-alpha has been found to be associated with increased CHD risk in adolescents (9). One potential mechanism of action, as proposed by the literature, is that negative affect increases pro-inflammatory cytokines by activating the autonomic nervous system causing vascular wall stress. While under stress, vascular walls will activate the cytokine cascade (10). Overall, research has indicated that cytokines maybe involved in heart failure and may be related to anger in some way; this study will provide an opportunity to thoroughly investigate the veracity of the cytokine hypothesis.

Causes of Re-hospitalizations

As aforementioned, the cost of treating heart failure patients on the national level consumes billions of dollars yearly. One part of rising costs of heart failure is the high-rate of hospital re-admissions. In a recent study by Dharmarajan et al (17), researchers examined the amount and causes of 30-day readmission in a sample of heart failure patients. They found that 24.8% of the original 1,330,157 hospitalized individuals were readmitted after 30 days. Researchers collected these hospitalizations by examining Medicare fee-for-service claims submitted from 2007-2009. They found that heart failure patients had multiple reasons for re-admissions, other than heart failure re-admissions. Other reasons for hospitalizations included: renal disorders, pneumonia, arrhythmias, septic shock, cardiorespiratory failure, chronic obstructive pulmonary disease, chronic angina and coronary artery disease, acute myocardial infarction, and complications of care. Taking this literature into consideration, this study will examine all-cause re-hospitalizations, in addition to heart failure related re-hospitalizations, as outcome variables.

CHAPTER 4: Summary and Rationale

Heart failure costs the United States health care systems billions of dollars each year in medication costs and lost productivity, and it is estimated that 1 in 5 individuals over the age of 40 are at risk of developing heart failure during their lifetime. As such, it has become increasingly important to better understand the mechanisms and risk factors that lead to heart failure. We have presented data to suggest that anger and hostility are risk factors for cardiovascular disease and individuals with heart failure, not only have a high re-admission rate, but also have multiple reasons for readmission. However, the connection of anger, hostility and their subcomponents to individuals with heart failure and their hospital readmissions is poorly understood. Therefore the purpose of this study is to examine the predictive ability of anger, hostility, and their subcomponents in negative outcomes (i.e., re-hospitalization, functional status and perceived symptoms) of individuals with heart failure. This study will also examine possible mediating factors, which include pro-inflammatory cytokines and depression, in this relationship.

SPECIFIC AIM 1:

The first aim of this study is to examine the relationships of anger, hostility and their subcomponents to outcome variables. Outcomes assessed consist of heart failure related hospitalizations, all-cause hospitalizations, and death. Anger and hostility were measured with the Spielberger State Trait Anger Expression Inventory and the Cook-Medley Hostility Scale.

Hypothesis 1a: We hypothesize that higher anger scores, most notably trait anger, anger expression out, anger expression in, and anger control out will be predictive of higher all-cause and heart failure related hospitalizations.

Hypothesis 1b: We hypothesize that higher anger control in scores will not be predictive of all-cause and heart failure related hospitalizations.

Hypothesis 1c: We hypothesize that higher hostility scores, most notably hostile affect, and cynicism, will be predictive of higher all-cause and heart failure related hospitalizations.

SPECIFIC AIM 2:

The second aim of this study is to explore the extent to which any relationships, between anger, hostility, the subcomponents and hospitalizations, are mediated by depression, while controlling for number of months in the study, gender, household income, baseline creatinine levels, baseline ejection fraction, history of smoking, and age.

Hypothesis 2a: We hypothesize that all relationships between anger/hostility and hospitalizations observed in this study will be mediated by depression, while controlling for our covariates.

SPECIFIC AIM 3:

The third aim of this study is to determine to which any relationships, between anger, hostility, the subcomponents and hospitalizations, are mediated by cytokines, while controlling for number of months in the study, gender, household income, baseline creatinine levels, baseline ejection fraction, history of smoking, and age.

Hypothesis 3a: We hypothesize that relationships between anger/hostility and hospitalizations observed in this study will be mediated by the presence of cytokines, while controlling for our covariates.

CHAPTER 5: Methods

This study is a part of a larger project (the BETRHEART study). Therefore the present methods section was adapted from the BETRHEART study protocol. This study employed a longitudinal analysis of the predictive value of anger and hostility measures for subsequent heart failure and all-cause hospitalizations.

STUDY PARTICIPANTS

150 study participants were recruited in the Heart Failure Clinic at the University of Maryland Hospital in Baltimore, MD. Patients were eligible to participate in the study if they were currently diagnosed with heart failure (left ventricular ejection fraction of less than or equal to 40% and functional status of II-IV for at least three months), in stable condition, and older than 21 (as most individuals with heart failure are adults). Patients were excluded if they met any of the following criteria: 1) documented myocarditis, 2) clinically significant mitral valve disease, 3) thyroid dysfunction 4) current alcohol abuse or abuse within the last six months, 5) implanted left ventricular assist device, 6) prior heart transplantation, 7) active cancer treatment, 8) living in a nursing home, 9) cognitive impairments interfering with consent and understanding of study materials. Study participants were included in the present analysis if they completed the basic demographic information packet at baseline and pertinent psychosocial variables at baseline and 3 months.

MEASUREMENTS

Hospitalizations

Hospitalizations were recorded during the 3-month study period and at six-month follow-up interviews during 36-month follow-up period. Once hospitalizations were collected they were coded as either heart failure related re-hospitalization or all-cause hospitalization. Heart failure hospitalizations were hospitalizations with a primary diagnosis of a heart failure exacerbation, characterized by pump failure or fluid overload. All-cause hospitalizations were any additional hospitalizations that were not directly tied to heart failure exacerbation (e.g., car accident, back pain). Dates of death were also collected and verified with hospitalization records or next of kin. Death (yes/no) was combined with all-cause hospitalization (yes/no) to create the composite death or hospitalization variable.

Due to study resources and nature of the longitudinal study, at the time of the preparation of this manuscript, only a portion of the hospitalizations will have been verified with the appropriate medical providers, therefore we will have hospitalization data two ways: verified and total. For verified hospitalizations study participants reported hospitalizations and proof of hospitalization was subsequently collected from the attending hospital. Total hospitalizations include both the hospitalizations that have been verified with the medical provider and self-reported hospitalizations that have not been verified.

Overall there are four linear hospitalization variables: verified all-cause hospitalizations, total all-cause hospitalizations, verified heart failure hospitalizations, and total heart failure hospitalizations. There are six dichotomous (yes/no) hospitalization variables: yes/no verified all-cause hospitalizations, yes/no total all-cause hospitalizations, yes/no verified heart failure hospitalizations, yes/no total heart failure

hospitalizations, yes/no verified death or hospitalization, and yes/no total death or hospitalization.

Kansas City Cardiomyopathy Questionnaire (KCCQ)

The KCCQ is a 23-item self-report measure that is designed to capture the perceived symptoms of heart failure and overall functional status (25). Green et al (25) found that the KCCQ's clinical summary score (which ranges from 0 to 100, with a higher score indicating fewer heart failure symptoms) demonstrated a Cronbach's alpha of .95. The KCCQ includes questions such as: "Compared to two weeks ago my heart failure symptoms have become…" and "how much has your heart failure symptoms limited your ability to dress yourself?" Overall, the KCCQ has been found to have high internal consistency (Cronbach's alpha of .92) and has demonstrated criterion validity (15). The total score of the KCCQ includes subscales such as: physical limitations, symptoms (including frequency, severity and change over time), self-efficacy/knowledge, social interference, and quality of life. The KCCQ symptoms subscale was used as a covariate in exploratory analyses.

