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Low heart rate variability and cancer-related fatigue in breast cancer survivors

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Summary Cancer-related fatigue is a common and often long lasting symptom for many breast cancer survivors. Fatigued survivors show evidence of elevated inflammation, but the physiological mechanisms driving inflammatory activity have not been determined. Alterations in the autonomic nervous system, and particularly parasympathetic nervous system activity, are a plausible, yet understudied contributor to cancer-related fatigue. The goal of this study was to replicate one previous study showing an association between lower parasympathetic activity and higher fatigue in breast cancer survivors (Fagundes et al., 2011), and to examine whether inflammation mediates this association. Study participants were drawn from two samples and included 84 women originally diagnosed with early stage breast cancer prior to age 50. Participants completed questionnaires, provided blood samples for determination of interleukin (IL)-6 and C-reactive protein (CRP), and underwent electrocardiography (ECG) assessment for evaluation of resting heart rate variability (HRV), a measure of parasympathetic activity. Results showed that lower HRV was associated with higher fatigue ($p < .05$), as predicted. In bivariate analyses, HRV was also correlated with circulating concentrations of IL-6 and CRP. However, path analyses did not support inflammation as a mediator of the association between HRV and fatigue; instead, associations among these variables appeared to be driven by age and BMI. These findings identify HRV as a potential contributor to cancer-related fatigue, but suggest that inflammation

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does not mediate this association in younger, healthy breast cancer survivors who are several years post-treatment. The autonomic nervous system merits additional attention in research on the etiology of cancer-related fatigue.

1. Introduction

Fatigue is one of the most common and distressing symptoms reported by breast cancer patients and survivors. Cancer-related fatigue is experienced by 30—60% of patients undergoing cancer treatment (Jacobsen et al., 1999; Servaes et al., 2002; Lawrence et al., 2004; Bower, 2008), and can persist for up to ten years post treatment (Bower et al., 2006). Cancer patients and survivors describe their fatigue as more severe, pervasive, and debilitating than "normal" fatigue caused by lack of sleep or overexertion (Poulson, 2003). Empirical evidence confirms that the intensity and duration of cancer-related fatigue is significantly greater than fatigue experienced by healthy controls (Andrykowski et al., 1998). Cancer-related fatigue negatively impacts quality of life, and may predict shorter survival (Andrykowski et al., 1998; Bower et al., 2000; Groenvold et al., 2007).

Given the prevalence and impact of cancer-related fatigue, there has been considerable interest in the biological mechanisms underlying this symptom. One proposed mechanism is elevated inflammation. Indeed, studies have shown an association between elevated inflammatory markers and fatigue during and after treatment (Bower and Lamkin, 2013). However, the processes that initiate and sustain inflammatory activity in the aftermath of cancer treatment have not been determined.

One possible driver of increased inflammation in fatigued cancer survivors may be the autonomic nervous system (ANS). The ANS is a key regulator of the immune system, including the inflammatory cytokine network. In general, activation of the sympathetic branch of the ANS leads to increased inflammation and activation of the parasympathetic branch leads to decreased inflammation (Thayer and Sternberg, 2006; Irwin and Cole, 2011), although these effects are complex and highly contextual (Sanders and Straub, 2002). Thus, increased activity in the sympathetic branch or decreased activity in the parasympathetic branch may play a role in inflammation and associated symptoms of cancer-related fatigue. In the current study, we focus exclusively on the role of parasympathetic activity. It has been hypothesized that parasympathetic nervous system stimulation (via the vagus nerve) leads to decreases in production of pro-inflammatory cytokines through the release of the neurotransmitter acetylcholine (Tracey, 2002, 2009). Indeed, studies have documented cross-sectional associations between higher parasympathetic activity, as indexed with heart rate variability (HRV), and lower levels of inflammation (e.g. Sajadieh et al., 2004; Sloan et al., 2007). Parasympathetic activity is typically measured by capturing HRV, which is the fluctuation of time between consecutive heartbeats (Task Force, 1996; Appelhans and Luecken, 2006). Although HRV is influenced by both branches of the autonomic nervous system, data processing techniques allow for the extraction of the unique influence of the parasympathetic branch on HRV.

