ORIGINAL ARTICLE

Pilot Randomized Study of a Gratitude Journaling Intervention on Heart Rate Variability and Inflammatory Biomarkers in Patients With Stage B Heart Failure

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ABSTRACT

Objective: Stage B, asymptomatic heart failure (HF) presents a therapeutic window for attenuating disease progression and development of HF symptoms, and improving quality of life. Gratitude, the practice of appreciating positive life features, is highly related to quality of life, leading to development of promising clinical interventions. However, few gratitude studies have investigated objective measures of physical health; most relied on self-report measures. We conducted a pilot study in Stage B HF patients to examine whether gratitude journaling improved biomarkers related to HF prognosis.

Methods: Patients (n = 70; mean [standard deviation] age = 66.2 [7.6]years) were randomized to an 8-week gratitude journaling intervention or treatment as usual. Baseline (T1) assessments included the six-item Gratitude Questionnaire, resting heart rate variability (HRV), and an inflammatory biomarker index. At T2 (midintervention), the six-item Gratitude Questionnaire was measured. At T3 (postintervention), T1 measures were repeated but also included a gratitude journaling task.

Results: The gratitude intervention was associated with improved trait gratitude scores (F = 6.0, p = .017, η^2 = 0.10), reduced inflammatory biomarker index score over time (F = 9.7, p = .004, η^2 = 0.21), and increased parasympathetic HRV responses during the gratitude journaling task (F = 4.2, p = .036, η^2 = 0.15), compared with treatment as usual. However, there were no resting preintervention to postintervention group differences in HRV (p values > .10).

Conclusions: Gratitude journaling may improve biomarkers related to HF morbidity, such as reduced inflammation; large-scale studies with active control conditions are needed to confirm these findings.

Trial Registration: Clinicaltrials.gov identifier: NCT01615094

Key words: heart failure, heart rate variability, inflammatory, gratitude, intervention.

INTRODUCTION

Heart failure (HF) is the end stage of most cardiac anomalies, affecting more than 5 million Americans, with rates expected to triple over the next 30 years as the population ages (1). The yearly number of hospitalizations for HF exceeds 1 million in the United States, and medical costs are more than $40 billion per year (2,3). A staging system developed by the American College of Cardiology in cooperation with the American Heart Association emphasizes the evolution and progression of chronic HF and the need for early intervention to prevent disease advancement and ultimately to diminish morbidity and mortality (4). In this staging system, patients with "Stage A" are at high risk for developing HF but do not have a structural disorder of the

ANCOVA = analysis of co-variance, **ANS** = autonomic nervous system, **BMI** = body mass index, **CRP** = C-reactive protein, **CVD** = cardiovascular disease, **ECG** = electrocardiogram, **GQ-6** = 6-item Gratitude Questionnaire, **HF** = heart failure, **HRV** = heart rate variability, **IL-6** = interleukin-6, **LTEQ** = Leisure-Time Exercise Questionnaire, **LV** = left ventricular, **MI** = myocardial infarction, **RMSSD** = root mean square successive differences, **SD1** = standard deviation of the distances of the RRi to the slope of the line, **sTNFr1** = soluble tumor necrosis factor-α receptor 1, **TAU** = treatment as usual, **TNF-α** = tumor necrosis factor α

SDC Supplemental Content

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heart. Patients with "Stage B" have a structural abnormality of the heart but are asymptomatic and are at high risk for developing symptomatic ("Stage C") HF. "Stage D" consists of advanced structural heart disease and symptoms even at rest. Progression from Stage B asymptomatic HF to Stage C symptomatic HF is associated with a five-fold increase in mortality risk (5). Thus, the Stage B level of disease presents an important therapeutic window for potentially halting disease progression, forestalling the development of HF symptoms and maintaining quality of life.

In the area of behavioral cardiology (6), there is increasing focus on relationships among positive psychological attributes such as gratitude, the potential mechanisms of action, and associated clinical outcomes (7–9). Gratitude is suggested to be an aspect of a broader life orientation toward noticing and appreciating the positive features of life (10). A body of evidence has emerged suggesting that gratitude is strongly related to well-being (e.g., mood, satisfaction with life, and health-related quality of life), leading to the development of promising clinical interventions (e.g., Refs. (11,12). A number of studies have examined gratitude interventions using a variety of approaches. Much of the existing research on gratitude has focused primarily on outcomes associated with psychological factors and social interactions. Emmons and McCullough (12) originally proposed gratitude diaries as a useful intervention for well-being enhancement. More recent work suggests it to be as effective as cognitive behavioral techniques used in clinical therapies for improving psychological well-being (12,13). Few studies have investigated the relationship between gratitude and physical health, particularly in clinical populations, and most have relied on self-report rather than objective measures of physical health. For example, a cross-sectional study from a nonclinical population of 962 individuals ranging in age from 19 to 84 years found that gratitude scores positively related to self-reported physical health. However, in a cross-sectional investigation of asymptomatic patients with HF, we found a relationship between gratitude levels and an index of inflammatory biomarkers known to be associated with adverse cardiac remodeling and progression to HF (14). There have been even fewer intervention studies examining the effects of increased gratitude on physical health. Emmons and McCullough found that people who were requested to list items for which they were grateful over a 10-week period reported fewer symptoms of physical illness than did controls. Further investigations using objective measures of physical health in randomized controlled trials (RCTs) are necessary to understand the potential disease-buffering effects of gratitude.