Psychosocial Variables

State Trait Anger Expression Inventory (STAXI)

The STAX-II has been found to be both reliable and valid (2; 55) and consists of 44 items that are coded on a 4-point Likert scale (for the trait-anger subscale responses are coded as "almost never", "sometimes", "often", and "almost always", state-anger subscale responses are coded as "not at all", "somewhat", "moderately so" and "very much so"). Questions that assess state-anger include prompts such as: "I am furious" and

"I feel irritated". When assessing for trait-anger participants are asked questions such as: "I am quick tempered" and "I have a fiery temper".

Cook-Medley Hostility Scale.

The Cook-Medley hostility scale is composed of six subscales: cynical hostility, hostile attributions, hostile affect, social avoidance, aggressive responding and other (4). Questions included in the subset measuring cynical hostility include: "I have often had to take orders from someone who did not know as much as I did", measuring hostile attribution: "someone has it in for me", measuring hostile affect "some of my family have habits that bother me and annoy me very much", measuring aggressive responding: "I don't blame anyone for trying to grab everything he can get in this world", measuring social avoidance: "I am likely not to speak to people until they speak to me", and measuring other: "I am against giving money to beggars". Each question is answered as a dichotomous true or false. The measure has shown to have both convergent and discriminant validity and reliability (51).

Beck Depression Inventory-II (BDI)

The Beck Depression Inventory-II (7) contains 21 items, each listing a symptom of depression and four statements increasing in depression severity. Higher scores indicate more severe depression symptomology, mild depression scores are in the 14-19 range, moderate depression is captured with a 20-28, and severe is 29 and above (7). Beck et al (6) found that the BDI-II had an alpha of .91 in a sample of 140 psychiatric outpatients. It has been found to be one of the most commonly used instruments in research and practice to measure the severity and presence of depression and has been

extensively validated (44). The questionnaire was administered during baseline and each subsequent follow-up visits over the 36-month follow-up period.

Immune and Inflammatory Biomarkers

Blood samples were collected at the initial baseline visit and at the three-month follow-up. The samples were collected using vacuum tubes (EDTA 4.5 mmol/l), then mixed gently for 30 seconds and set to rest at room temperature for 45 minutes. Plasma was separated using a temperature-controlled centrifugation at 3000 g for 15 minutes. Samples of the plasma and the blood serum were stored at -80° C until after the completion of the 3-month visit. Standard measurement procedure for C-reactive protein (CRP) was obtained from similar studies (37). Assays that measures CRP levels were conducted in the laboratory of Robert H. Christension, Ph.D., at the University of Maryland Medical center by an experienced technician.

Tumor Necrotic Factor-alpha (TNF-α) , Interleukin 6 (IL-6), and Interleukin 10 (IL-10) were measured using the blood samples by Singulex® using their Erenna® Immunoassay system. Detailed information regarding Singulex's® Erenna® Immunoassay system and specific procedures regarding the measurement of the IL-6, IL-10, and TNF-α can be downloaded from the Singulex website (http://www.singulex.com/assays.html).

Covariates

Covariates were chosen based on the literature for their relationship with at least one of the outcome variables (e.g., age, gender, household income, creatinine levels, ejection fraction, number of months in the study, history of smoking). Age was chosen as

a covariate because according to the National Hospital Discharge Survey (NHDS), capturing years 1979 to 2004, approximately 80% of individuals who were hospitalized due to heart failure were ≥65. Additionally, the NHDS reported that men had a higher hospitalization rate than women in all age groups, justifying gender as a covariate (19). Household income was included because it was found to be an independent risk factor for heart failure related re-hospitalizations (43). Renal functioning, as measured by creatinine levels was also included as a covariate, because was also found to be associated with significantly worse outcomes and increased hospitalizations in individuals with heart failure (21). Number of months in the study was controlled due to the on-going nature of the study, as some participants will have more hospitalizations due to the amount of follow-up that has been completed. Left ventricular function, as measured by ventricular ejection fraction, was found to be a strong predictor of cardiovascular outcomes in patients with heart failure, therefore it was also included as a covariate (52). Finally, history of smoking was included as a covariate, because smoking has been found to be a risk factor for developing heart failure and re-hospitalizations (27).

PROCEDURES

Once a physician identified a possible participant the research team approached them about study participation. Once informed consent was obtained, the participant was screened for all exclusion and inclusion criteria by one of the studies' primary investigators. As soon as eligibility criteria was confirmed and informed consent collected, the participants completed a packet of questionnaires including the measures of anger, hostility, and depression. Research staff also obtained a sample of blood and current height, weight and blood pressure. The patient's contact information was then

obtained and a follow-up interview (via phone) was scheduled. Follow-up interviews were collected every six months for 36 months following baseline and the 3-month study period.

Data Analysis

In order to best explore our aims zero order correlations will first be run to determine the relation, if any, which exists between variables. Our next set of analyses will be whole model hierarchical regressions (both linear and logistic) that will include our covariates (e.g., number of months in the study, gender, household income, baseline creatinine levels, baseline ejection fraction, history of smoking, and age) in the first model, and all of the anger and hostility measures in the second model, to determine predictive utility of anger and hostility for hospitalizations. Our second set of linear and logistic hierarchal regressions will include individual measures of anger and hostility in order to gain clarity of the role of each anger/hostility dimension. Finally, depression, and cytokine measures will be entered as a separate step in order to determine if they mediate the relationship between anger/hostility and hospitalizations (5).

Power

Power was determined using G*Power 3.1 and based on the small effect size established in Jenner et al (26). Jenner et al (26) found that anger, depression, anxiety, New York Heart Association level of symptom severity, and left ventricular ejection fraction accounted for R^2=.04, equating to a small Cohen's f^2 (12). Using this small effect size, linear regressions, 8 predictors/covariates, an *apriori* designation of alpha set at .05, power = 0.8, a total of sample of 156 participants were needed to adequately power the present study.

CHAPTER 5: Results

SAMPLE CHARACTERISTICS

A sample of 150 participants was initially recruited to take part in the study at the University of Maryland Medical Center and Baltimore VA heart failure clinic. Of the 150 recruited, 146 individuals completed the packet of baseline demographic information. The study was comprised of mostly men (n= 113, 76.9%) and African Americans (n=103, 70.1%). There were 43 individuals who identified as Caucasian (29.3%) and 1 individual that identified as American Indian/Alaskan Native (0.7%). The mean age was 56.82 years old (SD=11.43 years), and ranged from 23- 87 years. The sample was largely of low socioeconomic status. About one third of the participants lived on less than $15,000 a year ($n$ =51, 34.9%), 39 individuals made between $15-30,000 a year (26.7%), 43 individuals lived on $30-70,000 a year (29.5%) and 13 individuals lived on more than $70,000 a year (8.9). See Table 1 for additional sample characteristics and Table 2 for means and standard deviations for key variables.