Previous research examining the association between autonomic activity and fatigue in non-cancer samples has supported the importance of the parasympathetic nervous system. Studies have shown that individuals with chronic fatigue syndrome have reduced HRV compared to healthy controls (Boneva et al., 2007; Beaumont et al., 2012), as do women reporting stress-related fatigue (Olsson et al., 2009). Of note, a meta-analysis comparing HRV in healthy controls to individuals with functional somatic disorders (which are characterized by high levels of fatigue) found that the poor quality of studies and publication bias limits the ability to draw conclusions (Tak et al., 2009). To our knowledge, only one previous study has examined the association between HRV and cancer-related fatigue. In a sample of 109 breast cancer survivors who were 17 months post diagnosis on average, Fagundes et al. (2011) found that lower resting HRV was associated with higher levels of fatigue. Associations with inflammation were not examined in that study.

The primary goal of the current study was to examine the association between HRV and fatigue in a sample of younger female breast cancer survivors. This group was of interest because they are at elevated risk for fatigue and other negative consequences of cancer treatment (Howard-Anderson et al., 2012). Based on studies that show an association between HRV and fatigue in other disorders (Boneva et al., 2007; Beaumont et al., 2012) and in breast cancer survivors (Fagundes et al., 2011), we hypothesized that cancer-related fatigue would be associated with lower HRV. Our second goal was to examine inflammation as a potential mediating pathway between HRV and fatigue. Low HRV is associated with elevated levels of circulating proinflammatory cytokines (Sajadieh et al., 2004; Sloan et al., 2007), and inflammation in turn is correlated with elevated symptoms of fatigue in cancer survivors (Bower and Lamkin, 2013). Thus, we hypothesized that the association between HRV and fatigue would be mediated by elevations in circulating markers of inflammation.

2. Methods

2.1. Participants

The study data were drawn from two samples of younger breast cancer survivors. Sample 1 comes from an observational study of the psychological and physiological characteristics of younger breast cancer survivors ($n = 50$) conducted from August 2010 to July 2011. Sample 2 comes from a randomized controlled trial of mindfulness meditation for younger breast

cancer survivors ($n = 71$) conducted from April 2011 to June 2012. The current study focuses on a subset of women from each of these studies ($n = 24$ from Sample 1; $n = 60$ from Sample 2; total $n = 84$) for whom we have electrocardiogram (ECG) data. ECG data were collected to assess resting autonomic nervous system activity using identical protocols for data collection and data processing in each study.

Participants from the original studies were identified through several sources: the UCLA Health System tumor registry, offices of medical oncologists, and a listserv of women who had previously participated in research conducted by our group and agreed to be re-contacted for future studies. Eligibility criteria for both studies were as follows: (1) diagnosed with early stage breast cancer at age 50 years or less; (2) no current evidence of disease; (3) at least 1 year post initial cancer diagnosis and at least 3 months post treatment with radiation or chemotherapy (for Sample 1, the criteria was at least 6 months post treatment); (4) able to give informed consent; (5) able to read and write English. Women who had active medical conditions that were not controlled by medication were considered ineligible. If they had an acute illness on the day of their appointment, their assessment was rescheduled. All participants gave informed consent prior to completing the study, which was approved by the UCLA Institutional Review Board.

2.2. Procedures

Participants for both studies completed an in-person assessment at our research laboratory between 08:00 h and 10:00 h to control for potential diurnal variations in immune measures. Prior to the visit, participants completed a questionnaire battery that included information about demographics, cancer history, and fatigue. At the visit, height and weight were assessed, and blood was drawn via venipuncture. Participants had fasted prior to coming in to the lab to ensure no influence of caffeine or food intake on immune measurements. After the blood draw, spot electrodes were placed on each forearm and chest for ECG. Participants were asked to rest comfortably in their chair with both legs on the floor and arms in their laps or on the arm rests. They were asked to refrain from speaking and moving. They were not given reading material or other distraction. Resting ECG data was recorded for 15 min. Note that data from the baseline assessment (pre-intervention) for Sample 2 was used in all analyses.

2.3. Measures

2.3.1. Heart rate variability

HRV was computed from the continuous ECG recordings by analyzing the variability in the intervals between heart beats (R—R intervals; Task Force, 1996). A modified lead II electrode placement using three electrodes was used. The ECG was sampled at 1000 Hz and stored for off-line processing using AcqKnowledge (Biopac Systems Inc., USA) and Kubios (University of Kuopio, Finland). During the data processing, average HRV was calculated across 2—3 min segments of time, which were then averaged across the 15 min to come up with single indices of resting HRV.