Research evidence suggests that psychological factors such as chronic stress and depression are related to alterations in autonomic nervous system (ANS) function (15). In turn, it has long been known that dysregulation of ANS function is a predictor of worse cardiovascular disease (CVD) outcomes (16). Heart rate variability (HRV) is used to quantitatively assess variation in heartbeat intervals and is often used to detect changes in autonomic function (17). Healthy individuals exhibit a high level of HRV, whereas decreased HRV is implicated in CVD pathophysiology (18). In particular, reduced parasympathetic tone is a predictor of HF and is related to increased mortality in men and women at risk for CVD, as well as in patients who had a myocardial infarction (MI) (19–21).

Inflammation is also implicated in the pathogenesis and prognosis of HF (22). As suggested by Torre-Amione (23), HF is a systemic illness where deleterious processes can occur in response to cardiac injury regardless of the initial insult. Proinflammatory factors such as C-reactive protein (CRP), interleukin (IL)-6, tumor necrosis factor α (TNF-α), and soluble tumor necrosis factor α receptor 1 (sTNFr1) are activated beginning even at asymptomatic stages and continue to increase in relation to worsening HF (24). Although a vast amount of evidence links inflammation processes to CVD and HF, the efficacy of pharmacological interventions to reduce inflammation remains uncertain (25). Therefore, there is a significant need to develop novel therapeutic methods to address this critical problem.

In light of the evidence discussed above, in Stage B HF patients, we performed a pilot RCT examining the effects of an 8-week gratitude journaling intervention as compared with individuals receiving treatment as usual (TAU) on HRV and markers of inflammation. We hypothesized that the intervention would increase gratitude, elevate parasympathetic cardiac tone and reduce inflammatory biomakers. In addition, we conducted exploratory analyses to examine the relationships between gratitude and biomarkers of inflammation and parasympathetic activity.

METHODS

Participants

This is a substudy of a larger observational study examining the relationship among trait gratitude and biological factors linked with HF (14). Participants had a diagnosis of American Heart Association/American College of Cardiology classification Stage B HF for at least 3 months, were 18 years or older, and were recruited from the University of California, San Diego Medical Center Cardiology Programs and the Veterans Affairs San Diego Healthcare System. Data were collected from April 2013 to June 2014. The sample consisted of 70 men and women (mean [standard deviation {SD}] age = 66.2 [7.58] years) who were randomly assigned according to a computer algorithm to an intervention of either 8 weeks of gratitude journaling (n = 34) or TAU (n = 36). Allocation of group assignment was concealed until after baseline testing. Participants were assessed at preintervention, midintervention, and postintervention (Figure 1). Both groups were under the care of their primary care physician and cardiologist and were restricted from participation in other intervention studies during this period.

Presence of Stage B HF was defined as structural heart disease based on the American Society of Echocardiography guidelines (26). Criteria include left ventricular (LV) hypertrophy (mean LV wall thickness of septum and posterior wall ≥12 mm), LV enlargement (at least moderate in severity,