Table 3 depicts the number of verified and total hospitalizations. Overall, of the 212 all-cause hospitalizations that were reported, 200 were verified, and of the 105 heart failure related hospitalizations that were reported 94 were verified. Additionally, of the reported hospitalizations or death (87), 80 were verified. All-cause hospitalization, as aforementioned, included heart failure related hospitalizations, cardiac related hospitalizations that are unrelated to heart failure (e.g., myocardial infarction), and other cause hospitalizations. Cardiac related hospitalizations only include hospitalizations that are related to cardiac difficulties that are distinct from heart failure complications. The other hospitalizations include: accidents (n = 2), chronic disease (n = 16), illness (n = 17), injury (n = 5), and other (n = 27). The accidents included car accidents, the chronic

diseases ranged anywhere from diabetes to chronic obstructive pulmonary disease, illnesses included anything from flu to diarrhea, injury included mostly kidney injuries (i.e., problem with kidney function), and other was comprised of a variety of different causes from back surgery, to a hip/knee replacement.

Table 1.

Sample Characteristics

		Full Sample N=146
Gender	Male	113 (75.3%)
Age		56.82 ±11.43 (SD)
Race		
	African American	103 (70.5%)
	Caucasian	42 (28.8%)
	Other	(.7%)
Household Income		
	<$15,000	51 (35.2%)
	$15-30,000	39 (26.9%)
	$30-70,000	43 (29.7%)
	>$70,000	12 (8.3%)
Baseline Creatinine		1.38 ± .71 (SD)
Ejection fraction		23.14 ± 7.48 (SD)
History of Smoking		103 (70.5%)
Months in Study		10.3 ± 9.23 (SD)

Table 2.

Means and Standard Deviations of Key Variables

	Mean (SD)	Minimum	Maximum
KCCQTS Total Symptom Score– 3 month	72.67 (23.57)	11.46	100.00
CRP 3 Month	6.39 (6.84)	0.33	39.1
IL-6 3 month (pg/ml)	5.36 (5.55)	1.12	26.73
IL-10 3 Month (pg/ml)	1.93 (2.86)	0.54	30.66
TNF-α 3 month (pg/ml)	5.48 (3.04)	0	15.83
BNP (ng/ml)	459.65(823.58)	4	6960
Beck Depression Inventory Total Score – baseline	12.47(10.10)	0	47.00
KCCQ Total Symptom Score – baseline	72.67(23.57)	11.46	100.00
Number of Patients Deceased	21 (14.38%)		

Table 3 shows a breakdown of patients with different numbers of hospitalizations. 77 participants had zero verified all-cause hospitalizations within the follow-up window, 25 had one all-cause hospitalizations, 10 had two all-cause hospitalizations, 11 had three all-cause hospitalizations, 13 had four all-cause hospitalizations, and 14 had five or more hospitalizations. Overall, there was a small difference between total verified (200) and total verified and unverified (212) all cause hospitalizations. 110 participants had zero verified heart related hospitalizations, 14 participants had one heart failure related hospitalization, 7 had two heart failure related hospitalizations, 14 participants had three heart failure related hospitalizations, 1 participant had four hospitalizations, and 4 participants had five or more heart failure hospitalizations. Similar to all-cause hospitalizations, there was a small difference between total verified heart failure related hospitalizations (94) and total verified and unverified heart failure related hospitalizations (105).

Table 3.
Breakdown of Number of Hospitalizations per Patient

	N (%)
All-cause	
Verified	0 hospitalizations = 77(51.3) 1 hospitalization = 25 (16.7) 2 hospitalizations = 10 (6.7) 3 hospitalizations = 11 (7.3) 4 hospitalizations = 13 (8.7) 5 or more hospitalizations = 14 (9.3) Total hospitalizations (verified) = 200
Total	0 hospitalizations = 75 (50.0) 1 hospitalizations = 26 (17.3) 2 hospitalizations = 10 (6.7) 3 hospitalizations = 10 (6.7) 4 hospitalizations = 9 (6.0) 5 or more hospitalizations = 20 (13.3) Total hospitalizations (verified and unverified)= 212
Yes/No- Verified	Yes = 72 (48.0)
Yes/No- Total	Yes = 75 (50.0)
Heart Failure Related	
Verified	0 hospitalizations = 110 (73.3) 1 hospitalization = 14 (9.3) 2 hospitalizations = 7 (4.7) 3 hospitalizations = 14 (9.3) 4 hospitalizations = 1 (.7) 5 or more hospitalizations = 4 (2.7) Total hospitalizations (verified) = 94
Total	0 hospitalizations = 107 (71.3) 1 hospitalization = 14 (9.3) 2 hospitalizations =10 (6.7) 3 hospitalizations = 11(7.3) 4 hospitalizations = 2 (1.3) 5 or more hospitalizations = 6 (4.0) Total hospitalizations (verified and unverified) = 105
Yes/No- Verified	Yes = 40 (26.7)
Yes/No- Total	Yes = 43 (14.6)
Hosp or Death	
Verified	Yes = 81 (54.0)
Total	Yes = 87 (58.0)

Table 4.
Zero-order Correlation Matrix with Anger, Hostility, and Perceived Symptoms

	State Anger	Trait Ang	Anger Exp Out	Anger Exp In	Anger Con Out	Anger Con In	Cyn	Host	Hostile Affect	KCCCQ TS	BDI-II
State Anger	--	.47***	.38***	.37***	-.11	.01	-.10	.09	.04	.00	.05
Trait Anger	--	--	.80***	.56***	-.37***	-.22**	-.03	.05	-.12	-.05	-.02
Anger Expression Out	--	--	--	.42***	-.28***	-.11	-.01	.06	-.11	.00	-.07
Anger Expression In	--	--	--	--	-.10	.02	.01	.07	-.08	.06	-.02
Anger Control Out	--	--	--	--	--	.81***	-.08	-.09	.00	.03	-.02
Anger Control In	--	--	--	--	--	--	-.02	-.01	-.08	.05	-.09
Cynicism	--	--	--	--	--	--	--	.95***	.45***	-.21*	.31***
Hostility	--	--	--	--	--	--	--	--	.68***	-.30**	.49***
Hostile Affect	--	--	--	--	--	--	--	--	--	-.38***	.51***

Note: * denotes $p \leq .05$, ** is $p \leq .01$, *** is $p \leq .001$

AIM ONE

The zero order correlations between anger variables and heart failure outcomes are presented in Table 4 and Table 5. The zero order correlations were run in order to establish a relationship, if one exists, between anger and adverse heart failure outcomes. Overall, we found that there was no significant relationship between anger variables and the following outcome variables: heart failure related hospitalizations (both verified and self-report), all-cause hospitalizations (both verified and self-report), and death (see Table 4). Hospitalizations were then dichotomized into a yes/no variable (for all-cause and heart failure related and verified and self-report). Additionally, a composite variable of death and hospitalization was also created. The zero-order correlations between anger/hostility variables, hospitalizations, and death are presented in Table 5 and 6. The correlations revealed that only Anger Expression Out significantly correlated with Yes/No self-report all-cause hospitalizations ($r = .16$, $p = .05$, see Table 6).