HRV is influenced by both sympathetic and parasympathetic nervous system activity. Because of our focus on the parasympathetic nervous system, we chose two measures of HRV that are recommended as preferential measures of parasympathetic activity (Task Force, 1996). Through time domain analysis, the intervals of subsequent normal R—R waves are measured over a period of time. The root mean square of the successive differences in R—R intervals (RMSSD) is calculated and reported in milliseconds. RMSSD is thought to represent parasympathetically mediated HRV (Task Force, 1996). Low RMSSD at rest is a proposed index of poor autonomic regulation (Appelhans and Luecken, 2006).

The second HRV outcome was calculated through frequency domain analysis in which R—R time intervals are separated into frequency bands. Some heart rate oscillations are faster than others and thus frequency deconstruction enables the transformation of R—R intervals into high (.15—.40 Hz) and low frequency bands (.04—.15 Hz). High frequency HRV (HF-HRV) is a specific marker of parasympathetic activity. In our sample, RMSSD and HF-HRV were highly correlated, $r = .915$.

2.3.2. Inflammatory markers

Blood was obtained via venipuncture and stored in EDTA tubes at −80 °C for subsequent batch testing. We focused on two inflammatory markers, IL-6 and CRP, which have been associated with cancer-related fatigue (Schubert et al., 2007; Alfano et al., 2012) and with HRV (Sajadieh et al., 2004; Sloan et al., 2007). Plasma levels of IL-6 were determined by the Quantikine high-sensitivity ELISA kit (R&D Systems, Minneapolis, MN), with a lower detection limit of .039 pg/mL. Plasma CRP levels were determined by a high-sensitivity ELISA (Immundiagnostik; ALPCO Immunoassays, Salem, NH), with a lower limit of detection of .4 mg/l. All samples were run in duplicate, and intra- and inter-assay precision for both tests were less than or equal to 10%.

2.3.3. Fatigue

Items from the Fatigue Symptom Inventory (FSI) were used to assess subjective fatigue (Hann et al., 1998). This scale was developed for use in cancer patients and has strong psychometric properties (Donovan and Jacobsen, 2010). We used three items to capture specific aspects of cancer-related fatigue — amount, severity, and duration. Women rated their average level of fatigue in the past week (FSI average) and their level of fatigue on the day they felt most fatigued in the past week (FSI most) on an 11-point scale ranging from 0 (*not at all fatigued*) to 10 (*as fatigued as I could be*). Participants also indicated the number of days they felt fatigued in the past week (FSI days). On all dimensions, higher scores indicate worse fatigue.

2.3.4. Physical activity

Godin and Shepard's (1985) Leisure Time Exercise Questionnaire was used to capture amount of physical activity women participated in during a typical 7-day period. Women indicated how many times a week and for how long they engaged in mild (e.g. gentle yoga), moderate (e.g. fast walking), or strenuous (e.g. running) exercise. A composite score capturing the metabolic equivalent (MET) hours of physical activity per week was calculated (Jones et al., 2005). This scale has demonstrated concurrent validity and reliability (Jacobs et al., 1993), and is frequently used in cancer samples (e.g. Jones et al., 2005).

2.3.5. Demographics and cancer-treatment history

Demographic and cancer treatment information was determined from self-report questionnaires, which assessed racial/ethnic status, marital status, education, employment, income, and whether or not they currently smoked. Body mass index (BMI) was calculated from the in-person assessment of height and weight. Cancer-treatment variables included whether or not the women had received chemotherapy and/or radiation, what type of surgery they underwent (lumpectomy or mastectomy), and whether or not they were currently receiving endocrine therapy.

2.4. Statistical analyses

First, we assessed whether participants in Sample 1 and Sample 2 differed from each other in any systematic way. We conducted *t*-tests and chi-square analyses on all demographic, treatment-related, fatigue, HRV, and inflammation variables to examine whether there were significant differences between groups. There were no systematic differences between the two samples (see Tables 1 and 2) and thus for all of the following analyses the samples were combined.[1] All HRV and inflammatory markers were normalized using log transformations prior to any analyses. Raw values are provided in Table 2 for descriptive purposes.

