Examination of the potential association of stress with morbidity and mortality outcomes in patient with heart failure

Abdullah S Alhurani1,2, Rebecca Dekker1, Elizabeth Tovar1, Alison Bailey1, Terry A Lennie1, David C Randall1 and Debra K Moser1

Abstract

Objectives: The high mortality and morbidity rates associated with heart failure are still not well explained. A few psychosocial factors have been studied and explain some of this risk, but other factors, like stress, remain largely unexplored in heart failure. This study aimed to (1) examine the association of stress with 6-month cardiac event-free survival, (2) examine the relationship of stress with salivary cortisol, and (3) examine the association of salivary cortisol level with 6-month cardiac event-free survival.

Method: A total of 81 heart failure patients participated. Stress was measured using the brief Perceived Stress Scale. Cortisol was measured from unstimulated whole expectorated saliva. Cox regression analyses were used to determine whether stress predicted event-free survival, and if salivary cortisol predicted event-free survival. Linear and multiple regressions were used to determine the association of stress with salivary cortisol.

Results: Stress was not a significant predictor of event-free survival in heart failure (heart rate = 1.06; 95% confidence interval = 0.95–1.18; p = 0.32). Salivary cortisol was a significant predictor of event-free survival in the unadjusted model (heart rate = 2.30; 95% confidence interval = 0.99–5.927; p = 0.05), but not in the adjusted model. Stress (β = 1.06; 95% confidence interval = 0.95–1.18; p = 0.32) was not a significant predictor of salivary cortisol level.

Conclusion: Stress is a complex phenomenon, and our measure of stress may not have captured it well. Alternatively, the physical stressors acting in heart failure produce levels of neurohormonal activation that mask the effects of psychosocial stressors or an indirect association of stress with outcomes that is mediated through another construct. Future studies are needed to investigate stress in patients with heart failure to provide definitive answers.

Keywords
Stress, heart failure, cortisol, event-free survival, health outcomes

Date received: 22 April 2014; accepted: 26 August 2014

Introduction

Worldwide, heart failure (HF) is considered a major public health problem.1–9 Although there have been significant therapeutic advances in pharmacological and surgical treatment of HF, hospital admission and readmission rates are extremely high for exacerbations of HF, and the 1-year mortality rate of HF patients with progressive symptoms still approaches 40%.10–13 The high mortality and morbidity rates associated with HF are not completely explained by biological mechanisms,14 as psychological factors are important predictors of morbidity and mortality in HF. One psychological factor that might contribute to morbidity and mortality in patients with HF is stress.14–20

Stress is the condition that occurs when environmental demands exceed an individual’s ability to adapt to the demands.21 A prerequisite for stress to occur is the individual’s perception that stressors are perceived as a persistent threat to their physical and/or psychological health or
well-being. Stress is an umbrella term that summarizes the effects of psychological and environmental stressors on an individual’s physical and mental health. HF is commonly perceived by patients as a very stressful experience both physically and psychologically.

There is limited information about the relationship between stress and HF. However, in patients with cardiovascular disease, psychological stress was associated with multiple adverse effects on patient health outcomes. In patients with cardiovascular disease, psychological stress has been associated with decreased coronary artery blood supply, greater severity of cardiac disease, worse prognosis, and poorer cardiac function. Stress is also associated with multiple psychological factors such as anxiety and depression that have negative effects on health outcomes like mortality and morbidity in HF and cardiac disease.

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

**Method**

**Design, sample, and setting**

A prospective design was used in which patients were followed for 6 months to determine occurrence of 6-month cardiac event-free survival, defined as time to the combined endpoint of cardiac rehospitalization or all-cause death. This study was a part of the Heart Outcomes Prevention Evaluation (HOPE) study at the University of Kentucky that investigated depression among hospitalized patients with HF. The parent study and the current study were approved by the Institutional Review Board at the University of Kentucky. The sample consisted of 81 patients with confirmed HF who were hospitalized for cardiac reasons (i.e. hospitalization for HF, acute coronary syndrome, dysrhythmias) at the University of Kentucky Chandler Medical Center or Good Samaritan Hospital, which are located in Lexington, Kentucky.