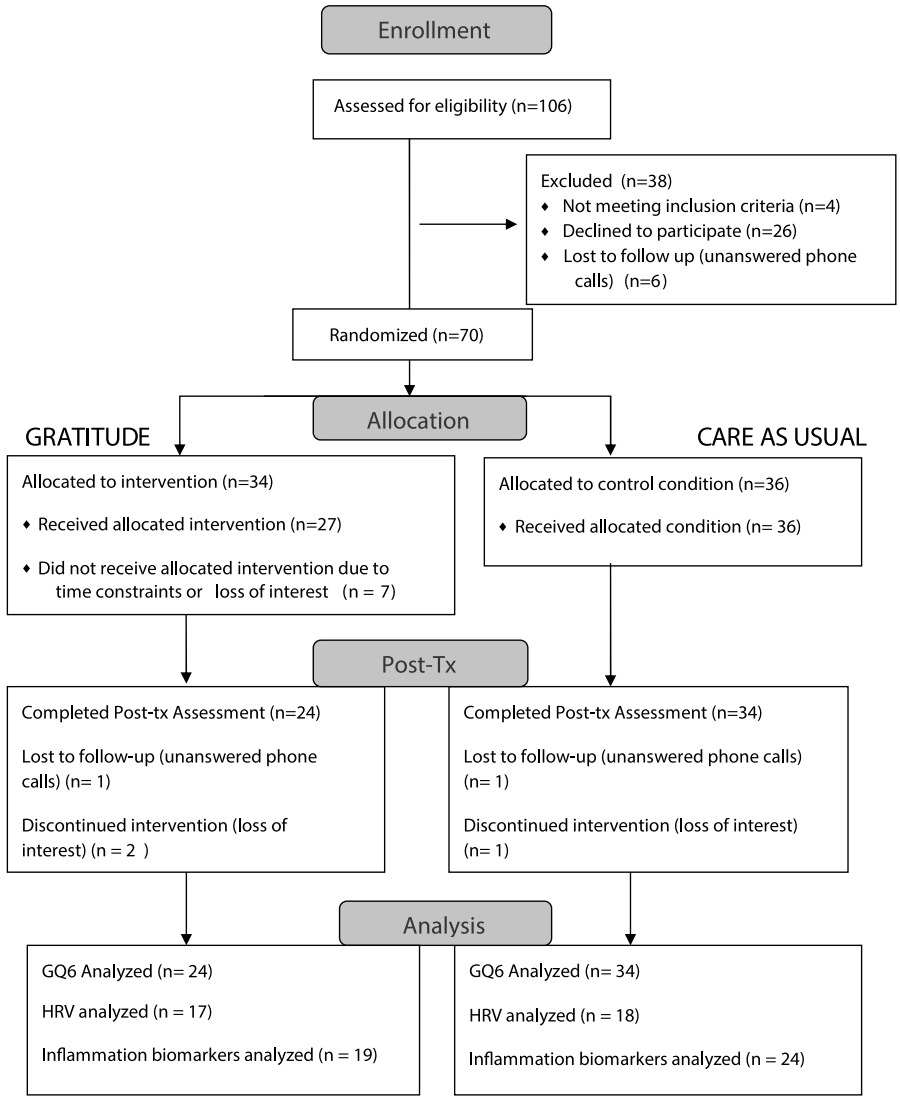

FIGURE 1. CONSORT diagram. GQ6 = 6-item Gratitude Questionnaire; HRV = heart rate variability.

with LV end-diastolic diameter ≥64 mm in men or ≥58 mm in women, or LV mass index ≥132 in men or ≥109 in women), LV systolic dysfunction (LV ejection fraction [LVEF] <55% or wall motion abnormality), LV diastolic dysfunction, asymptomatic valvular heart disease of at least moderate severity, or previous MI but without symptoms of HF. Measurements were made by sonographers naive to participant's other study characteristics. An important distinction of Stage B HF is the lack of symptoms such as shortness of breath during mild exercise, compared with Stage C HF which exhibits symptoms.

Procedures Overview

This study was approved by the University of California, San Diego and Veterans Affairs San Diego Healthcare System Institutional Review Boards, and participants gave written informed consent. It was carried out in accordance with the Declaration of Helsinki principles. Testing occurred at baseline (T1), 4 weeks (T2: midintervention; gratitude assessment only), and 8 weeks (T3: postintervention) visits. At T1 testing, participants arrived at the laboratory at various times of the day between 0800 and 1500 hours and were given a brief overview of the study and then were asked to sit quietly for 10 minutes and subsequently were administered a blood draw while in a seated upright position. After the blood draw, seated basal HRV data were recorded after a 5-minute acclimation interval. Participants filled out a gratitude and an exercise activities questionnaire, and then participants who were randomized to the gratitude journaling condition were given instructions for the 8-week intervention. Compliance in the gratitude journaling group was assessed by examining the number of journal entries per week and numbers of words written per journal entry. Both groups were told to continue their health care as usual. After 4 weeks (T2), participants in both conditions were mailed a six-item Gratitude Questionnaire (GQ-6) and preaddressed envelope, which they were told to complete and mail back. After the 8-week intervention period, the T3 visit was similar to the T1 visit where participants in both groups received a blood draw, filled out the GQ-6, and had a basal HRV assessment. In addition, participants in both groups were assessed for HRV responses to a gratitude journaling task. Participants were paid and thanked.

Gratitude

At T1 (baseline), T2 (midintervention), and T3 (postintervention) visits, gratitude was measured with the GQ-6 (27) where the frequency and intensity are assessed with six items in which grateful affect is experienced. Items are rated with a Likert-type scale: 1 (strongly disagree) to 7 (strongly agree). The GQ-6 produces a single-factor score and has convergent validity with other gratitude measures (27). The GQ-6 was chosen because it

is most often used in gratitude intervention studies (e.g., Emmons and McCullough (12)) as well as in larger cross-sectional studies measuring physical health (28) including patients with asymptomatic HF (14). In the present study, the Cronbach α for baseline GQ-6 was .83.

Leisure-Time Exercise Questionnaire

As a manipulation check to determine whether the control group differed at baseline or in changes in exercise activities, the Leisure-Time Exercise Questionnaire (LTEQ) (29) was administered at T1 and T3 in both groups (see Tables 1 and 2).

Heart Rate Variability

At both T1 (baseline) and T3 (postintervention) assessments, participants were fitted with the Equivital EQ-02 LifeMonitor (Hidalgo, UK). After an initial 5-minute acclimation interval, basal HRV data were recorded during the subsequent 5-minute period. At T3, after basal HRV recording, participants in both groups performed a gratitude journaling task where they were asked to write for 5 minutes about things for which they were grateful; HRV responsiveness to gratitude journaling was determined by measuring changes in HRV from rest to the journaling task period. Digitized electrocardiogram (ECG) data were analyzed to detect the R-wave peaks of the QRS complex and R-R interval artifacts were manually removed using linear interpolation. Ectopic beats were identified and removed using VivoSense software (Vivonoetics, Inc, San Diego, CA) automated ectopic beat detection algorithm.