Our primary hypothesis was that lower levels of resting HRV would be associated with higher levels of cancer-related fatigue. We first looked at the bivariate correlations between fatigue and HRV indices. Then we conducted regression analyses predicting three fatigue variables (FSI average, FSI most, FSI days) from HRV (RMSSD and HF-HRV), controlling for BMI and age because of their known associations with HRV and fatigue (e.g. Byrne et al., 1996; Britton et al., 2007; Zhang, 2007; Donovan et al., 2007). We also examined physical activity as a potential confound because of previous work linking physical activity to lower HRV (e.g. De Meersman, 1993) and lower inflammation (e.g. Reuben et al., 2003), and evidence that exercise interventions moderately reduce cancer-related fatigue (e.g. Brown et al., 2011). Smoking status may also be a confound in the relationship between HRV, fatigue, and inflammation. Seven women reported being current smokers. We ran all analyses with and without these women; results remained the same, thus they were left in the sample in the analyses reported here to maintain our sample size.

We then tested whether the association between HRV and fatigue was mediated by inflammation using path analysis with the sem command in STATA 12. Mediation is tested by evaluating the significance of the indirect effect, which is determined by comparing the total and direct effects (see Fig. 1; Iacobucci et al., 2007). Because the distribution of indirect effects is known to not be normally distributed, significance of the indirect effect was tested using 95% bias-corrected confidence intervals (BCI) based on 1000 replicates (MacKinnon et al., 2004; Fritz and MacKinnon, 2007). BMI and age were included as covariates in all paths in the model.

[1] We also tested whether there were any significant differences in demographic and treatment-related variables between the women from the parent studies who underwent ECG assessment and those who did not undergo ECG assessment. Women who underwent ECG assessment were significantly more likely to have received a mastectomy as opposed to a lumpectomy; there were no other significant differences.

3. Results

3.1. Participant characteristics

Table 1 displays the demographic and treatment-related characteristics of participants from whom we collected ECG data. For the total sample (across Sample 1 and Sample 2), women were on average 46 years old, the majority were Caucasian (73%), in a committed relationship (70%), employed at least part time (74%), and were 3.7 years from diagnosis. The majority of women had received chemotherapy (74%), radiation therapy (66%), and were currently receiving endocrine therapy (67%). Differences between the two samples in treatment received were only present for type of surgery. A smaller percentage of women in Sample 1 received a lumpectomy only (17%) compared to Sample 2 (48%).

Table 2 displays the mean fatigue, HRV, and inflammatory values for each sample. The mean FSI average score was 4.04 (SD = 1.94), which is above the clinically significant cutoff of 3 on this scale (Donovan and Jacobsen, 2010). The mean levels of RMSSD, HF-HRV, IL-6, and CRP, are comparable to those reported for healthy adults (Marsland et al., 2007; Gruenewald et al., 2009; Gordon et al., 2012).

We next examined the association between HRV and demographic, treatment-related, and other potential confounds. Consistent with previous research, women had lower HRV if they were older (RMSSD, $r = -.26$, $p = .016$; HF-HRV, $r = -.32$, $p = .003$) and had a higher BMI (RMSSD, $r = -.25$, $p = .025$; HF-HRV, $r = -.15$, $p < .1$). No other demographic or treatment related variables were associated with HRV. Physical activity was not associated with HRV (RMSSD, $r = .15$, $p = .178$; HF-HRV, $r = .079$, $p = .483$).

3.2. Associations between HRV and fatigue

Our primary analyses examined the association between measures of HRV and fatigue. Bivariate correlations between variables are presented in Table 3. As predicted, RMSSD was significantly negatively correlated with FSI average and FSI days, and marginally correlated with FSI most. Women with lower RMSSD scores, indicating lower HRV, reported higher average levels of fatigue, more days fatigued, and marginally greater fatigue severity. In regression analyses controlling for physical activity, the associations remained the same (for FSI average, $B = -.075$, $p = .02$; for FSI days, $B = -.056$, $p = .043$; for FSI most, $B = -.045$, $p = .084$). After controlling for age and BMI, the association between RMSSD and FSI average remained significant ($B = -.063$, $p = .043$), though the associations with FSI days and FSI most were attenuated ($B = -.042$, $p = .125$ and $B = -.036$, $p = 158$, respectively).