Table 5.
Zero-order Correlations between Anger, Hostility and Number of Hospitalizations (All Cause and Heart Failure), and Death

	All-Cause Verified *r*	**HF-Verified** *r*	**All-Cause Total** *r*	**HF-Total** *r*	**Death** *r*
State Anger	.14	-.05	.14	.04	-.06
Trait Anger	.14	.02	.13	.04	-.06
Anger Expression Out	.16	-.02	.15	-.01	-.07
Anger Expression In	.15	.08	.14	.10	.02
Anger Control In	.10	.09	.10	.12	-.06
Anger Control Out	.03	.09	.04	.13	-.06
Cynicism	.13	.07	.11	.06	.11
Hostile Affect	.15	.12	.14	.11	.10
Hostility	.11	.13	.10	.10	.02

Note: * denotes $p \leq .05$

Table 6.
Zero-order Correlations between Anger and Hostility and Yes/No Hospitalizations, and Death/Hospitalization Composite

	Y/N All Cause-Verified *r*	**Y/N Heart Failure-Verified** *r*	**Y/N All Cause- Total** *r*	**Y/N Heart Failure-Total** *r*	**Death and/or Hosp-Verified** *r*	**Death and/or Hosp- Total** *r*
State Anger	.11	-.01	.10	.10	.07	.11
Trait Anger	.12	.01	.14	.05	.07	.09
Anger Expression In	.12	.05	.13	.07	.08	.08
Anger Expression Out	.15	.04	.16*	.05	.09	.10
Anger Control In	.11	.11	.12	.15	.07	.04
Anger Control Out	-.02	.10	.00	.14	-.03	-.09
Cynicism	.14	.09	.13	.06	.09	.10
Hostility	.06	.10	.05	.05	.00	.02
Hostile Affect	.03	.09	.01	.08	-.01	-.01

Note: * denotes $p \leq .05$

To further explore our first aim, we ran multivariate regressions between anger and hospitalizations (see Table 7 for all-cause and Table 8 for heart failure). First, we ran a linear regression with two steps, the first step includes all covariates (age, gender, history of smoking, household income, baseline creatinine levels, baseline ejection fraction, and number of months in the study) and revealed that as a whole these covariates predicted verified all cause hospitalizations (R^2 = .18, F(8, 120) = 2.99, p=.005), total all cause hospitalizations (R^2 = .19, F(8, 120) = 3.26, p=.002), but not verified heart failure hospitalizations (R^2 = .12, F(8, 120) = 1.96, p=.058), or total heart failure hospitalizations (R^2 = .12, F(8, 120) = 1.84, p=.08). The second step includes all relevant anger and hostility variables (state anger, trait anger, anger expression out, anger expression in, anger control in, anger control out, hostility, hostile affect, and cynicism), this step revealed that taken together, anger and hostility predicts verified all-cause hospitalizations (R^2 = .26, R^2 Δ= .09, F(17, 120) = 2.14, p = .010), total all-cause hospitalizations (R^2 = .27, R^2 Δ= .10, F(17, 120) = 2.19, p = .008), but not verified heart failure hospitalizations (R^2 = .12, R^2 Δ= .10, F(17, 120) = 1.60, p = .08), or total heart failure hospitalizations (R^2 = .20, R^2 Δ= .10, F(17, 120) = 2.91, p = .10). Multicollinearity was examined and found to be at an acceptable level (VIF <10).

Logistic regressions (see Table 9) revealed that the covariates significantly predicted yes/no total all-cause hospitalizations (Cox and Snell R^2= .14, χ^2(8)= 18.66, p = .02), but not yes/no all-cause hospitalizations (see Table 8), yes/no heart failure hospitalizations (both verified and total, see Table 9), and yes/no death and/or hospitalization (both verified and total, see Table 10).

Next we ran additional logistic and linear regressions to determine the individual role of each anger and hostility dimension because the high inter-correlations among scales seen in Table 4. Linear regression analyses found that hostility significantly predicted both verified (R^2 Δ =.03, F Δ(1,117) = 4.19, B=.04, CI 95% =.001-.081, p=.04) and total (R^2 Δ = .03, F Δ(1,117) = 4.03, B= .04, CI 95% =.001-.081, p=.05) all-cause hospitalizations (see Table 12), relative to step one that controlling for covariates. Additionally, analyses found that hostile affect significantly predicted both verified (R^2 Δ =.04, F Δ(1,116) = 5.76, p=.02, B=.28, CI 95% =.05-.51, p=.02) and total all-cause hospitalizations (R^2 Δ = .04, F Δ(1,116) = 5.51, p=.02, B= .28, CI 95% =.04-.52, p=.02) (see Table 12), relative to step one that controlled for covariates. Linear regressions also found that Hostile Affect significantly predicted verified heart failure related hospitalizations (R^2 Δ =.03, F Δ(1,116) = 3.93, p<.05, B=.17, CI 95% =.00-.35, p<.05), and there was a trend (p=.06) for total hospitalizations (R^2 Δ =.03, F Δ(1,116) = 3.52, p=.06, B=.18, CI 95% = -.01-.36, p=.06) (see Table 13). Additionally, logistic regressions revealed that entering Cynicism into the model significantly improved model fit ($\chi^2(1)$=3.79, p= .05, Cox & Snell R^2= .14, see Table 14), but it was not significant when considered alone.

Regressions analyses found that no individual anger or hostility measures were able to significantly predict: verified yes/no heart failure hospitalizations, total yes/no heart failure hospitalizations, verified hospitalizations and/or death, and total hospitalizations and death.

Table 7.
Linear Regressions Predicting All-Cause Hospitalizations

	Verified All-Cause Hospitalizations[3]				Total All-Cause Hospitalizations[3]			
	R^2	F	*B*	CI (95%)	R^2	F	*B*	CI (95%)
Step One[1]	.18	2.99**			.19	3.26**		
Number of Months in Study			.36**	.20-.51			.39**	.23-.56
Gender			-.60	-1.35-.15			-.70	-1.5-.08
Race			.19	.56- -.46			.27	-.41-.95
Age			.00	-.03-.81			.00	-.03-.03
Income			.13	-.19-.45			.12	-.21-.46
History of Smoking			-.21	-.93-.51			-.17	-.92-.57
EF			.01	-.03-.05			.01	-.03-.06
Creatinine			.30	-.16-.76			.30	-.18-.77
Step Two[2]	.26	2.14*			.27	2.20**		
State Anger			-.03	-.11-.05			-.02	-.11-.06
Trait Anger			.03	-.09-.14			.03	-.09-.15
Exp Out			-.01	-.14-.12			-.02	-.15-.12
Exp In			.04	-.03-.12			.05	-.03-.12
Control Out			-.02	-.11-.07			-.01	-.10-.09
Control In			.06	-.03-.15			.05	-.04-.15
Cynicism			.02	-.22-.27			-.01	-.30-.25
Hostility			.01	-.10-.13			.02	-.10-.14
Hostile Affect			.25	-.12-.62			.23	-.16-.62

Note: * denotes $p \leq .05$, ** is $p \leq .01$

[1]Step one includes the following predictors: (constant), months in the study, gender, household income, baseline creatinine levels, baseline ejection fraction, history of smoking, and age.

[2] Step two includes the following predictors: (constant), days in study, gender, household income, baseline creatinine levels, baseline ejection fraction, history of smoking, age, and all hostility/anger measures.

[3]Due to skewness, all-cause hospitalizations were truncated at 5.

Table 8.