The Equivital EQ-02 LifeMonitor (Hidalgo, UK) is a multiparameter system that includes a two-lead ECG sensor belt and an ambulatory Sensor Electronics Module for recording ECG data. Cardiac data are sampled at 256 Hz and were analyzed with the VivoSense software platform (Vivonoetics, Inc). The accuracy and reliability of EQ-02 heart rate and R-R interval collection during rest and exercise have previously been validated (30–32). The objective was to quantify HRV indices of parasympathetic cardiac control using measures from time, frequency, and nonlinear

TABLE 1. Sociodemographic, Medical, Behavioral, and Inflammatory Biomarker Characteristics of Study Participants

Characteristics	Journal Group	*n*	TAU	*n*	*p*
Age, M (SD), y	66.43 (8.4)	24	66.0 (7.1)	34	.87
Sex, % male	95.2	24	86.4	34	.32
Race, % white	73.7	24	63.6	34	.27
College degree, %	38.5	24	29.2	34	.50
LVEF, % (SD)	62.9 (9.4)	24	62.9 (5.7)	34	.99
BMI, M (SD), kg/m^2	29.6 (5.5)	24	29.8 (4.2)	34	.87
GQ-6, M (SD)	32.0 (9.01)	24	33.6 (6.96)	34	.60
Marital, % married	55.0	24	47.4	34	.63
LTEQ, M (SD)	32.04 (30.14)	24	36.59 (26.89)	34	.67
Diabetes, %	36.8	24	27.8	34	.56
Etiology, %		24		34	.51
Myocarditis	0		3.0		
Hypertrophic	13.6		15.2		
MI	13.6		18.2		
Idiopathic	4.5		0		
Ischemic	18.2		0		
Hypertension	31.8		42.4		
Valvular	4.5		6.1		
Other	13.6		15.2		
Inflammatory factor	0.18 (0.82)	19	−0.26 (1.13)	24	.19
Log sTNFr1, pg/ml	7.03 (0.40)		7.04 (0.49)		.98
Log CRP, mg/dl	0.82 (1.26)		0.92 (1.66)		.84
Log TNF-α, pg/ml	1.06 (0.28)		0.94 (0.30)		.51
Log IL-6, pg/ml*	0.87 (0.61)		0.34 (0.55)		.010
Log RMSSD	3.53 (0.87)	17	3.41 (0.71)	18	.89
Log HF power	5.31 (2.13)	15	5.57 (0.86)	16	.78
Log SD1	3.09 (0.84)	17	3.05 (0.70)	18	.92

Independent *t* tests and Kruskal-Wallis tests were used to determine significant group differences.

TAU = treatment as usual; M = mean; SD = standard deviation; LVEF = left ventricular ejection fraction; BMI = body mass index; GQ-6 = six-item Gratitude Questionnaire; LTEQ = Leisure-Time Exercise Questionnaire; MI = myocardial infarction; sTNFr1 = soluble tumor necrosis factor receptor 1; CRP = C-reactive protein; IL-6 = interleukin 6; TNF-α = tumor necrosis factor α; RMSSD = root mean square successive differences; HF power = high-frequency power; SD1 = standard deviation of the distances of the RRi to the slope of the line

* $p < .05$.

TABLE 2. Group Resting Levels Across Time

Measure	Gratitude Journaling Group			Treatment as Usual			Observed		
	Pre	Mid	Post	Pre	Mid	Post	η^2	Power	p
GQ-6, M (SD)	31.7 (9.01)	35.04 (7.86)	33.48 (8.10)	33.6 (6.96)	33.60 (5.52)	34.86 (6.06)	0.10	0.67	.017
Log RMSSD, M (SD)	3.53 (0.87)	—	3.60 (0.67)	3.41 (0.71)	—	3.59 (0.80)	<0.001	0.05	.99
Log HF power, M (SD)	5.31 (2.13)	—	5.42 (1.66)	5.57 (0.86)	—	5.14 (1.41)	0.04	0.15	.35
Log SD1, M (SD)	3.09 (0.84)	—	3.23 (0.67)	3.05 (0.70)	—	3.22 (0.80)	0.002	0.06	.81
Inflammatory factor, M (SD)	0.16 (0.82)	—	−0.33 (0.91)	−0.25 (1.13)	—	−0.05 (0.97)	0.21	0.86	.004
Log CRP, mg/dl	0.82 (1.26)	—	0.09 (0.91)	0.92 (1.66)	—	0.61 (1.23)			
Log IL-6, pg/ml	0.87 (0.61)	—	0.59 (0.54)	0.34 (0.55)	—	0.49 (0.54)			
Log TNF-α, pg/ml	1.06 (0.28)	—	1.09 (0.35)	.94 (0.30)	—	1.06 (0.38)			
Log sTNFrI, pg/ml	7.03 (0.40)	—	6.82 (0.52)	7.04 (0.49)	—	6.95 (0.44)			
LTEQ, M (SD)	32.04 (30.14)	—	36.31 (28.62)	36.59 (26.89	—	37.56 (27.81)	0.003	0.06	.84

Data were analyzed with repeated-measures ANCOVAs, adjusting for %LVEF and Stage B etiology in all analyses plus BMI (kg/m^2) for inflammation biomarkers. p Values represent group by time interactions.