HF-HRV was marginally negatively correlated with FSI average, but not with the other two fatigue indices. When controlling for physical activity, the association with FSI average remained marginally significant ($B = -.11$, $p = .077$). After

Table 1 Baseline characteristics for total sample and individual samples.

	Total (N = 84)	Sample 1 (n = 60)	Sample 2 (n = 24)	p value[a]
Age, *M* (SD)	46.5 (6.8)	46.5 (7.2)	47.1 (5.7)	.739
Years since diagnosis, *M* (SD)	3.7 (2.2)	3.7 (2.3)	3.6 (1.8)	.768
Ethnicity, *N* (%)				.406
White	62 (73.2)	46 (76.7)	16 (66.7)	
African American	2 (2.4)	1 (1.7)	1 (4.2)	
Asian	10 (11.9)	6 (10.0)	4 (16.7)	
Other	10 (11.9)	7 (11.7)	3 (12.5)	
Marital status, *N* (%)				.174
In committed relationship	59 (70.2)	38 (63.3)	21 (87.5)	
Other	25 (29.8)	22 (36.7)	3 (12.5)	
Family yearly income, *N* (%)				.337
Under $60,000	15 (18.3)	12 (20.3)	3 (13.0)	
$60,001—$100,000	19 (23.2)	11 (18.6)	8 (34.8)	
Over $100,000	48 (58.5)	36 (61.0)	12 (52.2)	
Employment, *N* (%)				.386
Employed full time	46 (54.8)	31 (51.7)	15 (62.5)	
Employed part time	16 (19.1)	13 (21.7)	3 (12.5)	
Home maker	8 (9.5)	5 (8.3)	3 (12.5)	
Unemployed	6 (7.1)	6 (10.0)	0 (0)	
Other	8 (9.52)	5 (8.3)	3 (12.5)	
Cancer treatments received, *N* (%)				
Chemotherapy	62 (73.8)	43 (71.7)	19 (79.1)	.48
Radiation therapy	55 (65.5)	41 (68.3)	14 (58.3)	.384
Surgery type, *N* (%)				.018*
Lumpectomy only	33 (39.3)	29 (48.3)	4 (16.7)	
Mastectomy	50 (59.5)	31 (51.7)	19 (79.2)	
None	1 (1.2)	0 (0)	1 (4.1)	
Current endocrine therapy	56 (66.7)	40 (66.7)	16 (66.8)	1

[a] Comparison between studies was tested with *t*-tests or chi square.
* $p < .05$.

controlling for age and BMI, this association was attenuated (B = −.092, p = .121).

3.3. Associations between HRV and inflammation

In bivariate analyses, RMSSD was significantly negatively correlated with IL-6 and CRP (see Table 3). After controlling for physical activity, the association between RMSSD and IL-6 remained significant, B = −.344, p = .012, while the association between RMSSD and CRP was slightly attenuated, B = −.105, p = .061. After controlling for age and BMI, the associations were no longer significant (B = −.193, p = .193 for IL-6; B = −.033, p = .596 for CRP).

HF-HRV was also significantly negatively correlated with IL-6 and CRP. After controlling for physical activity, these associations remained significant (for IL-6, B = −.709,

Table 2 Means of key study variables for total sample and by individual sample.

Variable	Total (N = 84) *M* (SD)	Sample 1 (n = 60) *M* (SD)	Sample 2 (n = 24) *M* (SD)	p value[a]
Fatigue				
FSI average	4.04 (1.94)	3.93 (1.96)	4.29 (1.90)	.448
FSI most	6.11 (2.41)	6.05 (2.56)	6.25 (2.03)	.734
FSI days	4.24 (2.28)	4.33 (2.36)	4.02 (2.09)	.573
Heart rate variability				
RMSSD	29.01 (17.23)	30.47 (18.25)	25.40 (14.09)	.226
HF-HRV (power ms^2)	397.74 (400.83)	421.88 (438.43)	339.40 (290.55)	.4
Inflammation				
IL-6 (pg/ml)	1.27 (.76)	1.15 (.69)	1.35 (.75)	.217
CRP (mg/l)	1.43 (1.74)	1.21 (1.48)	1.35 (1.51)	.425

[a] Comparison between studies was tested with t-tests or chi square. All units reported in original scale, not log transformed.