Linear Regressions Predicting Heart Failure Hospitalizations

	Verified Heart Failure Hospitalizations[3]				Total Heart Failure Hospitalizations[3]			
	R^2	F	*B*	CI (95%)	R^2	F	*B*	CI (95%)
Step One[1]	.12	1.96			.12	1.84		
Number of Months in Study			.15*	.03-.27			.18**	.05-.30
Gender			-.25	-.82-.32			-.26	-.87-.35
Race			.14	-3.5-.63			.21	-.32-.74
Age			.00	-.03-.02			-.01	-.03-.02
Income			.17	-.07-.41			.17	-.09-.43
History of Smoking			-.30	-.85-.24			-.34	-.92-.25
EF			-.02	-.06-.01			-.02	-.05-.02
Creatinine			.25	-.10-.60			.24	-.13-.62
Step Two[2]	.21	1.6			.20	1.54		
State Anger			-.04	-.10-.03			-.03	-.10-.04
Trait Anger			.08	-.01-.17			.08	-.01-.18
Exp Out			-.07	-.17-.02			-.09	-.20-.02
Exp In			.03	-.03-.08			.03	-.03-.10
Control Out			.01	-.06-.08			.03	-.05-.10
Control In			.03	-.04-.10			.02	-.05-.10
Cynicism			.02	-.20-.21			.00	-.20-.20
Hostility			.00	-.09-.10			.02	-.10-.11
Hostile Affect			.18	-.11-.50			.13	-.17-.43

Note: * denotes $p \leq .05$, ** is $p \leq .01$

[1]Step one includes the following predictors: (constant), months in the study, gender, household income, baseline creatinine levels, baseline ejection fraction, history of smoking, and age.

[2] Step two includes the following predictors: (constant), days in study, gender, household income, baseline creatinine levels, baseline ejection fraction, history of smoking, age, and all hostility/anger measures.

[3]Due to skewness, all-cause hospitalizations were truncated at 5.

Table 9.

Logistic Regressions Predicting Yes/No All Cause Hospitalizations

	Verified All Cause Hospitalizations[3]				Total All Cause Hospitalizations[3]			
	$\chi^2(df)$	Cox & Snell R^2	Exp(B)	CI (95%)	$\chi^2(df)$	Cox & Snell R^2	Exp(B)	CI (95%)
Step One[1]	14.40(8)	.11			18.66(8)*	.14		
Number of Months in Study			1.43**	1.15-1.77			1.52***	1.22-1.90
Gender			.80	.32-2.02			.89	.35-2.27
Race			1.75	.71-4.27			1.66	.66-4.18
Age			1.00	.9-1.04			1.00	.96-1.03
Income			1.37	.91-2.06			1.40	.92-2.13
History of Smoking			.86	.35-2.13			.72	.29-1.80
EF			1.01	1.00-1.07			1.00	.95-1.06
Creatinine			1.24	.68-2.26			1.23	.68-2.21
Step Two[2]	13.06(9)	.20			15.27(9)	.24		
State Anger			.95	.86-1.06			.93	.83-1.03
Trait Anger			1.01	.87-1.18			1.06	.91-1.24
Exp Out			1.01	.85-1.20			.98	.82-1.18
Exp In			1.04	.94-1.14			1.04	.94-1.14
Control Out			.89	.78-1.01			.90	.78-1.03
Control In			1.18*	1.03-1.35			1.18*	1.03-1.36
Cynicism			1.24	.89-1.72			1.27	.91-1.79
Hostility			.99	.85-1.15			.99	.85-1.16
Hostile Affect			1.10	.68-1.80			1.03	.62-1.71

Note: * denotes $p \leq .05$, ** is $p \leq .01$, *** is $p \leq .001$

[1]Step one includes the following predictors: (constant), months in the study, gender, household income, baseline creatinine levels, baseline ejection fraction, history of smoking, and age.

[2] Step two includes the following predictors: (constant), days in study, gender, household income, baseline creatinine levels, baseline ejection fraction, history of smoking, age, and all hostility/anger measures.

[3]Due to skewness, all-cause hospitalizations were truncated at 5.

Table 10.

Logistic Regressions Predicting Yes/No Heart Failure Related Hospitalizations

	Verified Heart Failure hospitalization[3]				Total Heart Failure Hospitalization[3]			
	$\chi^2(df)$	Cox & Snell R^2	Exp(B)	CI (95%)	$\chi^2(df)$	Cox & Snell R^2	Exp(B)	CI (95%)
Step One[1]	12.27(8)	.10			14.20(8)	.11		
Number of Months in Study			1.28*	1.03-1.60			1.32*	1.06-1.65
Gender			.85	.30-2.39			1.05	.38-2.90
Race			1.07	.43-2.69			1.11	.44-2.81
Age			.99	.95-1.04			.99	.95-1.04
Income			1.25	.81-1.93			1.26	.82-1.94
History of Smoking			.500	.18-1.43			.46	.16-1.33
EF			.96	.91-1.02			.95	.90-1.02
Creatinine			1.68	.91-3.10			1.69	.92-3.09
Step Two[2]	9.34(9)	.16			10.90(9)	.19		
State Anger			1.00	.89-1.11			.98	.88-1.10
Trait Anger			1.13	.96-1.32			1.17	.99-1.37
Exp Out			.90	.76-1.08			.86	.71-1.04
Exp In			1.03	.93-1.14			1.03	.93-1.14
Control Out			1.06	.93-1.20			1.08	.95-1.23
Control In			1.03	.90-1.18			1.02	.89-1.17
Cynicism			1.21	.85-1.73			1.21	.85-1.73
Hostility			.93	.79-1.10			.93	.80-1.10
Hostile Affect			1.40	.79-2.35			1.33	.77-2.30

Note: * denotes $p \leq .05$, ** is $p \leq .01$, *** is $p \leq .001$

[1]Step one includes the following predictors: (constant), months in the study, gender, household income, baseline creatinine levels, baseline ejection fraction, history of smoking, and age.

[2] Step two includes the following predictors: (constant), days in study, gender, household income, baseline creatinine levels, baseline ejection fraction, history of smoking, age, and all hostility/anger measures.

[3]Due to skewness, all-cause hospitalizations were truncated at 5.

Table 11.

Logistic Regressions Predicting Hospitalizations and/or Death

	Verified Hospitalization and/or Death[3]				Total Hospitalization and/or Death[3]			
	$\chi^2(df)$	Cox & Snell R^2	Exp(B)	CI (95%)	$\chi^2(df)$	Cox & Snell R^2	Exp(B)	CI (95%)
Step One[1]	16.43(8)	.13			13.50(8)	.11		
Number of Months in Study			1.50**	1.19-1.85			1.40**	1.12-1.74
Gender			1.38	.54-3.5			1.15	.44-2.97
Race			.62	.52-3.01			1.07	.43-2.65
Age			1.01	.97-1.05			1.02	.98-1.06
Income			1.5	.97-2.23			1.36	.89-2.06
History of Smoking			.77	.31-1.91			.60	.24-1.50
EF			.99	.94-1.05			.99	.93-1.04
Creatinine			1.17	.65-2.10			1.22	.66-2.25
Step Two[2]	9.90(9)	.20			10.06(9)	.18		
State Anger			.93	.83-1.03			.97	.87-1.08
Trait Anger			1.01	.87-1.17			1.03	.89-1.20
Exp Out			.99	.83-1.17			.96	.81-1.14
Exp In			1.04	.94-1.14			1.02	.93-1.12
Control Out			.90	.79-1.02			.88*	.77-1.00
Control In			1.11	.98-1.30			1.12	.98-1.30
Cynicism			1.32	.94-1.85			1.30	.93-1.82
Hostility			.96	.82-1.12			.97	.83-1.13
Hostile Affect			1.04	.64-1.69			1.02	.62-1.65

Note: * denotes $p \leq .05$, ** is $p \leq .01$, *** is $p \leq .001$

[1]Step one includes the following predictors: (constant), months in the study, gender, household income, baseline creatinine levels, baseline ejection fraction, history of smoking, and age.