Patients with a diagnosis of chronic HF confirmed by echocardiogram and cardiologist were eligible for participation in the study if they met the following criteria: (1) admitted to the hospital with a primary or secondary diagnosis of exacerbation of chronic HF or any other cardiac diagnosis, (2) 21 years or older, (3) able to read and speak English, and (4) no obvious cognitive impairment. Patients with HF with either preserved or non-preserved ejection fraction were included. Patients were excluded from the study for the following reasons: (1) co-existing terminal illness likely to be fatal within the next 6 months; (2) presence of a left ventricular assist device, continuous inotropic infusion, or hospice care; (3) active suicidality (defined as choosing option 2 or 3 on item 9 of the Beck Depression Inventory-II); (4) history of the death of a spouse or child within the past month; (5) history of psychotic illness or bipolar illness; (6) current alcohol dependence or other substance abuse; and (7) new-onset HF.

**Measures**

**Stress**

Stress was measured using the brief version of the Perceived Stress Scale. The brief version consists of a 4-item scale which has been demonstrated to be reliable and valid. The 4 items are as follows: (1) How often have you felt that you were unable to control the important things in your life? (2) How often have you felt confident about your ability to handle your personal problems? (3) How often have you felt that things were going your way? (4) How often have you felt difficulties were piling up so high that you could not overcome them? Each item is rated by respondents on a scale ranging from 0 (never) to 5 (very often). Higher scores indicate greater levels of stress. In this study, the Cronbach’s alpha of the 4-items perceived stress scale was 0.70.

**Event-free survival**

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

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

Cortisol was measured from saliva obtained from patients at baseline through an unstimulated whole expectorated saliva collection protocol. Patients were provided a 20-mL vial containing freeze dried protease inhibitor. Patients were asked to swallow once and begin expectorating approximately every 20–30 s until 5 mL is collected. The specimen was kept on ice until returned to the lab. Salivary sample was obtained in the morning (9:00 a.m.) on the day of enrollment. The salivary samples were stored in a −80°C freezer until they were analyzed using a commercially available enzyme immunoassay kit designed for cortisol quantification in saliva (Salimetrics LLC, State College, PA, USA). This assay has a sensitivity of <0.007 µg/dL and is strongly correlated with serum cortisol measurement (0.91). Salivary cortisol is considered a more accurate and reliable measure for the clinical assessment of adrenocortical function than serum cortisol.40,41

Depressive symptoms

The Patient Health Questionnaire–9 (PHQ-9)42,43 was used to measure depressive symptoms. The PHQ-9 is a 9-item, self-reported measure of depressive symptom severity. Patients respond to each item on a Likert scale ranging from 0 (not at all) to 3 (nearly every day). The total summary score can range from 0 to 27; a higher score reflects more severe depressive symptoms. Good internal consistency, stability, construct, and concurrent validity of the PHQ-9 have been supported.42,44 The standard published cut point of 10 was selected in this study for PHQ-9 to identify those in the sample who had moderate to severe depressive symptoms.28 This cut point was reported to have 88% sensitivity and 88% specificity for diagnosing major depression.43,45 In this study, the Cronbach’s alpha of the PHQ-9 scale was 0.73.

Anxiety

The Brief Symptom Inventory (BSI) anxiety subscale was used to measure anxiety.46,47 The subscale consists of six questions, each of which is scored by patients using a scale that ranges from 0 (not at all) to 4 (extremely). The total score is calculated as the mean of the 6-item scores. Thus, the possible range of scores for the anxiety scale is 0–4, with higher scores indicative of higher levels of anxiety. The BSI has demonstrated internal consistency, stability, construct, and concurrent validity in other studies.46,47 In this study, the Cronbach’s alpha of the anxiety scale was 0.77. A standard published mean score of 0.35 was used to identify those in the sample who were anxious and those who were not anxious.48

Demographic and clinical variables

Data on demographic variables and clinical characteristics were collected by reviewing medical records and interviewing patients. These variables included age, gender, ethnicity, and NYHA class. The NYHA class indicates the level of functional impairment reported by patients as a result of symptoms and was rated by trained research nurses. These variables were selected because of their effects on the outcome variable as suggested in the literature.45,49

Procedure

Protocols for this study were approved by institutional review board of The University of Kentucky. All procedures were in accordance with institutional guidelines for research using human subjects. Hospitalized patients were identified by clinicians and referred to research staff. The research staff determined the patient’s eligibility. The study was thoroughly explained to each patient, and signed consent was obtained after answering any questions about the study. The research staff met with the patient to administer study questionnaires via the web-based SurveyMonkey. The questionnaires took approximately 20 min to complete. A paper copy also was offered to the patient if they did not feel comfortable with the web-based survey.