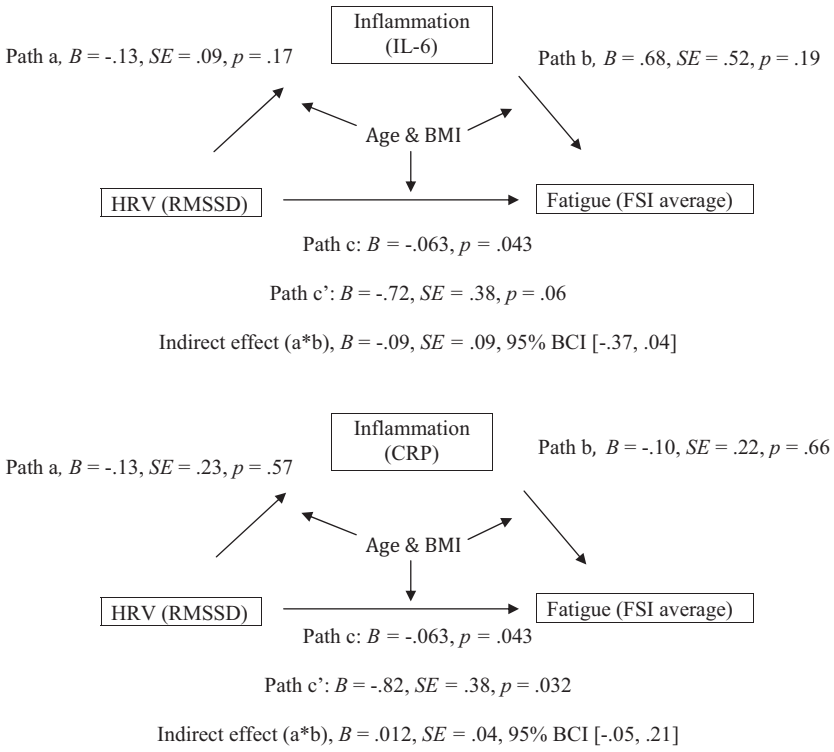

Figure 1 Path model examining the indirect effect of HRV on fatigue through IL-6 and CRP controlling for age and BMI in all paths. Path a represents the relationship between HRV and either IL-6 or CRP. Path b represents the relationship between IL-6 or CRP and average level of fatigue. Path c is the total effect of HRV on fatigue (parallel to the regression analyses), and path c′ is the direct effect of HRV on fatigue after controlling for either IL-6 or CRP. The difference between the total and direct effects, or indirect effect, was not significant for either IL-6 or CRP, indicating that neither marker was a significant mediator. BCI = bias corrected confidence interval.

$p = .006$; for CRP, $B = -.216$, $p = .041$). After controlling for age and BMI, the associations were attenuated ($B = -.496$, $p = .078$ for IL-6; $B = -.109$, $p = .364$ for CRP).

3.4. Associations between inflammation and fatigue

IL-6 was marginally positively correlated with fatigue (see Table 3). Women with higher IL-6 values reported marginally greater average levels of fatigue and fatigue severity. The associations between IL-6 and fatigue indices remained marginally significant when physical activity was added to the model (all p's < 15). After controlling for age and BMI, the associations between IL-6 and fatigue were not significant (for FSI average, $B = .038$, $p = .133$; for FSI days, $B = .015$, $p = .498$; for FSI most, $B = .03$, $p = .148$). CRP was not associated with any indices of fatigue.

3.5. Path analyses testing inflammation as a mediator of HRV and fatigue

Next, we conducted path analyses to test whether the association between HRV and fatigue was mediated by IL-6 or CRP. The models are illustrated in Fig. 1. We selected

Table 3 Correlations between fatigue, HRV, and inflammatory markers.

	1.	2.	3.	4.	5.	6.
1. FSI average	—					
2. FSI most	.816***	—				
3. FSI days	.734***	.638***	—			
4. RMSSD (ln)	−.269*	−.197†	−.229*	—		
5. HRV-HF (ln)	−.204†	−.167	−.172	.915***	—	
6. IL-6 (ln)	.213†	.203†	−.178	−.310**	−.322**	—
7. CRP (ln)	.028	.044	−.090	−.231*	−.244*	.609***

* $p < .05$.
** $p < .01$.
*** $p < 001$.
† $p < .10$.