[2] Step two includes the following predictors: (constant), days in study, gender, household income, baseline creatinine levels, baseline ejection fraction, history of smoking, age, and all hostility/anger measures.

[3]Due to skewness, all-cause hospitalizations were truncated at 5.

Table 12.

Linear Regressions Predicting All-Cause Hospitalizations

	Verified All-Cause Hospitalizations[3]				Total All Cause Hospitalizations[3]			
	$R^2\Delta$	F Δ (df)	B	CI 95%	$R^2\Delta$	F Δ (df)	B	CI 95%
Step One[1] Covariates	**Block Significant**							
Step Two[2]								
State Anger	.01	1.25(1,129)	.03	-.02-.08	.01	1.16(1,129)	.03	-.03-.08
Trait Anger	.01	1.66(1,129)	.03	-.02-.08	.01	1.52(1,129)	.03	-.02-.08
Exp Out	.01	2.02(1,129)	.04	-.02-.11	.01	1.63(1,129)	.04	-.02-.10
Exp In	.02	2.99(1,129)	.05	-.01-.10	.02	2.84(1,129)	.05	-.01-.11
Control Out	.00	.41(1,129)	.02	-.03-.06	.00	.45(1,129)	.02	-.03-.06
Control In	.01	1.97(1,129)	.03	-.01-.08	.01	1.65(1,129)	.03	-.02-.08
Cynicism	.02	2.74(1,115)	.09	-.02-.20	.02	2.21(1,115)	.08	-.03-.19
Hostility	.03*	4.19(1,117)*	.04*	.001-.08	.03*	4.03(1,117)*	.04*	.001-.08
Hostile Affect	.04	5.76(1,116)*	.28*	.05-.51	.04	5.51(1,116)*	.28*	.04-.52

Note: * denotes $p \leq .05$, ** is $p \leq .01$, *** is $p \leq .001$

[1]Step one includes the following predictors: (constant), months in the study, gender, household income, baseline creatinine levels, baseline ejection fraction, history of smoking, and age.

[2] Step two includes the following predictors: (constant), days in study, gender, household income, baseline creatinine levels, baseline ejection fraction, history of smoking, age, and an individual hostility/anger measure.

[3]Due to skewness, all-cause hospitalizations were truncated at 5.

Table 13.

Linear Regressions Predicting Heart Failure Hospitalizations

	Verified Heart Failure Hospitalizations				Total Heart Failure Hospitalizations			
	$R^2\Delta$	F Δ (df)	B	CI 95%	R^2 Δ	F Δ (df)	B	CI 95%
Step One[1] Covariates				**Block Significant†**				
Step Two[2]								
State Anger	.00	.67(1,129)	-.02	-.06-.02	.00	.02(1,129)	.00	-.04-.05
Trait Anger	.00	.14(1,129)	.01	-.03-.04	.00	.31(1,129)	.01	-.03-.05
Exp Out	.00	.03(1,129)	.00	-.05-.04	.00	.01(1,129)	.00	-.05-.05
Exp In	.01	1.18(1,129)	.02	-.02-.06	.01	1.48(1,129)	.03	-.02-.07
Control Out	.01	.98(1,129)	.02	-.02-.05	.01	1.98(1,129)	.03	-.01-.06
Control In	.01	1.29(1,129)	.02	-.02-.06	.01	1.99(1,129)	.03	-.01-.07
Cynicism	.01	1.15(1,115)	.05	-.04-.13	.01	1.18(1,115)	.05	-.04-.14
Hostility	.02	3.07(1,117)	.03	.00-.06	.02	2.76(1,117)	.03	-.01-.06
Hostile Affect	.03	3.93(1,116)*	.17*	.00-.35	.03	3.52(1,116)ξ	.18ξ	-.01-.36

Note: * denotes $p \leq .05$, ** is $p \leq .01$, *** is $p \leq .001$

[1]Step one includes the following predictors: (constant), months in the study, gender, household income, baseline creatinine levels, baseline ejection fraction, history of smoking, and age.

[2] Step two includes the following predictors: (constant), days in study, gender, household income, baseline creatinine levels, baseline ejection fraction, history of smoking, age, and an individual hostility/anger measure.

[3]Due to skewness, all-cause hospitalizations were truncated at 5.

†Covariate block was not significant for cynicism and hostility variables

ξ Indicates trend level significance, p=.06

Table 14.

Logistic Regressions Predicting Yes/No All Cause Hospitalizations

	Verified Yes/No All Cause Hospitalizations				**Total Yes/No All Cause Hospitalizations**			
	$\chi^2(df)$	Cox & Snell R^2	Exp(B)	CI (95%)	$\chi^2(df)$	Cox & Snell R^2	Exp(B)	CI (95%)
Step One[1] Covariates	**Block Significant†**							
Step Two[2]								
State Anger	.45(1)	.13	1.03	.95-1.11	.14(1)	.16	1.02	.94-1.10
Trait Anger	.88(1)	.14	1.03	.97-1.10	1.63(1)	.17	1.04	.98-1.11
Exp Out	2.00(1)	.14	1.06	.98-1.15	2.44(1)	.18	1.07	.98-1.17
Exp In	1.32(1)	.14	1.04	.97-1.12	1.52(1)	.17	1.05	.97-1.12
Control Out	.08(1)	.13	.99	.94-1.05	.00(1)	.16	1.00	.94-1.06
Control In	1.71(1)	.14	1.04	.98-1.11	2.26(1)	.18	1.05	.99-1.12
Cynicism	3.58(1)	.12	1.14	.99-1.31	3.79(1)*	.14	1.15‡	1.00-1.32
Hostility	2.29(1)	.12	1.04	.99-1.10	2.32(1)	.14	1.04	.99-1.10
Hostile Affect	.78(1)	.11	1.114	.85-1.52	.42(1)	.13	1.10	.82-1.48

Note: * denotes $p \leq .05$, ** is $p \leq .01$, *** is $p \leq .001$

[1]Step one includes the following predictors: (constant), months in the study, gender, household income, baseline creatinine levels, baseline ejection fraction, history of smoking, and age.

[2] Step two includes the following predictors: (constant), days in study, gender, household income, baseline creatinine levels, baseline ejection fraction, history of smoking, age, and an individual hostility/anger measure.

[3]Due to skewness, all-cause hospitalizations were truncated at 5.

†Covariate block was not significant for cynicism and hostile affect variable of verified hospitalizations.

‡p=.06

AIM TWO

Our second aim was to explore the extent to which any relationships attained would be attributable to depression, and also to explore the cytokines hypothesis. Drawing on the literature between anger and depression we ran linear and logistic regressions to examine whether the effect of Hostility and Hostile Affect on all-cause hospitalizations and the effect of Cynicism on yes/no all-cause hospitalizations was merely due to the presence of depression. Specifically, our regressions contained three steps: step one- controlled for months in the study, gender, household income, baseline creatinine levels, baseline ejection fraction, history of smoking, and age, step two- controlled for depression (using the Beck Depression Inventory Total Score), and step three- contained either Hostility or Cynicism.

