J Behav Med (2015) 38:407–415
DOI 10.1007/s10865-014-9615-0

Depressive symptoms and spiritual wellbeing in asymptomatic heart failure patients

Paul J. Mills · Kathleen Wilson · Navaid Iqbal · Fatima Iqbal · Milagros Alvarez · Meredith A. Pung · Katherine Wachmann · Thomas Rutledge · Jeanne Maglione · Sid Zisook · Joel E. Dimsdale · Ottar Lunde · Barry H. Greenberg · Alan Maisel · Ajit Raisinghani · Loki Natarajan · Shamini Jain · David J. Hufford · Laura Redwine

Received: August 11, 2014 / Accepted: December 10, 2014 / Published online: December 23, 2014

Abstract Depression adversely predicts prognosis in individuals with symptomatic heart failure. In some clinical populations, spiritual wellness is considered to be a protective factor against depressive symptoms. This study examined associations among depressive symptoms, spiritual wellbeing, sleep, fatigue, functional capacity, and inflammatory biomarkers in 132 men and women with asymptomatic stage B heart failure (age 66.5 years ± 10.5). Approximately 32 % of the patients scored ≥10 on the Beck Depression Inventory, indicating potentially clinically relevant depressive symptoms. Multiple regression analysis predicting fewer depressive symptoms included the following significant variables: a lower inflammatory score comprised of disease-relevant biomarkers ($p < 0.02$), less fatigue ($p < 0.001$), better sleep ($p < 0.04$), and more spiritual wellbeing ($p < 0.01$) (overall model $F = 26.6$, $p < 0.001$, adjusted R square = 0.629). Further analyses indicated that the meaning ($p < 0.01$) and peace ($p < 0.01$) subscales, but not the faith ($p = 0.332$) subscale, of spiritual wellbeing were independently associated with fewer depressive symptoms. Interventions aimed at increasing spiritual wellbeing in patients lives, and specifically meaning and peace, may be a potential treatment target for depressive symptoms asymptomatic heart failure.

Keywords Depressed mood · Spiritual wellbeing · Heart failure · Inflammation · Sleep · Fatigue

P. J. Mills (✉) · K. Wilson · M. Alvarez · M. A. Pung · K. Wachmann · T. Rutledge · J. Maglione · S. Zisook · J. E. Dimsdale · L. Redwine
Department of Psychiatry, University of California, San Diego, 9500 Gilman Dr. #0804, La Jolla, CA 92093-0804, USA
e-mail: pmills@ucsd.edu

P. J. Mills · S. Jain · D. J. Hufford
Samueli Institute, Alexandria, VA, USA

P. J. Mills · L. Natarajan
Family and Preventive Medicine, University of California, San Diego, La Jolla, CA, USA

N. Iqbal · F. Iqbal · O. Lunde · B. H. Greenberg · A. Maisel · A. Raisinghani
Department of Medicine, University of California, San Diego, La Jolla, CA, USA

S. Zisook
San Diego VA Health Care System, La Jolla, CA, USA

D. J. Hufford
Doctors Kienle Center for Humanistic Medicine, Penn State College of Medicine, Hershey, PA, USA

Introduction

Heart Failure is a major public health concern, affecting 5–6 million Americans, with rates expected to nearly triple over the next three decades as the population ages (Krum and Stewart 2006). It is the end stage of most cardiac anomalies, with the annual number of hospitalizations exceeding 1 million, and U.S. direct costs exceeding $40 billion/year (Desai and Stevenson 2012; Wang et al. 2010).

Depression may play a significant role in the development and progression of heart failure (Pelle et al. 2008; Rutledge et al. 2006) and is a common co-morbid condition in patients with cardiovascular disease. In a meta-analytic review of the literature, we reported that the incidence of Major Depressive Disorder in New York Heart Association class (NYHA) stages I–IV heart failure ranges from 11 to 45 %, depending on heart failure severity (Rutledge et al. 2006). The incidence of clinically significant depressive

symptoms (Beck Depression Inventory ≥10) in symptomatic heart failure is higher, ranging from 36 to 65 %, depending on heart failure severity. Moreover, symptoms of depression among symptomatic heart failure patients are associated with significantly increased risk of cardiovascular hospitalization and mortality after controlling for heart failure severity and left ventricular (LV) ejection fraction (Johnson et al. 2012; Kato et al. 2012). Risk factors associated with depression in heart failure include increasing age, poor social support, poor physical fitness, poor sleep, fatigue, and inflammation (Alosco et al. 2013; Jimenez and Mills 2012; Mills et al. 2009; Shimizu et al. 2013; Sin 2012; Tang et al. 2010) .

Spiritual/religious wellness is of increasing interest in the medical literature (Masters 2007; Mills 2002; Vermandere et al. 2011) and may protect against depressive symptoms. A recent review of the literature, for example, reported that spirituality/religiousness is correlated with better overall mental health, including less depression (Bonelli and Koenig 2013), although such associations have not always been observed (Morgenstern et al. 2011). In patients with symptomatic heart failure, there is a negative correlation between spiritual wellbeing and depression (Whelan-Gales et al. 2009). In chronic symptomatic heart failure, the religion/spirituality component of forgiveness is prospectively related to less depression whereas daily spiritual experiences are linked with higher existential wellbeing (Park et al.2014). In contrast, sense of religious struggle is associated with higher depression and predicts more hospitalization in chronic heart failure (Park et al. 2011). Additionally, symptomatic heart failure patients with lower measures of spiritual wellbeing have worse overall heart failure-related health status (Bekelman et al. 2009).