As a part of HOPE study, patient were contacted by phone to complete the follow-up questionnaire at 2 weeks, 3 months, and 6 months from hospital discharge. At each telephone contact, the research staff asked the patient whether he or she has been hospitalized or visited the emergency unit. At the end of the study period and intermittently thereafter, hospital records were reviewed to confirm deaths, re-hospitalizations, or emergency department visits.

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

Statistical analysis

Data were analyzed using SPSS software, version 20.0 (SPSS Inc., Chicago, IL, USA). Descriptive statistics, including mean, standard deviation, and frequency distribution, were used to describe sample characteristics. To test Specific Aim 1, unadjusted, followed by adjusted, Cox regression analyses were used to determine whether stress independently predicted event-free survival. The following covariates were considered in the adjusted analysis and entered hierarchically: age, gender, NYHA class, and anxiety and depression. Demographic and clinical variables were entered first into the model. Then, anxiety and depressive symptoms were entered. Finally, stress as a continuous level variable was entered into the model. The same analysis was conducted using categorical level variables with the mean and median as cut-points.

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

### Results

Demographic and clinical characteristics of patients (N=81) are summarized in Table 1. The average stress score in this sample was 9.47 ± 3.86, with a range of 4–20. No cut point has been defined for this instrument to date; however, the mean stress score in this study was higher than has been reported in other studies for the same scale. For example, in a study of college students, the mean score was 5.6 ± 3.6, and in a study of Chinese patients with cardiac conditions, the mean was 6.0 ± 2.0. The average anxiety score was 0.58 ± 0.68. Using the published BSI average in the general population of 0.35, 46.7% scored as anxious. The average depressive symptoms score was 8.00 ± 4.87, and using the standard published PHQ-9 cut point 10, 29.6% of the sample was suffering from depressive symptoms. The average salivary cortisol level was 0.32 ± 0.23 µg/dL.

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

A total of 28 (35%) patients had an event. Six (7.4%) died and 22 (27.2%) were hospitalized for cardiac reasons during the study. In the unadjusted model, stress (heart rate (HR) = 1.04; 95% confidence interval (CI) = 0.95–1.13; p = 0.46) was not a predictor of event-free survival. In the adjusted model with age, gender, NYHA, anxiety, and depressive symptoms as covariates, the overall model (χ² = 3.14, df=6; p = 0.79) was not significant (Table 2). None of the variables were significant in any step of the hierarchical Cox regression. In the final model, stress (HR = 1.06; 95% CI = 0.95–1.18; p = 0.32) was not a predictor of event-free survival. An additional exploratory Cox regression analysis was conducted using stress as a categorical variable. The results were similar in that stress did not predict the outcome.

### Specific aim 2: association of stress and salivary cortisol

The linear and multiple regressions (n=70) showed that stress level was not a significant predictor of salivary cortisol (Tables 3 and 4). In addition, none of the covariate variables (age, gender, NYHA, and anxiety) in the multiple regression analysis was a significant predictor of salivary cortisol except age (HR = 0.26; 95% CI = 0.00–0.01; p = 0.04) (Table 4). An additional exploratory Cox regression analysis was conducted using salivary cortisol as a categorical variable. The results were similar in that salivary cortisol did not predict the outcome.
Table 3. Linear regression of stress level associated with salivary cortisol of patients with heart failure.

| Predictor variable | β    | 95% CI     | p    |
|--------------------|------|------------|------|
| Stress             | −0.06| −0.02 to 0.01 | 0.60 |
| Overall model (adjusted R² = −0.01, F = 0.28; p = 0.60) |      |            |      |

Table 4. Multiple linear regression of variables associated with salivary cortisol of patients with heart failure.