GQ-6 = six-item Gratitude Questionnaire; M = mean; SD = standard deviation; RMSSD = root mean square successive differences; HF power = high-frequency power; SD1 = standard deviation of the distances of the RRi to the slope of the line; CRP = C-reactive protein; CRP = C-reactive protein; IL-6 = interleukin 6; TNF-α = tumor necrosis factor α; sTNFr1 = soluble tumor necrosis factor receptor 1; LTEQ = Leisure-Time Exercise Questionnaire. ANCOVAs = analyses of covariance; LVEF = left ventricular ejection fraction; BMI = body mass index; BMI = body mass index.

domains during the 5-minute periods of rest and gratitude journaling. In the time domain, the root mean square of successive differences (RMSSD) was determined, which has been shown to reflect vagal activity (15). In the frequency domain, high-frequency (high frequency: 0.15–0.40 Hz) power spectral density was measured, which has also been used as an index of vagal activity and reflects primarily parasympathetic influences (15). Because the ANS is not a linear system, it has been argued that nonlinear analysis would be informative for HRV (33) and nonlinear measures have also been proposed to be more accurate at predicting cardiac dysfunction, including ventricular tachycardia and sudden cardiac death (34,35) when compared with traditional time and frequency domain analyses. Poincare analyses are commonly used as a nonlinear measures of HRV (36), including SD of the distances of the RRi to the slope of the line (SD1), which represents a measure of rapid changes in R-R intervals. Because vagal effects on the sinus node are known to develop faster than sympathetically mediated effects, it is considered a parasympathetic index of sinus node control (37,38). SD1 was calculated by determining the SDs of the distances of the RRi to the slope of the line $x = y$, where x = RR (i +1) and y = (RRi).

Inflammatory Biomarkers

Inflammation is implicated in the pathogenesis of HF and inflammatory biomarkers are used for risk stratification and prognosis (22). Therefore, we assessed an index of relevant inflammatory biomarkers known to be involved in adverse remodeling of the heart and the progression to HF, which included CRP, TNF-α, IL-6, and sTNFr1 (38a,38b) at both T1 (baseline) and T3 (postintervention). After a 10-minute rest period, whole blood was drawn into a 10-ml vacutainer tube preserved with EDTA while participants were in an upright sitting position. Blood samples were immediately placed on ice, centrifugation was performed within 30 minutes, and plasma was aliquoted and immediately stored at −80 ° C until assay. Circulating levels of these biomarkers were determined by commercial high-sensitivity enzyme-linked immunosorbent assay (Meso Scale Discovery, Rockville, MD) and performed in duplicate. Median lower limit of detection was 1.33 pg/ml for CRP, 0.06 pg/ml for IL-6, and 0.04 pg/ml for TNF-α, and minimum detectable dose for sTNF RI was 0.77 pg/ml. Intra-assay and interassay coefficients were less than 7%.

Journaling Intervention

At the T1 visit, participants were provided written and oral instructions for keeping a daily gratitude journal diary. To aid comparison with previous work, journaling instructions were modeled after Emmons and McCullough (12) and read, "For the next eight weeks you will be asked to record 3–5 things for which you are grateful on a daily basis. Think back over your day and include anything, however small or great, that was a source of gratitude that day. Make the list personal, and try to think of different things each day." In accordance with existing protocols, we did not set any specific requirements for the length of the text (how many words or lines written), time spent journaling (minutes per day), or set a daily schedule (e.g., having entries occur in morning or evening). The first journal was mailed back at 4 weeks (T2), and the second journal was returned during the postintervention (T3) testing visit.

Statistical Analyses

Analyses were performed using IBM SPSS Statistics for Windows Version 23.0 (IBM Corp, Armonk, NY). To maximize statistical power, imputations were performed for missing GQ-6 data using a multiple regression approach. Age, sex, and race were each used as predictor variables. Reported analyses for GQ-6 were conducted using imputed data. Initial power analyses focused on the anticipated change in gratitude score from baseline to immediate postintervention for the journaling and TAU groups: the primary end point being the difference between gratitude at baseline and the end of the 8-week intervention. Assuming an SD of approximately 4 units for both the baseline and 8-week measurements of gratitude and a 20% dropout rate, an initial sample size of 80 participants per treatment group was expected to provide approximately 80% power to detect a difference of approximately 3 units in mean change in gratitude scores between groups, with a two-sided significant level of .05. Additional analyses examining biomarkers (HRV and inflammatory factor) were considered exploratory given the