The American College of Cardiology/American Heart Association (ACC/AHA) heart failure staging system denotes "Stage B patients" as asymptomatic but at high risk for developing symptomatic (Stage C) heart failure. The ACC/AHA heart failure staging system emphasizes both the evolution and the progression of chronic heart failure and seeks to identify and implement early therapeutic interventions to ultimately reduce morbidity and mortality (Hunt American College of, C., and American Heart Association Task Force on Practice G 2005). In this staging system, Stage A consists of patients at high risk of developing heart failure but without structural heart disease or heart failure symptoms (e.g., hypertension, metabolic syndrome). Stage B consists of patients who have developed structural heart disease with specific LV dysfunction that is associated with the development of heart failure but who have never shown signs or symptoms of heart failure (e.g., previous myocardial infarction, asymptomatic valvular disease). Stage C heart failure further includes structural or functional abnormality and exercise limitation from dyspnea or fatigue. Stage D includes severe 'end-stage' heart failure.

The stage B level of disease presents an important therapeutic window into potentially halting disease progression and improving quality of life. Progression from asymptomatic stage B heart failure to symptomatic stage C heart failure is associated with a fivefold increase in mortality risk (Ammar et al. 2007). Since depression is associated with increased cardiovascular morbidity and progression of disease, a better understanding of psychosocial factors associated with depression in this population could provide insight about modifiable factors that could reduce disease progression and benefit health.

Although there has been much research on spirituality and wellbeing in *symptomatic* heart failure, there have been few if any such studies in *pre, asymptomatic* heart failure patients. The purpose of this study was to examine potential associations among depressive symptoms and spiritual wellbeing in an earlier stage of heart failure, stage B patients, which could potentially support novel treatment strategies for depressive symptoms and slow disease progression in this population.

Methods

Study participants

Participants were 18 years or older with AHA/ACC classification Stage B heart failure with a diagnosis for at least 3 months. The sample consisted of 132 men and women. Patients were recruited from the Veterans Affairs San Diego Healthcare System (VASDHS) and the University of California, San Diego (UCSD) Medical Center Cardiology Programs as part of a larger study on the effects of depression on clinical outcomes.

Presence of Stage B heart failure was defined as structural heart disease (based on recommendations and cut-points from the American Society of Echocardiography guidelines (Lang et al. 2005)). Measurements were made by sonographers blinded to participant's study characteristics. Criteria included LV hypertrophy (defined as mean LV wall thickness of septum and posterior wall ≥12 mm), LV enlargement (at least moderate in severity, defined as LV end diastolic diameter ≥64 mm in men or ≥58 mm in women, or LV mass index ≥132 in men or ≥109 in women). In addition, included were presence of LV systolic dysfunction (defined as LV ejection fraction <55 % or wall motion abnormality), LV diastolic dysfunction, asymptomatic valvular heart disease of at least moderate severity, or previous myocardial infarction but without symptoms of heart failure.

Protocol

The protocol was approved by the VASDHS and UCSD Human Subjects Institutional Review Boards. Upon presentation to the laboratory, a blood draw was obtained using a 21 or 23-gauge butterfly needle. Patients performed a 6-min walk test to assess functional capacity (O'Keeffe et al.1998). Left ventricular ejection fraction (%LVEF) was assessed by echocardiography as part of the patient's routine medical evaluation.

Patients completed the following questionnaires:

Depressive symptom severity

Symptoms of depression were assessed with the 21-item Beck Depression Inventory (BDI) where scores $\geq$10 indicate possible clinical depression (Beck 1978). The BDI shows high reliability and structural validity and capacity to discriminate between depressed and non-depressed subjects with broad applicability for research and clinical practice worldwide (Wang and Gorenstein 2013). The BDI assesses symptoms related to sadness, feelings of guilt, perceptions of self-worth, suicidal ideation, and changes in appetite and body weight, among other characteristics. In this cohort, Cronbach's alpha for BDI was good ($\alpha = 0.87$). Subjects were also administered a modified Mood Disorders module of the Structured Clinical Interview for DSM-IV-TR Axis I Disorders, Research Version, Non-Patient Edition (SCID-I-RV N/P) (American Psychiatric Association 1994) to evaluate for possible Major Depressive Disorder. If suspected of having major depression, they were presented with a list of options and referred to their treating physician.

Spiritual wellbeing

The Functional Assessment of Chronic Illness Therapy Spiritual Well-Being Scale (FACIT-sp) was used to assess spiritual wellbeing (Peterman et al. 2002). The FACIT-sp is a psychometrically sound, self-administered 12 item scale designed to measure the extent to which patients experienced spiritual wellbeing over the past week (0 = not at all; 4 = very much). The FACIT-sp was developed using qualitative contributions from patients with chronic life-threatening illnesses. Internal consistency reliability coefficients have ranged from 0.81 to 0.88 and convergent validity estimates show moderate to strong correlations with other measures of spirituality and religiousness (Peterman et al. 2002). Whereas original work with the FACIT-sp examined two factors of meaning/peace and faith (Peterman et al. 2002), more recent studies have utilized a 3-factor solution, namely of meaning, peace, and faith, and shown this to be psychometrically superior to the original two-factor construct as it further discriminates and provides unique variance among components most often associated with quality of life and coping (Bai et al. 2014; Canada et al. 2008; Whitford and Olver 2012). The three-factor model was used in this study and was calculated as follows: meaning (items 2, 3, 5, 8), peace (items 1, 4, 6, 7), and faith (items 9, 10, 11, 12) (Bai et al. 2014; Canada et al. 2008; Haugan 2014). Coefficient alphas for each FACIT-sp subscale in this sample were: meaning $\alpha = 0.76$, peace $\alpha = 0.80$, and faith $\alpha = 0.85$.