| Predictor variables | β | 95% CI     | p    |
|---------------------|---|------------|------|
| Age                 | 0.26 | 0.00 to 0.01 | 0.04 |
| Female gender       | −0.20 | −0.25 to 0.03 | 0.11 |
| NYHA class III/IV compared to I/II | 0.15 | −0.07 to 0.23 | 0.27 |
| Anxiety             | −0.002 | −0.12 to 0.12 | 0.99 |
| Stress              | −0.09 | −0.03 to 0.01 | 0.55 |
| Overall model (adjusted R² = 0.056, F = 1.769; p = 0.133) | | | |

Discussion

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

Our hypotheses were based on the physiological mechanisms whereby stress may affect the progression of cardiovascular disease in general. Stress is thought to involve the hypothalamic–pituitary–adrenocortical (HPA). Much of the research on animals and humans suggests that psychological factors can influence the HPA axis, which controls the release of cortisol, a glucocorticoid that is secreted by the adrenal cortex to support and control physiological functions. Over the past decades, many investigators have concluded that physical and psychological stressors are capable of activating the HPA axis and increasing cortisol level in the bloodstream. Through cortisol, the HPA supports physiological functions and regulates other systems. However, prolonged elevation in cortisol due to frequent stress is associated with many negative biological effects such as suppression of the immune system, damage to hippocampal neurons, and development and progression of chronic diseases like diabetes and hypertension. In HF, cortisol may contribute to the progression of cardiac damage by acting as a mineralocorticoid receptor (MR) agonist in the cardiac muscle where cortisol mimics the physiological and pathophysiological effects of aldosterone. Given these data, it is crucial to determine whether the stressors that are associated with HF activate the cortisol system and contribute to the onset or exacerbation of certain health outcomes.

Although there is evidence suggesting a relationship between stress and poor outcomes in cardiac patients without HF, the overall picture presented by the literature is one of conflicting findings. Stress, variably defined as psychological, psychosocial, and mental stress, has been shown to predict mortality and morbidity in patients with cardiovascular diseases. Others, with large sample sizes, have found no association between stress level and increased admission rates related to cardiovascular disease. In fact, some of...
these investigators demonstrated an inverse relationship between stress and all-cause mortality, as well as cardiac mortality.64 Other investigators have demonstrated a difference between men and women in the prediction of mortality by stress in hospitalized medical patients.50,51 Stress in male patients predicted all-cause mortality; however, no association was found between stress and mortality among women.65,66 Investigators explained those results by stating that men are more vulnerable to stress than women. In addition, they expressed concerns that use of the two-question short version of the perceived stress scale did not capture some aspects of the stress phenomena.65,66

Our neutral finding about the relationship between stress and outcomes may be related to our small sample size, yet other investigators with very large sample sizes have similarly failed to find an association.64 Although patients in our sample had a higher stress level compared to other populations,39,51 the average score on the stress instrument was only moderately high. Thus, it may be that patients in this sample did not experience a stress level high enough to demonstrate the hypothesized relationship. Another potential explanation for our finding is that the instrument did not adequately capture stress. We used the 4-item perceived stress scale, which has been demonstrated to be valid and reliable; nonetheless, the full instrument may have provided more complete information about stress level than the short version.39,51,67 The 6-month follow-up period may have been too short to capture the effect of stress on the health outcomes in patients with HF. Another possible explanation is that there is no relationship between stress level and outcomes in patients with HF. This explanation is supported by the number of investigations in which no relationship has been found in patients with a variety of health conditions.64,68,69 A final possible explanation is that there is an indirect association of stress with outcomes that is mediated through another construct such as coping.