Linear regressions found that once depression was controlled Hostility no longer significantly predicted all-cause hospitalizations (both verified and unverified, see Table 15). A logistic regression found that even after controlling for depression, Cynicism still significantly predicted yes/no total (i.e., unverified) all-cause hospitalizations ($\chi^2(1) = 4.11$, $p = .05$, Cox and Snell $R^2 = .15$, Exp(B) = 1.16, CI 95% = 1.00-1.35). Using linear regressions we found that Hostile Affect no longer significantly predicted verified heart failure hospitalizations once depression was entered into the equation ($R^2 \Delta = .02$, $F \Delta(1,115) = 2.72$, B=.17, CI 95% = -.03-.37). However, Hostile Affect still predicted both verified ($R^2 \Delta = .04$, $F \Delta(1,116) = 5.76$, $p = .02$, B=.28, CI 95% =.05-.51, $p = .02$) and total all-cause hospitalizations ($R^2 \Delta = .04$, $F \Delta(1,116) = 5.51$, $p = .02$, B=.28, CI 95% =.04-.52, $p = .02$).

Table 15.

Linear Regressions Predicting All-Cause Hospitalizations Controlling for Depression

	Verified All-Cause Hospitalizations[3]				Total All-Cause Hospitalizations[3]			
	$R^2\Delta$	F Δ (df)	B	CI 95%	$R^2\Delta$	F Δ (df)	B	CI 95%
Step One[1]								
Covariates			**Block Significant**					
Step Two[2]								
BDI-II	.01	1.13(1,117)	.02	-.01-.05	.01	1.12(1,117)	.02	-.02-.05
Step Three								
Hostility	.02	3.01(1,116)	.04	.09-.69	.02	2.87(1,116)	.04	-.01-.09
Hostile Affect	.04	5.76(1,116)*	.28*	.05-.51	.04	5.51(1,116)*	.28*	.04-.52

Note: * denotes $p \leq .05$, ** is $p \leq .01$, *** is $p \leq .001$

[1]Step one includes the following predictors: (constant), months in the study, gender, household income, baseline creatinine levels, baseline ejection fraction, history of smoking, and age.

[2] Step two includes the following predictors: (constant), days in study, gender, household income, baseline creatinine levels, baseline ejection fraction, history of smoking, age, and BDI-II score for depression.

[3]Due to skewness, all-cause hospitalizations were truncated at 5.

In order to investigate the cytokine hypothesis we ran zero order correlations between anger and hostility and the following cytokines (see Table 16): IL-6, IL-10, TNF- ∝, and CRP. All cytokines werelog transformed first due to skewness. We found that there was no significant correlation between anger/hostility and the cytokines, except we did find a significant negative correlation between CRP and Trait Anger. This lack of significant correlation between cytokines and anger and hostility scales does not support our mediation hypothesis and does not lend support to the cytokine hypothesis. Therefore, we did not pursue further analyses looking at cytokines.

Table 16.

Zero-order Correlations of Anger/Hostility Subtypes and Cytokines

	Log IL-6	**Log IL-10**	**Log TNF-α**	**Log CRP**
State Anger	-.05	.04	.07	-.03
Trait Anger	-.04	.00	.04	-.19*
Anger Expression Out	-.04	.01	.10	-.16
Anger Expression In	-.02	.05	.05	.02
Anger Control Out	-.04	.01	.05	.09
Anger Control In	-.11	.00	-.09	.02
Cynicism	.01	.04	-.03	-.08
Hostility	.05	.04	.08	-.12
Hostile Affect	.06	-.03	-.05	-.01

Note: * denotes $p \leq .05$

Exploratory analysis

Following the significant correlation between KCCQTS heart failure symptom score and anger/hostility, we conducted exploratory analyses to determine whether perceived heart failure symptoms (as measured by the KCCQ) would explain the connection between Cynicism, Hostile Affect, and hospitalizations. A logistic regression found that once symptoms ($\chi^2(1) = 8.03$, $p = .005$, Cox and Snell $R^2 = .18$, Exp(B) = .98, CI 95% = .96-.99) were controlled for, Cynicism no longer significantly predicted yes/no total all-cause hospitalizations ($\chi^2(1) = 2.27$, $p = .13$, Cox and Snell $R^2 = .19$, Exp(B) = 1.12, CI 95% =.97-1.23). Additionally, linear regressions revealed that once symptoms were controlled, Hostile Affect no longer predicted both verified and total all-cause hospitalizations (see Table 16).

Table 16.

Linear Regressions Predicting for All-Cause Hospitalizations Controlling for Heart Failure Symptoms (KCCQTS)

	Verified All-Cause Hospitalizations[3]				Total All-Cause Hospitalizations[3]			
	$R^2\Delta$	F Δ (df)	B	CI 95%	$R^2\Delta$	F Δ (df)	B	CI 95%
Step One[1]								
Covariates				**Block Significant**				
Step Two[2]								
KCCQTS	.07	11.10(1,115)	-.02**	-.03- -.01	.07	10.66(1,115)	-.02**	-.04- -.01
Step Three								
Hostile Affect	.01	1.75(1,114)	.16	-.08-.40	.01	1.64(1,114)	.16	-.09-.41

Note: * denotes $p \leq .05$, ** is $p \leq .01$

[1]Step one includes the following predictors: (constant), months in the study, gender, household income, baseline creatinine levels, baseline ejection fraction, history of smoking, and age.

[2] Step two includes the following predictors: (constant), days in study, gender, household income, baseline creatinine levels, baseline ejection fraction, history of smoking, age, and KCCQTS score for heart failure symptoms.

[3]Due to skewness, all-cause hospitalizations were truncated at 5.

CHAPTER 6: Discussion

Summary of Results

Overall, there was no significant difference between verified and un-verified hospitalization, therefore we will focus on discussing verified hospitalizations. In sum, we found that hostility and its subcomponents significantly predicted all-cause hospitalizations, but not heart failure related hospitalizations. However, we found that hostility and its subcomponents were no longer significant after controlling for depression and heart failure symptoms in separate analyses. More specifically, with respect to study Aim I, our analyses found that, that the block containing anger and hostility predicted all-cause hospitalizations. Individual regression analyses revealed that Hostility and its subcomponents Hostile Affect and Cynicism significantly predicted all-cause hospitalizations, while anger and its subcomponents did not. In addition, with the exception of the Cynicism scale, which predicted both yes/no and number of hospitalizations, Hostility components only predicted number of hospitalizations and not, whether or not patients were hospitalized or death. Concerning aim two, when we controlled for depression, Hostility no longer predicted hospitalizations, however, Hostile Affect and Cynicism remained significant. Although, when heart failure symptoms were controlled for, Cynicism and Hostile Affect no longer significantly predicted any hospitalizations.

This is the first study, to our knowledge, that has specifically examined the connection between anger and hostility and hospitalizations within a population of heart failure patients. Only Jenner et al (26) has looked at hospitalizations and anger/hostility within a heart failure population, but they did not look at heart failure related hospitalizations or the individual components of anger or hostility. This study provides a

more nuanced view of the relationship between anger/hostility and hospitalizations. Another unique aspect of this study is the use of hospitalizations as an end point. A majority of studies in the current literature use medical end points such as myocardial infarction, and other related manifestations of coronary heart disease. However, with the continual rise of the cost of health care, it is important for researchers to find and address the sources of excessive hospitalizations. This study allowed us to explore anger and hostility as a possible source of additional hospitalizations.