Sleep quality

The Pittsburgh Sleep Quality Index (PSQI) was used to assess sleep (Smyth 2000). The PSQI is widely used in sleep research and measures sleep disturbance and usual sleep habits. Its internal reliability and construct validity are high, correlating well with measures of sleep quality and sleep problems (Carpenter and Andrykowski 1998). Component scores include subjective sleep quality, sleep latency, sleep duration, habitual sleep efficiency, sleep disturbances, use of sleeping medication, and daytime dysfunction, and also yields a global score (Buysse et al. 1989). Internal consistency of the PSQI global score in our sample was high with α at 0.84.

Fatigue

The Multidimensional Fatigue Symptom Inventory-Short Form (MFSI-sf) was used to assess total fatigue (Stein et al. 2004). The MFSI-sf has strong psychometric properties and is useful in medically ill and non-medically ill individuals (Donovan et al. 2014). In this cohort, coefficient α for MFSI-sf was 0.87.

Inflammatory markers

Given linkages between inflammation and depression in the heart failure and cardiovascular disease lieterature (Jimenez and Mills 2012; Vaccarino et al. 2007), we assessed a relevant panel of inflammatory biomarkers (Sun et al. 2014), including C-reactive protein (CRP), Interleukin-6 (IL-6), Tumor Necrosis Factor-alpha (TNF-alpha), soluble Intercellular Adhesion Molecule-1 (sICAM-1), and Interleukin-1Receptor Antagonist (IL-1RA). Whole blood was preserved with ethylenediaminetetraacetic acid. Following centrifugation, the plasma was stored at $-80°$ C until assay. Biomarker levels were determined by commercial ELISA (MSD, Rockville, MD). Intra- and inter-assay coefficients were <10 %.

Statistical analyses

All calculations were performed using SPSS (version 22.0) software packages (IBM, Armonk, NY). Results were

considered statistically significant at the $p < 0.05$ level and all tests were two-tailed. Prior to statistical analyses all data were tested for normality and homogeneity of variance using the Kolmogorov–Smirnov test. A multiple regression analysis was run with BDI score as the dependent variable with independent variables entered in blocks: block 1: standard covariates of age, gender, and body mass index (Luchner et al. 2013; Vardeny et al. 2013); block 2: an inflammatory index factor analysis score comprised of circulating levels of CRP, IL-6, TNF-alpha, sICAM-1, IL-1RA (SPSS Dimension Reduction factor analysis program, Eigenvalue 2.431; 48.6 % of variance), %LVEF, and 6-min walk test; block 3: fatigue; block 4: sleep; block 5: spiritual wellbeing. In addition, we conducted an exploratory longitudinal regression analysis of a subset of 24 patients for whom BDI was available at 12-months post initial testing.

Results

Table 1 presents biological, medical and inflammatory biomarker characteristics whereas Table 2 presents psychosocial characteristics of the study subjects. Approximately 32 % of the stage B patients scored ≥10 on the BDI, indicating potentially clinically relevant depressive symptoms. At the time of study, 12 patients were determined to meet criteria for major depression. Table 3 presents bivariate correlations among the psychosocial instruments.

The multiple regression analysis predicting depressive symptoms was comprised of the following significant variables: an inflammatory index factor analysis score comprised of circulating levels of CRP, IL-6, TNF-alpha, sICAM-1, IL-1RA ($p < 0.02$), fatigue ($p < 0.001$), sleep ($p < 0.04$), and spiritual wellbeing ($p < 0.01$) (overall model $F = 26.6$, $p < 0.001$, adjusted R square $= 0.629$) (Table 4). Further regression analysis including the three FACIT-sp subscales in the last variable block yielded a significant contribution for the meaning subscale (standardized beta $= -0.343$, $p < 0.01$) and peace subscale (standardized beta $= -0.252$, $p < 0.01$) but not for the faith subscale (standardized beta $= -0.071$, $p = 0.332$).

A multiple regression analysis in the subgroup of patients for whom 12-month BDI was available, and using predictor variables age, gender, body mass index, BDI score at baseline, and spiritual wellbeing at baseline, showed these significant variables: depressive symptoms at baseline (standardized beta $= 0.635$, $p < 0.001$) and total spiritual wellbeing (standardized beta $= -0.482$, $p < 0.01$). Follow-up analysis with the three FACIT-sp subscales yielded a significant contribution for the meaning (standardized beta $= -0.511$, $p < 0.01$) and peace subscales (standardized beta $= -0.357$, $p < 0.01$) but not for the faith subscale (standardized beta $= 0.011$, $p = 0.822$).

Table 1 Sociodemographic, medical, and inflammatory biomarker characteristics of the study subjects (Mean ± SD or percentage value)

Age (years)	66.5 (10.5)
Body mass index (kg/m^2)	30.1 (4.7)
Gender (% men)	93 %
Race (%)	
Asian	4
African-American	11
Native Hawaiian/Pacific Islander	1
Caucasian	80
Native-American	2
More than one race	2
Systolic blood pressure (mmHg)	134.5 (19.6)
Diastolic blood pressure (mmHg)	76.2 (12.5)
Left ventricular ejection fraction (%)	64.8 (8.95)
6-min walk test (meter)	1,085.5 (309)
Concomitant disease (%)	
Diabetes mellitus	31.5
Myocardial infarction	16
Medications (%)	
ACE-blocking agents	38.7
Beta blockers	43.2
Calcium channel blockers score	19.9
Statin	53.1
Aspirin	39.7
Diuretics	31.5
Anti-arrhythmics	4.1
Warfarin	11.3
Digoxin	2.1
Inflammatory biomarkers	
CRP (mg/dl)	5.16 (7.14)
IL-6 (pg/ml)	2.07 (1.78)
TNF-alpha (pg/ml)	4.71 (3.46)
sICAM-1 (ng/ml)	373.9 (172)
IL-1RA (pg/ml)	283.3 (221)