We found no association between stress level and salivary cortisol level. Our findings are consistent with a study of breast cancer patients that showed no significant relationship between stress and salivary cortisol level.70 Our study was similar to this study of breast cancer patients in that medically ill individuals with conditions that may be stressful were studied. In a literature review71 designed to evaluate salivary cortisol as a biomarker of self-reported mental stress in field studies of healthy adults, the authors examined 14 studies published in medium or high quality journals. Results from eight studies demonstrated no association between self-reported mental stress and cortisol response: in four studies, there was a positive association, and in two studies a negative association.71 They concluded that in healthy adults,

---

**Table 6.** Adjusted Cox proportional hazards regression model of variables associated with cardiac event-free survival (salivary cortisol model).

| Predictor variables                  | Hazard ratio | 95% CI    | p     |
|--------------------------------------|--------------|-----------|-------|
| Age                                  | 1.01         | 0.97–1.04 | 0.69  |
| Female gender                        | 0.64         | 0.27–1.52 | 0.31  |
| NYHA class III/IV compared to I/II   | 0.74         | 0.33–1.65 | 0.50  |
| High cortisol level compared to low level | 2.03         | 0.84–4.927 | 0.12  |

Overall model ($\chi^2 = 5.34$, df = 4; p = 0.25)

CI: confidence interval; NYHA: New York Heart Association.
there were insufficient data to support a relationship and postulated that the association, if present, might only be evident in those with extremely high levels of stress. There are no other reviews more relevant to our sample of HF patients, but the suggestion that patients may need to experience very high levels of stress for the association to become evident is valid to our sample.

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

**Study strengths and limitations**

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

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

**Conclusion**

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

**Acknowledgement**

All the authors take responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation.

**Declaration of conflicting interests**

The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institute of Nursing Research or the National Institutes of Health. Financial sponsors played no role in the design, execution, analysis, and interpretation of data or writing of the study.

**Funding**

This work was supported by the National Institutes of Health, National Institute of Nursing Research (NIH, NINR P20 Center funding 5P20NR010679; NIH, NINR 1R01 NR009280 (Terry Lennie, PI) and R01 NR008567 (Debra Moser, PI)), and K23 NR013480.

**References**

1. Roger VL, Go AS, Lloyd-Jones DM, et al. Heart disease and stroke statistics—2011 update: a report from the American Heart Association. *Circulation* 2011; 123: e18–e209.
2. Ambrosy AP, Fonarow GC, Butler J, et al. The global health and economic burden of hospitalizations for heart failure: lessons learned from hospitalized heart failure registries. *J Am Coll Cardiol* 2014; 63: 1123–1133.
3. Atherton JJ, Hayward CS, Wan Ahmad WA, et al. Patient characteristics from a regional multicenter database of acute decompensated heart failure in Asia Pacific (ADHERE International-Asia Pacific). *J Card Fail* 2012; 18: 82–88.
4. Guo Y, Lip GY and Banerjee A. Heart failure in East Asia. *Curr Card Rev* 2013; 9: 112–122.
5. Pillai HS and Ganapathi S. Heart failure in South Asia. *Curr Card Rev* 2013; 9: 102–111.
6. Sakata Y and Shimokawa H. Epidemiology of heart failure in Asia. *Circ J* 2013; 77: 2209–2217.
7. Sayago-Silva I, Garcia-Lopez F and Segovia-Cubero J. Epidemiology of heart failure in Spain over the last 20 years. *Rev Esp Cardiol* 2013; 66: 649–656.
8. Sliwa K and Mayosi BM. Recent advances in the epidemiology, pathogenesis and prognosis of acute heart failure and cardiomyopathy in Africa. *Heart* 2013; 99: 1317–1322.
9. Jouven X and Desnos M. Epidemiology of heart failure. *Rev Prat* 2002; 52: 1641–1643.
10. Adams KF Jr and Zannad F. Clinical definition and epidemiology of advanced heart failure. *Am Heart J* 1998; 135: S204–S215.
11. MacMahon KM and Lip GY. Psychological factors in heart failure: a review of the literature. *Arch Intern Med* 2002; 162: 509–516.
12. White HD, Aylward PE, Huang Z, et al. Mortality and morbidity remain high despite captopril and/or Valsartan therapy in elderly patients with left ventricular systolic dysfunction, heart failure, or both after acute myocardial infarction: results from the Valsartan in Acute Myocardial Infarction Trial (VALIANT). *Circulation* 2005; 112: 3391–3399.
13. Ather S, Chan W, Bozkurt B, et al. Impact of noncardiac comorbidities on morbidity and mortality in a predominantly male population with heart failure and preserved versus reduced ejection fraction. *J Am Coll Cardiol* 2012; 59: 998–1005.
14. Bennett SJ, Pressler ML, Hays L, et al. Psychosocial variables and hospitalization in persons with chronic heart failure. *Prog Cardiovasc Nurs* 1997; 12: 4–11.
15. Alhurani A, Dekker R, Abed M, et al. The association of co-morbid Symptoms of depression and anxiety with all-cause mortality and cardiac rehospitalization in patients with heart failure. *Psychosomatics*, in press.