AIM ONE

With respect to Aim I, results of this study indicate that anger and hostility are both related to all-cause hospitalizations, but not heart failure related hospitalizations or death. Indicating that aim one is partially supported. There may be multiple reasons for this finding. One explanation may be that these all-cause hospitalizations are due to angry or risky behaviors rather than heart failure complications alone. For example, two participants within our study were hospitalized for car accidents. Although it cannot be assumed that this car accident was caused by the participant's anger, anger and/or hostility may be a contributing factor (48). This study by Schwebel et al (48) not only showed that anger/hostility individually contributes to risky driving, but it also interacts and drives sensation-seeking behavior. Sensation-seeking behavior comes in many forms, but may explain additional all-cause hospitalizations. Other reasons for hospitalizations include: chronic illness (e.g., cancer, and chronic obstructive pulmonary disease), illness (e.g., flu), injury (e.g., acute kidney injury), and other (e.g., hip replacement and back surgery), which suggests that hostility may be a contributing factor to broader health concerns.

An additional explanation may be that hostility could be impacting medication compliance and symptom report. Lee et al (30) found, in a sample of 620 hypertensive men, that individuals who were higher in hostility reported skipping more medication dosages than those with lower hostility scores. Additionally, there was a positive correlation between hostility and number of symptoms (the symptoms were consistent with those who do not take a consistent regime of antihypertensive drugs) reported. These findings suggest that those in our study, with high total hostility may have poor medication adherence and thus cause more hospitalizations that are not related to fluid pump overload or pump failure. More specifically, it would seem as if individuals with high scores in cynical hostility might be less likely to adhere to their medication because of their cynical attitude toward their ability to recover.

Another possible explanation may be that those high in hostility, most particularly Hostile Affect, may have less social support than those with little Hostile Affect. Research has consistently shown the social support is crucial to the health of patients with heart failure. Sayers et al (47) found that in patients with heart failure, perceived social support (typically from a spouse), was associated with better self-care in such domains as: medication and dietary adherence, and daily weighing. In a meta-analysis Luttik et al (33) found that social support had a positive impact on outcomes such as hospitalizations and mortality. Knowing the importance of social support to the health and well-being of patients with heart failure, it is logical to infer that if one is high in hostile affect it may decrease the amount of social support offered by those around them and therefore increase the amount of subsequent hospitalizations.

In sum, we have suggested several explanations for why Hostility may predict total hospitalizations, however these explanations cannot account for why Hostility did not predict heart failure related hospitalizations. Medication compliance, symptom report, and social support should all impact heart failure hospitalizations, not merely all-cause hospitalizations. It may be that we lacked sufficient power to detect nay impact on heart failure hospitalizations, so this should be the subject of future research.

Aim Two

Hypotheses for Aim 2 were partially supported. We found that once depression is accounted for, some hostility domains no longer predict hospitalizations, and once heart failure symptoms are accounted for no hostility component predicts hospitalizations. However, we found that cytokines failed to correlate with any anger or hostility measures, not lending support to the cytokine hypothesis. This finding offers an additional explanation for why hostility may predict all-cause hospitalizations. Research has shown us that depression is a complicating factor for those with heart failure (46) and theoretically anger and depression often overlap with one another, therefore anger may work to worsen an individual's depression, worsening their heart failure. Additionally, it is logical to surmise that individuals with heightened heart failure symptoms would be hospitalized with higher frequency. From our analysis we found that symptom score was highly correlated with hostility and its components, perhaps suggesting that hostility may fuel greater perceived symptoms. However, this causal relationship remains a matter of conjecture because our measures of hostility and perceived symptoms are cross-sectional.

Our second aim also revealed that, while depression did not predict all-cause hospitalizations and therefore cannot be a mediator, heart failure symptoms did predict

all-cause hospitalizations independently of Hostile Affect, therefore according to Baron and Kenny (5) is a mediator (small effect size, B=-.02).

Role of Hostility

Another finding of this study was that hostility and some of its components significantly predicted all-cause hospitalizations, but anger and its components did not. This is consistent with previous literature that has found that hostility scores can significantly predict clinical coronary disease and total mortality (4). As previously mentioned, anger is conceptualized as an emotional state, while hostility is thought of as a complex set of attitudes that can inform or propel aggressive behavior (53). It may be the case in this sample that the participants held hostile attitudes toward their ability to recover, which spanned the entire time in the study, effectively sabotaging their recovery efforts; while any anger they experienced was fleeting and therefore did not contribute significantly enough to subsequent hospitalizations. In other words, individuals who are high in hostility may direct this negative set of attitudes towards their medical care, doctor's advice, and overall ability to overcome their condition, effectively causing more hospitalizations over time. Furthermore, research has found that hostility is relatively stable over time and at times can even increase (61), suggesting that hostility can impact a patient at every disease stage, therefore contributing more to hospitalizations than anger. However, this explanation is untested because no measure of hostility chronicity was used within the study.

Prior Literature

The present study findings are consistent with the larger literature that finds that hostility is linked to other negative health outcomes in patients with coronary heart

disease, and total mortality (4; 11). However, our study is not consistent this same literature that found the role of anger was also significant in predicting negative outcomes in patients with coronary heart disease (11), as we found that anger was not a significant predictor of hospitalizations. Additionally, our study does not support the link of hostility to negative cardiovascular events that has been found in previous literature (4). Put simply, our study supports the finding that hostility may contribute to broader negative health outcomes in patients with heart failure, however it does not support a connection between hostility and heart failure related hospitalizations, nor does it support anger's connection with hospitalizations.

Study Limitations

The results of this study should be considered in light of several caveats. The first issue to bear in mind is with the number of regressions and other analyses run in the study, there is always the risk of inflating the Type I error rate. Another caveat is that the sample consists mainly of African Americans and does not have an adequate sample size to generalize the findings to other ethnicities. Furthermore, this sample also consists mainly of men; therefore generalizing these findings to a sample of female heart failure patients would not be appropriate. Additionally, the BETRHEART study is still in its' final stages of completion, therefore not all participants have the full 36 month follow-up completed, which reduces our ability to see the true link between anger/hostility and hospitalizations. Furthermore, our population, as seen from the numerous different types of hospitalizations, was highly comorbid, suffering from multiple other health conditions aside from heart failure. This high comorbidity may have been a confounding factor within the study, suppressing the true relationship between anger, hostility, and

hospitalizations. Finally, our study is correlational in nature and correlation does not equate causation.

Future Directions

It is clear from this study that hostility predicts hospitalizations within a heart failure population. The mechanism through which hostility works to affect hospitalizations is not entirely clear. However, hostility might operate by impacting numerous factors including: risky behavior, medication compliance, social support, depression, and perceived heart failure symptoms. The next step in this research would to identify those individuals at greater risk for hostility and any possible interventions. Additionally, future studies can examine these factors as possible mediators of the relationship between hostility and all-cause hospitalizations. Finally, more research is needed to tease apart why hostility predicts all-cause but not heart failure related hospitalizations.

Clinical Implications

Our findings indicate that hostility may have broader health consequences, than impacting heart failure directly. Instead, hostility may work through a variety of avenues to influence and shape behavior, which drives negative health outcomes. These findings suggest that hostility needs to be recognized and addressed in not only heart failure patients, but perhaps also the health community at large, because according to our findings, hostility may contribute to a wider range of hospitalizations. By addressing hostility, health care professionals may be able to identify at risk individuals in order to apply interventions to reduce hospitalizations. Our results also suggest that physicians should focus on treating the patient, and not merely the heart failure.

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