Discussion

The presence of depressive symptoms in cardiovascular diseases such as heart failure is associated with significantly increased risk of cardiovascular hospitalization and mortality (Johnson et al. 2012; Kato et al. 2012). Typical risk factors associated with depression in heart failure include increasing age, poor physical fitness, poor sleep, fatigue, and inflammation (Alosco et al. 2013; Jimenez and Mills 2012; Kupper et al. 2012; Mills et al. 2009; Shimizu et al. 2013; Sin 2012), factors that were controlled for in

Table 2 Psychosocial characteristics of the study subjects (Mean ± SD)

Beck depression inventory (BDI)	8.51 (7.1)
Functional assessment of chronic illness therapy	
Spiritual well-being scale (FACIT-sp)	33.52 (9.9)
Meaning subscale	9.95 (2.60)
Peace subscale	8.98 (2.61)
Faith subscale	9.71 (4.89)
Pittsburgh sleep quality index (PSQI)	4.00 (2.23)
Multidimensional fatigue symptom inventory-short form (MFSI-sf)	31.13 (21.6)

this study. For ACC/AHA Stage B heart failure patients, finding correlates of depressive symptoms is particularly important as an avenue for potentially forestalling development of symptomatic Stage C disease, which is significantly associated with reduced quality of life and increased morbidity and mortality (Ammar et al. 2007).

In this study we used the FACIT-sp as a measure of spiritual wellbeing—not spirituality per se—and found that self-rated spiritual wellbeing is strongly and independently associated with fewer depressive symptoms in stage B patients. More specifically, we found that it was the spiritual feelings of meaning and peace but not faith that were associated with fewer depressive symptoms. In the FACIT-sp, the meaning subscale consists of four items such as "I have a reason for living" and "I feel a sense of purpose in my life"; the peace subscale consists of four items such as "I feel peaceful" and "I feel a sense of harmony in myself"; the faith subscale contains four items including "I find comfort in my faith or spiritual beliefs" and "I know that whatever happens with my illness things will be okay". These findings in asymptomatic patients are consistent with a study in symptomatic NYHA class II-IV heart failure patients which reported that a greater sense of meaning and peace was associated with fewer depressive symptoms as assessed by the Geriatric Depression Scale-Short Form (Bekelman et al. 2007). In a group of cancer survivors, using the FACIT-sp, Canada et al. reported that the peace factor was related to better mental health, the meaning factor was related to both better physical and mental health, and the faith factor was negatively associated with mental health (Canada et al. 2008). In our study, faith was unrelated with mental health. Furthermore, in our longitudinal analysis of a subset of patients for whom twelve-month BDI was available, we found that in addition to depressive symptoms at baseline, spiritual wellbeing at baseline significantly and independently predicted fewer depressive symptoms a year later.

The FACIT-sp was chosen as a measure of spiritual wellbeing because it is widely used and validated and we wanted to be able to examine our findings in the context of the existing literature. It has been suggested that a common problem in spiritual wellbeing and health research is that some instruments conflate psychological and spiritual variables, as well as often lack clarity distinguishing spiritual versus religious concepts (Hufford 2010). It is not always clear in the literature how such overlapping components of psychological health with spiritual wellbeing are determined. Depression questions in the BDI, for example, do not appear to specifically measure meaning and peace and it is more likely that the relationship is indirectly mediated through psychological factors derived from meaning and peace (e.g. gratitude, resilience). Recent research by Lindeman et al. (2012) show that spirituality is strongly related to "inner peace and finding life exciting and purposeful" but not independent of general mental and physical health (Lindeman et al. 2012). This supports the idea that the FACIT-sp' meaning and peace subscales have a distinctly spiritual association with important quality of life factors. In related work, Peterman et al. found that the FACIT-sp faith subscale was correlated with religious activity and intrinsic religiousness, whereas the combined

Table 3 Bivariate correlations among psychosocial characteristics

	FACIT-sp total score	FACIT-sp meaning subscale	FACIT-sp peace subscale	FACIT-sp faith subscale	PSQI	MFSI-sf
Beck depression inventory (BDI)	−0.580***	−0.524***	−0.486***	−0.261***	0.394***	0.757***
Functional assessment of chronic illness therapy spiritual well-being scale (FACIT-sp)		0.697***	0.713***	0.801***	−0.202**	−0.569***
Meaning subscale			0.681***	0.389***	−0.201**	−0.484***
Peace subscale				0.377***	−0.169*	−0.471***
Faith subscale					−0.023	−0.196***
Pittsburgh sleep quality index (PSQI)						0.474***

* $p < 0.05$

** $p < 0.01$

*** $p < 0.001$

Table 4 Predictors of BDI depressive symptoms

Variables in each regression block	Significant individual predictor variables with standardized ß coefficient and *p* value	Model F, adjusted R^2, *p* value
1. Age, BMI, gender	–	NS
2. Age, BMI, gender, inflammatory index, 6-min walk test, %LVEF	Inflammatory index (0.241, 0.006)	2.25, 0.048, 0.042
3. Age, BMI, gender, inflammatory index, 6-min walk test, %LVEF, MFSI-sf	Inflammatory index (0.126, 0.030) Fatigue (0.739, <0.001)	29.8, 0.577, <0.001
4. Age, BMI, gender, inflammatory index, 6-min walk test, %LVEF, MFSI-sf, PSQI	Inflammatory index (0.232, 0.022) Fatigue (0.678, <0.001) Sleep (0.125, 0.051)	27.1, 0.585, <0.001
5. Age, BMI, gender, inflammatory index, 6-min walk test, %LVEF, MFSI-sf, PSQI, FACIT-sp	Inflammatory index (0.157, 0.013) Fatigue (0.573, <0.001) Sleep (0.130, 0.036) Spiritual wellbeing (−0.194, 0.002)	26.6, 0.629, <0.001

BMI body mass index, *%LVEF* left ventricular ejection fraction, *inflammatory index* factor score of CRP, IL-6, TNF-alpha, sICAM-1, IL1-RA, *PSQI* Pittsburgh sleep quality index, *MFSI-sf* multidimensional fatigue symptom inventory-short form, *FACIT-sp* functional assessment of chronic illness therapy spiritual well-being scale

meaning and peace subscale was not correlated with existing measures of religiosity but rather to measures that assess purpose in life (Peterman et al. 2013). Distinguishing specific constructs of meaning, peace and faith is increasingly relevant to understanding wellbeing (Saguil and Phelps 2012; Skarupski et al. 2013).