16. Konstam V, Moser DK and De Jong MJ. Depression and anxiety in heart failure. *J Card Fail* 2005; 11: 455–463.

17. Newhouse A and Jiang W. Heart failure and depression. *Heart Fail Clin* 2014; 10: 295–304.

18. Widdershoven J, Kessing D, Schiffer A, et al. How are depression and type D personality associated with outcomes in chronic heart failure patients? *Curr Heart Fail Rep* 2013; 10: 244–253.

19. De Jong MJ, Chung ML, Wu JR, et al. Linkages between anxiety and outcomes in heart failure. *Heart Lung* 2011; 40: 393–404.

20. Pelle AJ, Gidron YY, Szabo BM, et al. Psychological predictors of prognosis in chronic heart failure. *J Card Fail* 2008; 14: 341–350.

21. Cohen SKR and Gordon UL. Strategies for measuring stress in studies of psychiatric and physical disorder. New York: Oxford University Press, 1995, pp. 3–26.

22. Grant KE, Compas BE, Stuhlmacher AF, et al. Stressors and child and adolescent psychopathology: moving from markers to mechanisms of risk. *Psychol Bull* 2003; 129: 447–466.

23. Esch T. Health in stress: change in the stress concept and its significance for prevention, health and life style. *Gesundheitswesen* 2002; 64: 73–81.

24. Selye H. The evolution of the stress concept. *Am Sci* 1973; 61: 692–699.

25. Moser DK, Dracup K, Evangelista LS, et al. Comparison of prevalence of symptoms of depression, anxiety, and hostility in elderly patients with heart failure, myocardial infarction, and a coronary artery bypass graft. *Heart Lung* 2010; 39: 378–385.

26. Jiang W, Babyak M, Krantz DS, et al. Mental stress—induced myocardial ischemia and cardiac events. *JAMA* 1996; 275: 1651–1656.

27. Sullivan MD, LaCroix AZ, Spertus JA, et al. Five-year prospective study of the effects of anxiety and depression in patients with coronary artery disease. *Am J Cardiol* 2000; 86: 1135–1138, A6, A9.

28. Verrier RL and Mittelman MA. Cardiovascular consequences of anger and other stress states. *Baillieres Clin Neurol* 1997; 6: 245–259.

29. Demollet J, Tekle FB, van der Voort PH, et al. Age-related differences in the effect of psychological distress on mortality: type D personality in younger versus older patients with cardiac arrhythmias. *Biomed Res Int* 2013; 2013: 246035.

30. Wei J, Rooks C, Ramadon R, et al. Meta-analysis of mental stress-induced myocardial ischemia and subsequent cardiac events in patients with coronary artery disease. *Am J Cardiol* 2014; 114: 187–192.

31. Kaplan JR and Manuck SB. Status stress, and atherosclerosis: the role of environment and individual behavior. *Ann N Y Acad Sci* 1999; 896: 145–161.

32. Yeung AC, Veksstein VI, Krantz DS, et al. The effect of atherosclerosis on the vasomotor response of coronary arteries to mental stress. *N Engl J Med* 1991; 325: 1551–1556.

33. Forthofer MS, Janz NK, Dodge JA, et al. Gender differences in the associations of self esteem, stress and social support with functional health status among older adults with heart disease. *J Women Aging* 2001; 13: 19–37.

34. McEwen BS. Protective and damaging effects of stress mediators. *N Engl J Med* 1998; 338: 171–179.

35. Hemingway H and Marmot M. Evidence based cardiology: psychosocial factors in the aetiology and prognosis of coronary heart disease. Systematic review of prospective cohort studies. *BMJ* 1999; 318: 1460–1467.