nature of this pilot study and the fact that few, if any, other studies have examined these in response to a gratitude journaling intervention. Consequently, sample size calculations did not consider these planned but exploratory analyses, as one aim of this pilot study was to generate effect sizes for these biomarkers to inform future, larger-scale studies. Skewed data distribution was determined by the Kolmogorov-Smirnov test, and variables not normally distributed were log transformed to more closely approximate normality. HRV and inflammation biomarkers were log transformed and achieved normal distribution. Group differences in sociodemographic and medical characteristics (Table 1) were computed using independent *t* tests or, for categorical data, Kruskal-Wallis tests. To reduce the number of repeated measures tests and risk of Type I error, a factor analysis was used to calculate a composite inflammatory index score comprising circulating levels of CRP, TNF-α, IL-6, and sTNFrI. The resultant factor score eigenvalue was 1.8, accounting for 45.2% of inflammatory variance. To measure differences between groups for changes in gratitude levels (GQ-6), a repeated-measures analyses of covariance (ANCOVA) was performed using a 2 × 3 design (two groups: gratitude journaling and TAU; three time points: T1, preintervention; T2, midintervention; T3, postintervention). Repeated-measures ANCOVAs were performed to examine changes over time for basal HRV and inflammatory biomarkers using a 2 × 2 design (two groups: gratitude journaling and TAU; two time points: T1 and T3). Group differences in HRV responses to the T3 postintervention gratitude journaling task were examined by measuring changes in HRV during the task from resting HRV, using a repeated-measures ANCOVA 2 × 2 design (two groups: gratitude journaling and TAU; two time points: T3, postintervention basal HRV and T3 postintervention HRV during the gratitude journaling task). Percentage of LVEF (%LVEF) and Stage B HF etiology (myocarditis, hypertension, MI, hypertrophy, valvular, ischemic, idiopathic, or other) was adjusted during all analyses, and body mass index (BMI) was used as an additional covariate for analyses including proinflammatory biomarkers. The effect sizes for repeated-measures ANCOVAs are reported as partial eta squared (η^2). Cohen (39, p283) suggests for η^2 where 0.010 constitutes a small effect, 0.059 a medium effect, and 0.138 a large effect. To determine whether alterations in gratitude levels were related to changes in biomarkers, partial correlations of GQ-6 (midintervention and postintervention) were conducted in relation to HRV responses and basal inflammatory biomarker levels (postintervention), while adjusting for baseline (T1) values.

RESULTS

Table 1 presents baseline characteristics of the study sample. Baseline participant characteristics revealed statistical differences for inflammation biomarker IL-6 ($p < .05$). From the original 70 participants, 21% ($n = 7$) of those randomized to the journaling intervention dropped out before beginning the intervention. Of the 26 participants who began the journaling intervention, 89% completed the study. The total gratitude intervention completion rate was 71%. Of the 36 participants allocated to the TAU group, 94% of the participants completed the study. HRV biomarker data were analyzed from a subsample of 34 participants. Inflammatory biomarker data were analyzed from 43 participants.

Participants in the gratitude journaling condition that completed the study averaged 5.29 days per week (SD = 1.98) of journaling and averaged 1482.82 words (SD = 819.78) over the 8-week period. Although there were reductions, there were no significant differences between the first 4 weeks and the last 4 weeks of the intervention for average (SD) numbers of journaling days per week (5.46 [1.99] versus 5.05 [2.31]) or numbers of words journaled (766.12 [418.75] versus 716.71 [538.38]; *p* values > .10). There were no group differences in exercise activities over time measured with the LTEQ ($p > .10$). There were no differences in age, %LVEF, Stage B HF etiology, education, BMI, baseline gratitude levels, LTEQ levels, inflammation biomarkers, or HRV biomarkers between those who dropped out from those who remained in the study (all *p* values > .05).

Gratitude

Missing GQ-6 values (9.6%) at one of the three time points were replaced with imputed values. Adjusting for %LVEF and etiology, a repeated-measures ANCOVA of GQ-6 scores, at T1 (preintervention), T2 (midintervention), and T3 (postintervention) revealed a quadratic group by time interaction ($F = 6.0$, $p = .017$, $\eta^2 = 0.10$) with a medium effect size (see Table 2). Pairwise comparisons revealed significant differences between groups across time from T1 to T2, with the gratitude journaling group increasing in gratitude scores from preintervention to midintervention to a greater degree than the TAU group ($p = .038$). Also, there were group differences across time from T1 to T3 ($p = .044$), with the gratitude journaling group increasing in gratitude scores from preintervention to postintervention to a greater extent than the TAU group. Table S1, Supplemental Digital Content 1 (http://links.lww.com/PSYMED/A280), contains partial correlations among GQ-6 gratitude scores (midintervention and postintervention), and journaling task HRV responses (postintervention), while adjusting for respective baseline (T1) levels.

Basal HRV

Repeated-measures ANCOVAs revealed that there were no group by time interactions for basal HRV in time (RMSSD), frequency (high-frequency power), and nonlinear (SD1) domains, adjusting for %LVEF and etiology (all *p* values > .10).

HRV Response to Gratitude Task

A repeated-measures ANCOVA revealed significant T3 (postintervention) group by time effects for the gratitude journaling task for parasympathetic HRV measures, RMSSD ($F = 4.5$, $p = .049$, $\eta^2 = 0.14$) and SD1, ($F = 4.2$, $p = .036$, $\eta^2 = 0.15$) and a trend for high-frequency power ($F = 3.2$, $p = .084$, $\eta^2 = 0.12$), while adjusting for %LVEF and etiology. Medium to large effect sizes were revealed for all three analyses. At postintervention, HRV increased in the gratitude intervention group in response to the journaling task, whereas there were lower HRV responses during the task in the TAU group (see Table 3).