Traditional treatment approaches for depression in cardiovascular diseases include pharmacotherapy, psychotherapy, and exercise. The success of these methods varies widely due, in part, to poor adherence related to factors such as adverse side effects and difficulty maintaining intervention demands (Gelhorn et al. 2011; Jimenez et al. 2012; Shelton 2009; Smart and Murison 2013). Spirituality/religiousness predicts less cardiovascular related mortality and morbidity (Masters and Hooker 2013). Spirituality-based interventions for depression in cardiovascular disease populations have shown promising outcomes and demonstrate good adherence in several pilot studies. Delaney et al. for example, reported reduced depression scores among community-dwelling patients with cardiovascular disease following an individualized 1-month spirituality-based intervention on health-related outcomes (Delaney et al. 2011). Warber et al. (2011) examined the effects of a nondenominational spiritual retreat on depression and other measures of wellbeing in post acute coronary syndrome patients. The 4-day spiritual retreat included guided imagery, meditation, drumming, journal writing, and nature-based activities. A control intervention included nutrition education, exercise, and stress management. Both retreat groups received follow-up phone coaching biweekly for up to 3 months. Compared with the control group, patients assigned to the spiritual retreat group had significantly lower depression scores post-intervention, which were maintained 3 months later. As noted earlier, findings also suggest that specifically religious interventions may not be especially helpful for most people and may be negative for some (Lindeman et al. 2012).

Therapeutic approaches that are consistent with the increasing recognition of the need to embrace multidisciplinary therapeutic approaches in heart failure that include spirituality as part of more routine psychosocial support could be beneficial (Naghi et al. 2012). Included in this broad based approach is the importance of resilience in relation to health (Steptoe et al. 2009). Indeed, spiritual wellbeing is a strong predictor of resilience (Min et al. 2013; Vahia et al. 2011), and therefore therapeutic approaches that enhance spiritual wellbeing may bolster resilience to stressful events and decrease the likelihood of developing stress-induced depression, and positively impact health (Southwick et al.2005). More recent findings also point to the role of gratitude, which is viewed as a component of spiritual wellbeing as well as a psychosocial resource, in alleviating depression and struggles and improving quality of life in heart failure (Sacco et al. 2014). In addition to supporting improved quality of life, the ability to successfully reduce depression also has positive influences on slowing disease process by supporting better adherence to medical therapy (Corottoet al. 2013; Jimenez et al. 2012).

Limitations of our study include the limited demographics of mostly white older men, so generalizability is limited. Additionally, few people in the sample met criteria for major depression so we were not able to examine how important a factor spiritual wellbeing is for major depression over and above depressive symptoms. Finally, we

recognize that our regression analysis of patients who had twelve-month BDI scores was limited due to the small sample size, but we present it as purely exploratory and as a potential direction for future research.

Summary

Consistent with prior studies, these findings suggest that among factors known to be associated with depressive symptoms in cardiac populations, higher ratings of spiritual wellbeing are independently associated with fewer depressive symptoms in stage B heart failure patients. Prior intervention strategies that increase a sense of spiritual wellbeing have been shown to be beneficial to reduce depressed mood in heart failure patients; specifically, focusing on increasing meaning and peace in patients' lives may be a potential novel treatment target for depressive symptoms in this population. Given the significant role of depression in the development and progression of heart failure (Pelle et al. 2008; Rutledge et al. 2006), such successful interventions would also play a significant role in reducing morbidity and mortality. This study population largely consisted of people with low to moderate levels of depressive symptoms, with only a small proportion having major depression. A possible future direction of this work would be to look at whether interventions that enhance spiritual wellbeing and/or meaning and peace can reduce and/or protect against the development of major depression.

Acknowledgments This work was supported by Grants HL-073355, HL-096784, and 5UL1 TR000100-05 from the National Institutes of Health.

Conflict of interest Author Paul J. Mills, Author Kathleen Wilson, Author Navaid Iqbal, Author Fatima Iqbal, Author Milagros Alvarez, Author Meredith A. Pung, Author Katherine Wachmann, Author Thomas Rutledge, Author Jeanne Maglione, Author Sid Zisook, Author Joel Dimsdale, Author Ottar Lunde, Author Barry H. Greenberg, Author Alan Maisel, Author Ajit Raisinghani, Author Loki Natarajan, Author Shamini Jain, Author David J. Hufford, and Author Laura Redwine declare that they have no conflict of interest.

Human and Animal Rights and Informed Consent All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2000 (Forster et al. 2001). Informed consent was obtained from all patients for being included in the study.

References

Alosco, M. L., Spitznagel, M. B., van Dulmen, M., Raz, N., Cohen, R., Sweet, L. H., & Gunstad, J. (2013). Depressive symptomatology, exercise adherence, and fitness are associated with reduced cognitive performance in heart failure. *Journal of Aging and Health, 25*, 459–477. doi:10.1177/0898264312474039

American Psychiatric Association. (1994). *Diagnostic and statistical manual of mental disorders* (4th ed.). Washington DC: American Psychiatric Association.