36. Dracup K, Westlake C, Erickson VS, et al. Perceived control reduces emotional stress in patients with heart failure. *J Heart Lung Transplant* 2003; 22: 90–93.

37. Rusli BN, Edimansyah BA and Naing L. Working conditions, self-perceived stress, anxiety, depression and quality of life: a structural equation modelling approach. *BMC Public Health* 2008; 8: 48.

38. Jiang W, Kuchibhatla M, Cuffe MS, et al. Prognostic value of anxiety and depression in patients with chronic heart failure. *Circulation* 2004; 110: 3452–3456.

39. Cohen S, Kamarck T and Mermelstein R. A global measure of perceived stress. *J Health Soc Behav* 1983; 24: 385–396.

40. Vining RF, McGinley RA, Maksyvits JJ, et al. Salivary cortisol: a better measure of adrenal cortical function than serum cortisol. *Ann Clin Biochem* 1983; 20(Pt 6): 329–335.

41. Gozansky WS, Lynn JS, Laudenslager ML, et al. Salivary cortisol determined by enzyme immunoassay is preferable to serum total cortisol for assessment of dynamic hypothalamic–pituitary–adrenal axis activity. *Clin Endocrinol* 2005; 63: 336–341.

42. Kroenke K, Spitzer RL and Williams JB. The PHQ-9: validity of a brief depression severity measure. *J Gen Intern Med* 2001; 16: 606–613.

43. Spitzer RL, Kroenke K and Williams JB. Validation and utility of a self-report version of PRIME-MD: the PHQ primary care study. Primary Care Evaluation of Mental Disorders. Patient Health Questionnaire. *JAMA* 1999; 282: 1737–1744.

44. Dekker RL, Lennie TA, Albert NM, et al. Depressive symptom trajectory predicts 1-year health-related quality of life in patients with heart failure. *J Card Fail* 2011; 17: 755–763.

45. Song EK, Moser DK, Frazier SK, et al. Depressive symptoms affect the relationship of N-terminal pro B-type natriuretic peptide to cardiac event-free survival in patients with heart failure. *J Card Fail* 2010; 16: 572–578.

46. Derogatis LR and Melisaratos N. The Brief Symptom Inventory: an introductory report. *Psychol Med* 1983; 13: 595–605.

47. Khalil A, Hall L, Moser D, et al. The psychometric properties of the Brief Symptom Inventory depression and anxiety subscales in patients with heart failure and with or without renal dysfunction. *Arch Psychiatr Nurs* 2011; 25: 419–429.

48. Moser DK. “The rust of life”: impact of anxiety on cardiac patients. *Am J Crit Care* 2007; 16: 361–369.

49. Wu JR, Moser DK, Chung ML, et al. Objectively measured, but not self-reported, medication adherence independently predicts event-free survival in patients with heart failure. *J Card Fail* 2008; 14: 203–210.

50. Hurley KM, Black MM, Papas MA, et al. Maternal symptoms of stress, depression, and anxiety are related to nonresponsive feeding styles in a statewide sample of WIC participants. *J Nutr* 2008; 138: 799–805.
51. Leung DY, Lam TH and Chan SS. Three versions of Perceived Stress Scale: validation in a sample of Chinese cardiac patients who smoke. *BMC Public Health* 2010; 10: 513.

52. Middlekauff HR, Nguyen AH, Negrao CE, et al. Impact of acute mental stress on sympathetic nerve activity and regional blood flow in advanced heart failure: implications for ‘triggering’ adverse cardiac events. *Circulation* 1997; 96: 1835–1842.

53. Vasunilashorn S, Glei DA, Weinstein M, et al. Perceived stress and mortality in a Taiwanese older adult population. *Stress* 2013; 16: 600–606.

54. Dickerson SS and Kemeny ME. Acute stressors and cortisol responses: a theoretical integration and synthesis of laboratory research. *Psychol Bull* 2004; 130: 355–391.

55. Bernhagen J. Macrophage migration and function: from recruitment in vascular disease to redox regulation in the immune and neuroendocrine networks. *Antioxid Redox Signal* 2005; 7: 1182–1188.