Inflammatory Index

Repeated-measures ANCOVA revealed significant group by time interactions for the composite inflammatory index

TABLE 3. Group Responses to the Journaling Task Postintervention

	Gratitude Journaling		Treatment as Usual				
HRV Measure	Rest	Journaling	Rest	Journaling	η^2	Observed Power	p
Log RMSSD, M (SD)	3.68 (0.75)	3.85 (0.80)	3.56 (0.80)	3.32 (0.81)	0.14	0.51	.049
Log HF power, M (SD)	5.60 (1.89)	5.91 (1.72)	5.51 (1.52)	4.88 (1.45)	0.12	0.41	.084
Log SD1, M (SD)	3.31 (0.75)	3.48 (0.78)	3.19 (0.80)	2.98 (0.79)	0.15	0.57	.036

Group differences were determined using repeated-measures ANCOVAs, adjusting for %LVEF and Stage B etiology. p Values represent group by time interactions.

η^2 = partial eta squared; RMSSD = root mean square successive differences; M = mean; SD = standard deviation; HF power = high-frequency power; SD1 = standard deviation of the distances of the RRi to the slope of the line; ANCOVAs = analyses of co-variance; LVEF = left ventricular ejection fraction.

score derived from CRP, IL-6, sTNFrI, and TNF-α adjusting for %LVEF, etiology, and BMI ($F = 9.7, p = .004, \eta^2 = 0.21$).

Post Hoc Analyses

Partial correlation analyses, adjusting for baseline values, did not find significant relationships between midintervention or postintervention (T3) GQ-6 scores and HRV (RMSSD, HF, and SD1) journaling task responses ($p > .10$) or basal inflammatory biomarker index scores ($p > .10$; Table 3).

DISCUSSION

There is a need for early employment of interventions to prevent disease advancement and ultimately to diminish morbidity and mortality for patients with HF (4). Transition from asymptomatic Stage B to symptomatic Stage C HF is related to a large increase in mortality risk (5), and thus finding a means to protect against HF progression at early stages of the disease are vital. The current pilot study of patients with asymptomatic Stage B HF found that in response to the gratitude intervention, there were potential improvements in objective measures of physical health that have been associated with HF prognosis. These biomarker improvements paralleled increases in gratitude levels across the intervention period. Although these findings are encouraging, definitive conclusions cannot be made due to the modest sample size. However, the present pilot study suggests that large-scale RCTs with active control conditions are warranted to ascertain whether improvements in physiologically relevant biomarkers associated with gratitude interventions can be achieved.

In the present study, gratitude levels increased to a greater extent in the journaling intervention group after the first 4 weeks of the intervention compared with TAU and, although dipping by the end of the 8-week gratitude journaling intervention, still showed a significant improvement from baseline compared with TAU. Heightened gratitude levels at 4 weeks may result from the new practice of identifying or noticing areas in life to be grateful for, which may then lead to a new set point (a "new normal") at 8 weeks. However, caution should be taken in interpreting our findings because there were no significant differences in gratitude levels after intervention, suggesting the possibility of a regression to the mean. Future large-scale studies are needed to confirm our findings and to determine whether elevated gratitude levels are maintained for a prolonged period.

The present investigation saw no resting HRV differences from pre–gratitude journaling to post–gratitude journaling compared with TAU, but group differences in postintervention responses to the laboratory-based gratitude journaling task were observed. Parasympathetic HRV measures within time (RMSSD), nonlinear (SD1), and a trend for frequency (high-frequency power) domains seemed to increase in response to the gratitude journaling task after the 8-week gratitude journaling intervention compared with TAU. Acute challenges create a window into complicated physiological processes and can reveal alterations in physiological regulation that may be masked under resting conditions (40). Moreover, increases in parasympathetic cardiac tone during the laboratory-based journaling task may reflect state changes that occur while contemplating items or feelings of gratitude during daily life. On the other hand, because we did not perform a gratitude journaling task at baseline, we cannot rule out whether group differences were present preintervention and carried forward to postintervention. Rash et al. (41), the only other gratitude study that we are aware of that examined HRV (high-frequency, low-frequency, and very low frequency power) albeit in healthy young adults also observed increases in HRV with a gratitude induction task when compared with a memorable event induction task. However, their study differed from ours in that both groups were naive to journaling about these topics when participants performed the tasks.

Exercise training intervention studies that assess changes in HRV are more widely investigated in patients with CVD. Oliveira and colleagues (42) suggest that despite conflicting findings, exercise training seems to improve autonomic function in patients with CVD and to have prognostic implications. However, among patients with CVD, only 14% to 35% of eligible patients who have an MI participate in exercise training through cardiac rehabilitation (43,44). In

patients with HF, aerobic exercise therapy has even lower adherence rates (45). Gratitude journaling requires little equipment, can be performed safely at home, and can be conducted by adult patients of any age with most comorbidities. In addition, gratitude interventions may complement treatment regimens, which could potentially make up for shortfalls in exercise compliance, although further research on this is needed.