Ammar, K. A., Jacobsen, S. J., Mahoney, D. W., Kors, J. A., Redfield, M. M., Burnett, J. C, Jr, & Rodeheffer, R. J. (2007). Prevalence and prognostic significance of heart failure stages: Application of the American college of cardiology/American heart association heart failure staging criteria in the community. *Circulation, 115*, 1563–1570. doi:10.1161/106.666818

Bai, M., Lazenby, M., Jeon, S., Dixon, J., & McCorkle, R. (2014). Exploring the relationship between spiritual well-being and quality of life among patients newly diagnosed with advanced cancer. *Palliative and Supportive Care,*. doi:10.1017/S1478951514000820

Beck, A. T. (1978). *Depression inventory*. Philadelphia: Center for Cognitive Therapy.

Bekelman, D. B., Dy, S. M., Becker, D. M., Wittstein, I. S., Hendricks, D. E., Yamashita, T. E., & Gottlieb, S. H. (2007). Spiritual well-being and depression in patients with heart failure. *Journal of General Internal Medicine, 22*, 470–477. doi:10.1007/s11606-006-0044-9

Bekelman, D. B., Rumsfeld, J. S., Havranek, E. P., Yamashita, T. E., Hutt, E., Gottlieb, S. H., & Kutner, J. S. (2009). Symptom burden, depression, and spiritual well-being: A comparison of heart failure and advanced cancer patients. *Journal of General Internal Medicine, 24*, 592–598. doi:10.1007/s11606-009-0931-y

Bonelli, R. M., & Koenig, H. G. (2013). Mental disorders, religion and spirituality 1990 to 2010: A systematic evidence-based review. *Journal of Religion and Health, 52*, 657–673. doi:10.1007/s10943-013-9691-4

Buysse, D. J., Reynolds, C. F, 3rd, Monk, T. H., Berman, S. R., & Kupfer, D. J. (1989). The Pittsburgh sleep quality index: A new instrument for psychiatric practice and research. *Psychiatry Research, 28*, 193–213.

Canada, A. L., Murphy, P. E., Fitchett, G., Peterman, A. H., & Schover, L. R. (2008). A 3-factor model for the FACIT-Sp. *Psychooncology, 17*, 908–916. doi:10.1002/pon.1307

Carpenter, J. S., & Andrykowski, M. A. (1998). Psychometric evaluation of the Pittsburgh Sleep Quality Index. *Journal of Psychosomatic Research, 45*, 5–13.

Corotto, P. S., McCarey, M. M., Adams, S., Khazanie, P., & Whellan, D. J. (2013). Heart failure patient adherence: Epidemiology, cause, and treatment. *Heart Failure Clinics, 9*, 49–58. doi:10.1016/j.hfc.2012.09.004

Delaney, C., Barrere, C., & Helming, M. (2011). The influence of a spirituality-based intervention on quality of life, depression, and anxiety in community-dwelling adults with cardiovascular disease: A pilot study. *Journal of Holistic Nursing, 29*, 21–32. doi:10.1177/0898010110378356

Desai, A. S., & Stevenson, L. W. (2012). Rehospitalization for heart failure: Predict or prevent? *Circulation, 126*, 501–506. doi:10.1161/112.125435

Donovan, K. A., Stein, K. D., Lee, M., Leach, C. R., Ilozumba, O., & Jacobsen, P. B. (2014). Systematic review of the multidimensional fatigue symptom inventory-short form. *Supportive Care in Cancer,*. doi:10.1007/s00520-014-2389-7

Forster, H. P., Emanuel, E., & Grady, C. (2001). The 2000 revision of the declaration of Helsinki: A step forward or more confusion? *Lancet, 358*, 1449–1453. doi:10.1016/S0140-6736(01)06534-5

Gelhorn, H. L., Sexton, C. C., & Classi, P. M. (2011). Patient preferences for treatment of major depressive disorder and the impact on health outcomes: A systematic review. *The Primary Care Companion for CNS Disorders,*. doi:10.4088/PCC.11r01161

Haugan, G. (2014). The FACIT-Sp spiritual well-being scale: An investigation of the dimensionality, reliability and construct validity in a cognitively intact nursing home population. *Scandinavian Journal of Caring Science,*. doi:10.1111/scs.12123

Hufford, D. (2010). Strengths and weaknesses in the field of spirituality and health. In William Grassie (Ed.), *Advanced methodologies in the scientific study of religion and spirituality* (pp. 73–116). Philadelphia: Metanexus Institute.

Hunt, S. A., & American College of, C., & American Heart Association Task Force on Practice, G. (2005). ACC/AHA 2005 guideline update for the diagnosis and management of chronic heart failure in the adult: A report of the American college of cardiology/American heart association task force on practice guidelines (writing committee to update the 2001 Guidelines for the evaluation and management of heart failure). *Journal of the American College of Cardiology, 46*, e1–e82. doi:10.1016/j.jacc.2005.08.022

Jimenez, J. A., & Mills, P. J. (2012). Neuroimmune mechanisms of depression in heart failure. *Methods in Molecular Biology, 934*, 165–182. doi:10.1007/978-1-62703-071-7_9

Jimenez, J. A., Redwine, L. L., Rutledge, T. R., Dimsdale, J. E., Pung, M. A., Ziegler, M. G., & Mills, P. J. (2012). Depression ratings and antidepressant use among outpatient heart failure patients: Implications for the screening and treatment of depression. *The International Journal of Psychiatry in Medicine, 44*, 315–334.