56. Funder JW. Is aldosterone bad for the heart? *Trends Endocrinol Metab* 2004; 15: 139–142.

57. Funder JW. RALES, EPHESUS and redox. *J Steroid Biochem Mol Biol* 2005; 93: 121–125.

58. Nagata K, Obata K, Xu J, et al. Mineralocorticoid receptor antagonism attenuates cardiac hypertrophy and failure in low-aldosterone hypertensive rats. *Hypertension* 2006; 47: 656–664.

59. Guder G, Bauersachs J, Frantz S, et al. Complementary and incremental mortality risk prediction by cortisol and aldosterone in chronic heart failure. *Circulation* 2007; 115: 1754–1761.

60. Dimsdale JE. Psychological stress and cardiovascular disease. *J Am Coll Cardiol* 2008; 51: 1237–1246.

61. Ohlin B, Nilsson PM, Nilsson JA, et al. Chronic psychosocial stress predicts long-term cardiovascular morbidity and mortality in middle-aged men. *Eur Heart J* 2004; 25: 867–873.

62. Iso H, Date C, Yamamoto A, et al. Perceived mental stress and mortality from cardiovascular disease among Japanese men and women: the Japan Collaborative Cohort Study for Evaluation of Cancer Risk Sponsored by Monbusho (JACC Study). *Circulation* 2002; 106: 1229–1236.

63. Molloy GJ, Perkins-Porras L, Strike PC, et al. Type-D personality and cortisol in survivors of acute coronary syndrome. *Psychosom Med* 2008; 70: 863–868.

64. Macleod J, Davey Smith G, Heslop P, et al. Psychological stress and cardiovascular disease: empirical demonstration of bias in a prospective observational study of Scottish men. *BMJ* 2002; 324: 1247–1251.

65. Nielsen NR, Kristensen TS, Schnohr P, et al. Perceived stress and cause-specific mortality among men and women: results from a prospective cohort study. *Am J Epidemiol* 2008; 168: 481–491; discussion 492–496.

66. Joikinen J and Nordstrom P. HPA axis hyperactivity and cardiovascular mortality in mood disorder inpatients. *J Affect Disord* 2009; 116: 88–92.

67. Andreou E, Alexopoulos EC, Lionis C, et al. Perceived Stress Scale: reliability and validity study in Greece. *Int J Environ Res Public Health* 2011; 8: 3287–3298.

68. Hange D, Mehlig K, Lissner L, et al. Perceived mental stress in women associated with psychosomatic symptoms, but not mortality: observations from the Population Study of Women in Gothenburg, Sweden. *Int J Gen Med* 2013; 6: 307–315.

69. Kojima M, Wakai K, Tokudome S, et al. Perceived psychological stress and colorectal cancer mortality: findings from the Japan Collaborative Cohort Study. *Psychosom Med* 2005; 67: 72–77.

70. Vedhara K, Miles J, Bennett P, et al. An investigation into the relationship between salivary cortisol, stress, anxiety and depression. *Biol Psychol* 2003; 62: 89–96.

71. Hjortskov N, Garde AH, Orbaek P, et al. Evaluation of salivary cortisol as a biomarker of self-reported mental stress in field studies. *Stress Health* 2004; 20: 91–98.

72. Yamaji M, Tsutamoto T, Kawahara C, et al. Serum cortisol as a useful predictor of cardiac events in patients with chronic heart failure: the impact of oxidative stress. *Circ Heart Fail* 2009; 2: 608–615.

73. Whitehead DL, Perkins-Porras L, Strike PC, et al. Cortisol awakening response is elevated in acute coronary syndrome patients with type-D personality. *J Psychosom Res* 2007; 62: 419–425.

74. Barth J, Schumacher M and Herrmann-Lingen C. Depression as a risk factor for mortality in patients with coronary heart disease: a meta-analysis. *Psychosom Med* 2004; 66: 802–813.

75. Van Melle JP, De Jonge P, Spijkerman TA, et al. Prognostic association of depression following myocardial infarction with mortality and cardiovascular events: a meta-analysis. *Psychosom Med* 2004; 66: 814–822.

76. Hammash MH, Hall LA, Lennie TA, et al. Psychometrics of the PHQ-9 as a measure of depressive symptoms in patients with heart failure. *Eur J Cardiovasc Nurs* 2013; 12: 446–453.