To our knowledge, there are no other gratitude intervention studies measuring inflammatory biomarkers. HF is characterized by chronic inflammation, with elevated circulating inflammatory cytokines associated with ventricular remodeling by inducing ventricular hypertrophy, fibrosis, and apoptosis (25). A specific panel of inflammatory markers, CRP, IL-6, TNF-α, and sTNFr1, was chosen to form an inflammatory biomarker index for the present study that are associated in patients with HF with both worse self-reported health status (46) and disease progression and mortality (47,48). We found that patients with Stage B HF in the gratitude journaling group had a reduction of the basal plasma inflammatory index compared with TAU controls. These results are consistent with our recent naturalistic study (n = 186) that found patients expressing more gratitude also had lower levels of an inflammatory biomarker index (14). However, in the current pilot study, IL-6 levels included in the inflammatory biomarker index differed at baseline, and thus, caution should be taken in interpreting the results and further research is clearly needed to make definitive conclusions about the effects of gratitude journaling on inflammatory biomarker alterations.

There were no relationships found between gratitude levels at midintervention and postintervention and HRV responses to the gratitude induction task postintervention or with postintervention basal inflammatory biomarker index scores. Because biomarkers were not measured at midintervention, it is unknown whether there was a correspondence with gratitude levels at midintervention. Future larger-scale studies with added biomarker time points during the gratitude intervention will help to determine relationships between changes in gratitude levels and physiological outcomes. Thus, it is not clear from our study by what mechanism gratitude journaling affects HRV and inflammation. Other psychological or behavioral factors may be mediating the changes observed in HRV and inflammatory biomarkers in response to the intervention. Wood et al. (10) suggest that gratitude interventions potentially operate through other mechanisms such as engaging in protective health behaviors such as regular exercise, a healthy diet, and seeking regular health care (49). The identification of other potential mediating factors that affect biological changes associated with the practice of gratitude will enable the determination of the mechanisms of action. Changes in symptoms of depression as a mediating factor would be of particular interest in future investigations, because various studies have associated depression with inflammation, as well as HRV (e.g., Refs. (50,51).

Limitations of the Current Study That Should Be Addressed in a Larger-Scale RCT

This pilot study was composed of a modest sample size. In addition, the optimal dose of journaling frequency and duration for patients with asymptomatic HF is not yet known. A follow-up study is needed examining various doses of the journaling intervention. We chose an 8-week intervention duration because Emmons and McCullough (12) found reductions in self-reported health-related complaints with a longer intervention time, but not at shorter intervals of 2 or 3 weeks. Although we found improvements in gratitude levels at midintervention, we did not assess physiological measures at that time point and so it is unknown whether physiological effects may have occurred earlier than 8 weeks.

Despite randomization, there was a significant preintervention (baseline) group difference in IL-6 (see Table 1). Generalizability of inflammatory biomarker findings may be limited because there may have been systemic differences between the two groups. Changes over time for both groups could have resulted from a regression to the mean. It is suggested that a potential limitation of small clinical trials (n < 100) is that simple randomization methods may result in imbalanced baseline characteristics among treatment and control groups (52,53). Also, a limitation was the lack of standardization of baseline and posttreatment times of laboratory visits which could have affected our results, because many inflammatory factors are characterized by diurnal variation (54). Other factors might have confounded the results, including depressive symptoms and medication use. Another limitation was the absence of an HRV gratitude journaling task at baseline to determine whether the associations found postintervention were not due to individual differences present at baseline. Also, the decrease in parasympathetic HRV signal in the control group may have been the result of a cognitive task in which they were unfamiliar.

This pilot study lacked an active control condition; therefore, it is unknown whether participant expectations affected outcome measures. In addition, because the TAU group was not restricted in their activities other than participation in outside studies, it is unknown whether they participated in healthy life-style changes during the study period that affected results. However, the LTEQ was administered at baseline and postintervention and there were no group differences in leisure time exercises, suggesting that the TAU group did not add physical activities during participation in the study.

Finally, there were differences in attrition between the groups, with reasons reported for dropping out by those who could be contacted being time constraints and loss of

interest in participation. However, by not having a matching journaling control group, we are unable to determine whether greater attrition in the gratitude journaling group was due to differences in propensity for journaling, resulting in a selection bias that could have affected outcomes of the study. However, there were no differences in those who dropped out in age, education, health-related factors such as %LVEF, and etiology. As a pilot study, our aim was to preliminarily explore intervention-related changes, and thus, we did not perform an intent-to-treat analysis and thus did not include participants who did not participate in the gratitude journaling intervention. Future studies should consider including interviews and focus groups, which may provide additional information to better determine for whom gratitude journaling is an appropriate intervention.

CONCLUSIONS

The results of the present pilot study suggest that a future large-scale clinical trial with an active control group is warranted to further examine autonomic and inflammatory biomarkers in response to a gratitude journaling intervention. Research suggests that HRV levels are associated with CVD prognosis. Also, it is known that circulating levels of inflammatory biomarkers are related to morbidity and mortality in patients with HF (22–24). Our preliminary results show a potential for the gratitude journaling intervention as a novel tool for improving physiological factors associated with CVD prognosis. Future larger-scale studies are necessary to confirm the benefits of gratitude journaling on physiological alterations and to determine potential clinical relevance for CVD outcomes.

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