Johnson, T. J., Basu, S., Pisani, B. A., Avery, E. F., Mendez, J. C., Calvin, J. E, Jr, & Powell, L. H. (2012). Depression predicts repeated heart failure hospitalizations. *Journal of Cardiac Failure, 18*, 246–252. doi:10.1016/.2011.12.005

Kato, N., Kinugawa, K., Shiga, T., Hatano, M., Takeda, N., Imai, Y., & Nagai, R. (2012). Depressive symptoms are common and associated with adverse clinical outcomes in heart failure with reduced and preserved ejection fraction. *Journal of Cardiology, 60*, 23–30. doi:10.1016/.2012.01.010

Krum, H., & Stewart, S. (2006). Chronic heart failure: Time to recognize this major public health problem. *Medical Journal of Australia, 184*, 147–148.

Kupper, N., Widdershoven, J. W., & Pedersen, S. S. (2012). Cognitive/affective and somatic/affective symptom dimensions of depression are associated with current and future inflammation in heart failure patients. *Journal of Affective Disorders, 136*, 567–576. doi:10.1016/j.jad.2011.10.029

Lang, R. M., Bierig, M., Devereux, R. B., Flachskampf, F. A., Foster, E., Pellikka, P. A., & European Association of, E. (2005). Recommendations for chamber quantification: A report from the American society of echocardiography's guidelines and standards committee and the chamber quantification writing group, developed in conjunction with the European association of echocardiography, a branch of the European society of cardiology. *Journal of the American Society of Echocardiography, 18*, 1440–1463. doi:10.1016/.2005.10.005

Lindeman, M., Blomqvist, S., & Takada, M. (2012). Distinguishing spirituality from other constructs: Not a matter of well-being but of belief in supernatural spirits. *The Journal of Nervous and Mental Disease, 200*, 167–173. doi:10.1097/NMD.0b013e3182439719

Luchner, A., Behrens, G., Stritzke, J., Markus, M., Stark, K., Peters, A., & Heid, I. M. (2013). Long-term pattern of brain natriuretic peptide and N-terminal pro brain natriuretic peptide and its determinants in the general population: Contribution of age, gender, and cardiac and extra-cardiac factors. *European Journal of Heart Failure, 15*, 859–867. doi:10.1093/eurjhf/hft048

Masters, K. S. (2007). Religiosity/spirituality and behavioral medicine: Investigations concerning the integration of spirit with body. *Journal of Behavioral Medicine, 30*, 287–289. doi:10.1007/s10865-007-9116-5

Masters, K. S., & Hooker, S. A. (2013). Religiousness/spirituality, cardiovascular disease, and cancer: Cultural integration for health research and intervention. *Journal of Consulting and Clinical Psychology, 81*, 206–216. doi:10.1037/a0030813

Mills, P. J. (2002). Spirituality, religiousness, and health: From research to clinical practice. *Annals of Behavioral Medicine, 24*, 1–2.

Mills, P. J., Dimsdale, J. E., Natarajan, L., Ziegler, M. G., Maisel, A., & Greenberg, B. H. (2009). Sleep and health-related quality of life in heart failure. *Congestive Heart Failure, 15*, 228–233. doi:10.1111/j.1751-7133.2009.00106.x

Min, J. A., Jung, Y. E., Kim, D. J., Yim, H. W., Kim, J. J., Kim, T. S., & Chae, J. H. (2013). Characteristics associated with low resilience in patients with depression and/or anxiety disorders. *Quality of Life Research, 22*, 231–241. doi:10.1007/s11136-012-0153-3

Morgenstern, L. B., Sanchez, B. N., Skolarus, L. E., Garcia, N., Risser, J. M., Wing, J. J., & Lisabeth, L. D. (2011). Fatalism, optimism, spirituality, depressive symptoms, and stroke outcome: A population-based analysis. *Stroke, 42*, 3518–3523. doi:10.1161/STROKEAHA.111.625491

Naghi, J. J., Philip, K. J., Phan, A., Cleenewerck, L., & Schwarz, E. R. (2012). The effects of spirituality and religion on outcomes in patients with chronic heart failure. *Journal of Religion and Health, 51*, 1124–1136.

O'Keeffe, S. T., Lye, M., Donnellan, C., & Carmichael, D. N. (1998). Reproducibility and responsiveness of quality of life assessment and six minute walk test in elderly heart failure patients. *Heart, 80*, 377–382.

Park, C. L., Lim, H., Newlon, M., Suresh, D. P., & Bliss, D. E. (2014). Dimensions of religiousness and spirituality as predictors of well-being in advanced chronic heart failure patients. *Journal of Religion and Health, 53*, 579–590. doi:10.1007/s10943-013-9714-1

Park, C. L., Wortmann, J. H., & Edmondson, D. (2011). Religious struggle as a predictor of subsequent mental and physical well-being in advanced heart failure patients. *Journal of Behavioral Medicine, 34*, 426–436. doi:10.1007/s10865-011-9315-y

Pelle, A. J., Gidron, Y. Y., Szabo, B. M., & Denollet, J. (2008). Psychological predictors of prognosis in chronic heart failure. *Journal of Cardiac Failure, 14*, 341–350.

Peterman, A. H., Fitchett, G., Brady, M. J., Hernandez, L., & Cella, D. (2002). Measuring spiritual well-being in people with cancer: The functional assessment of chronic illness therapy–spiritual well-being scale (FACIT-Sp). *Annals of Behavioral Medicine, 24*, 49–58.

Peterman, A. H., Reeve, C. L., Winford, E. C., Cotton, S., Salsman, J. M., McQuellon, R., & Campbell, C. (2013). Measuring meaning and peace with the FACIT-spiritual well-being scale: Distinction without a difference? *Psychological Assessment,*. doi:10.1037/a0034805

Rutledge, T., Reis, V. A., Linke, S. E., Greenberg, B. H., & Mills, P. J. (2006). Depression in heart failure a meta-analytic review of prevalence, intervention effects, and associations with clinical outcomes. *Journal of the American College of Cardiology, 48*, 1527–1537. doi:10.1016/.2006.06.055

Sacco, S. J., Park, C. L., Suresh, D. P., & Bliss, D. (2014). Living with heart failure: Psychosocial resources, meaning, gratitude and well-being. *Heart and Lung, 43*, 213–218. doi:10.1016/j.hrtlng.2014.01.012

Saguil, A., & Phelps, K. (2012). The spiritual assessment. *American Family Physician, 86*, 546–550.

Shelton, C. (2009). Factors impacting the selection of antidepressant treatment in patients with major depressive disorder at risk for nonadherence. *CNS Spectrums, 14*, 15–19.

Shimizu, Y., Suzuki, M., Okumura, H., & Yamada, S. (2013). Risk factors for onset of depression after heart failure hospitalization. *Journal of Cardiology,*. doi:10.1016/.2013.11.003

Sin, M. K. (2012). Personal characteristics predictive of depressive symptoms in Hispanics with heart failure. *Issues in Mental Health Nursing, 33*, 522–527. doi:10.3109/01612840.2012.687438

Skarupski, K. A., Fitchett, G., Evans, D. A., & Mendes de Leon, C. F. (2013). Race differences in the association of spiritual experiences and life satisfaction in older age. *Aging and Mental Health, 17*, 888–895. doi:10.1080/13607863.2013.793285

Smart, N. A., & Murison, R. (2013). Rate of change in physical fitness and quality of life and depression following exercise training in patients with congestive heart failure. *Congestive Heart Failure, 19*, 1–5. doi:10.1111/chf.12002

Smyth, C. (2000). The Pittsburgh sleep quality index (PSQI). *Insight, 25*, 97–98.

Southwick, S. M., Vythilingam, M., & Charney, D. S. (2005). The psychobiology of depression and resilience to stress: Implications for prevention and treatment. *Annual Review of Clinical Psychology, 1*, 255–291. doi:10.1146/.1.102803.143948

Stein, K. D., Jacobsen, P. B., Blanchard, C. M., & Thors, C. (2004). Further validation of the multidimensional fatigue symptom inventory-short form. *Journal of Pain and Symptom Management, 27*, 14–23.

Steptoe, A., Dockray, S., & Wardle, J. (2009). Positive affect and psychobiological processes relevant to health. *Journal of Personality, 77*, 1747–1776. doi:10.1111/j.1467-6494.2009.00599.x

Sun, R. R., Lu, L., Liu, M., Cao, Y., Li, X. C., Liu, H., & Zhang, P. Y. (2014). Biomarkers and heart disease. *European Review for Medical and Pharmacological Sciences, 18*, 2927–2935.

Tang, W. R., Yu, C. Y., & Yeh, S. J. (2010). Fatigue and its related factors in patients with chronic heart failure. *Journal of Clinical Nursing, 19*, 69–78. doi:10.1111/j.1365-2702.2009.02959.x

Vaccarino, V., Johnson, B. D., Sheps, D. S., Reis, S. E., Kelsey, S. F., Bittner, V., & Blood, I. (2007). Depression, inflammation, and incident cardiovascular disease in women with suspected coronary ischemia: The National heart, lung, and blood institute-sponsored WISE study. *Journal of the American College of Cardiology, 50*, 2044–2050. doi:10.1016/j.jacc.2007.07.069

Vahia, I. V., Depp, C. A., Palmer, B. W., Fellows, I., Golshan, S., Thompson, W., & Jeste, D. V. (2011). Correlates of spirituality in older women. *Aging and Mental Health, 15*, 97–102. doi:10.1080/13607863.2010.501069

Vardeny, O., Gupta, D. K., Claggett, B., Burke, S., Shah, A., Loehr, L., & Solomon, S. D. (2013). Insulin resistance and incident heart failure the ARIC study (atherosclerosis risk in communities). *Journal of the American College of Cardiology: Heart Failure, 1*, 531–536. doi:10.1016/.2013.07.006

Vermandere, M., De Lepeleire, J., Smeets, L., Hannes, K., Van Mechelen, W., Warmenhoven, F., & Aertgeerts, B. (2011). Spirituality in general practice: A qualitative evidence synthesis. *British Journal of General Practice, 61*, e749–e760. doi:10.3399/bjgp11X606663

Wang, Y. P., & Gorenstein, C. (2013). Psychometric properties of the beck depression inventory-II: A comprehensive review. *Revista Brasileira de Psiquiatria, 35*, 416–431. doi:10.1590/1516-4446-2012-1048

Wang, G., Zhang, Z., Ayala, C., Wall, H. K., & Fang, J. (2010). Costs of heart failure-related hospitalizations in patients aged 18 to 64 years. *The American Journal of Managed Care, 16*, 769–776.

Warber, S. L., Ingerman, S., Moura, V. L., Wunder, J., Northrop, A., Gillespie, B. W., & Rubenfire, M. (2011). Healing the heart: A randomized pilot study of a spiritual retreat for depression in acute coronary syndrome patients. *Explore (NY), 7*, 222–233. doi:10.1016/.2011.04.002

Whelan-Gales, M. A., Quinn Griffin, M. T., Maloni, J., & Fitzpatrick, J. J. (2009). Spiritual well-being, spiritual practices, and depressive symptoms among elderly patients hospitalized with acute heart failure. *Geriatric Nursing, 30*, 312–317. doi:10.1016/.2009.04.001

Whitford, H. S., & Olver, I. N. (2012). The multidimensionality of spiritual wellbeing: Peace, meaning, and faith and their association with quality of life and coping in oncology. *Psychooncology, 21*, 602–610. doi:10.1002/pon.1937