RMSSD as the predictor variable and FSI average as the dependent variable for these analyses based on results from the correlation and regression analyses. Note that mediational effects may still be present when the relationship between the independent and dependent variable is weak (Stanton et al., 2013). Age and BMI were included as covariates in all models. Results showed that neither IL-6 nor CRP were significant mediators of the association between RMSSD and average fatigue.

4. Discussion

Cancer-related fatigue is a significant problem for many cancer survivors, and particularly younger women diagnosed with premenopausal breast cancer (Howard-Anderson et al., 2012). The drivers of persistent post-treatment fatigue remain largely unknown. The current project tested an understudied contributor to cancer-related fatigue — parasympathetic nervous system activity. Results supported the hypothesis that lower parasympathetic activity, as measured by resting HRV, was associated with higher levels of fatigue. Specifically, breast cancer survivors who had lower levels of RMSSD reported higher levels of average fatigue in the past week, controlling for age, BMI, and physical activity. These findings are consistent with an earlier report that found an association between HRV and fatigue in breast cancer survivors within one year post treatment (Fagundes et al., 2011), and extend these results to demonstrate an association with fatigue in longer-term (and younger) survivors.

Our second goal was to test inflammation as a mediator of the association between HRV and fatigue. Bivariate analyses supported the possibility of inflammation as a mediator, as RMSSD was correlated with plasma levels of IL-6 and CRP, and IL-6 was marginally correlated with fatigue measures. However, these bivariate associations were attenuated after controlling for age and BMI. Moreover, a path model that included age and BMI as control variables did not support either inflammatory marker as a mediator in this young, relatively healthy sample. Together, these findings suggest that BMI may be playing an important role in driving inflammatory activity in this young, healthy sample, and may account in part for links between inflammation and cancer-related fatigue, as seen in previous research (Alfano et al., 2012).

These findings suggest that there may be other pathways linking HRV to cancer-related fatigue. Some investigators have suggested that sluggish autonomic responses to environmental demands or an imbalance between sympathetic and parasympathetic branches may contribute to physical fatigability and avoidance of physically demanding tasks (Pagani and Lucini, 1999), leading to reduced physical activity, deconditioning, and increased fatigue. Indeed, patients with chronic fatigue syndrome show reduced parasympathetic and increased sympathetic responsiveness to standard lab stimuli tests (i.e. walking, paced breathing) and mental stress tasks (Pagani et al., 1994; Sisto et al., 1995; Cordero et al., 1996). To our knowledge, only one study has tested the association between fatigue and autonomic responses to challenge in cancer survivors. Fagundes et al. (2011) found that in response to the Trier Social Stress Test, fatigued breast cancer survivors had significantly lower HRV and higher norepinephrine during the baseline and recovery periods than less fatigued women, though the magnitude of changes in HRV throughout the task did not differ based on fatigue level. There is also evidence that breast cancer survivors with persistent fatigue show blunted HPA responses to acute stress (Bower et al., 2005). Future studies should examine autonomic and endocrine responses to challenge among individuals with cancer-related fatigue. Perhaps more important, longitudinal studies are needed that assess ANS activity at the beginning of the cancer trajectory, to determine whether HRV predicts the development and persistence of cancer-related fatigue and underlying mechanisms for this association.

There are several limitations to our study. First, we used a cross-sectional design to examine associations between fatigue, HRV, and inflammation. Although this design can provide insight into factors that contribute to cancer-related fatigue, longitudinal studies are required to determine whether these factors play an etiological role in fatigue onset or persistence, or are instead a consequence of fatigue. Second, we choose to focus on resting HRV given evidence linking resting HRV with fatigue and inflammation in non-cancer samples. Future research should include more comprehensive assessment of ANS function both at rest and in response to acute stress. Third, we focused on two inflammatory markers that have been associated with fatigue and HRV in previous research; evaluation of other markers (e.g., soluble TNF receptor type II) would provide a more comprehensive assessment of the pro-inflammatory cytokine network and may have enhanced our ability to identify associations with cancer-related fatigue (Bower et al., 2002, 2011). In addition, associations between cancer-related fatigue and biological processes may be more evident in samples specifically selected for reporting severe and persistent fatigue (e.g., Bower et al., 2002; Collado-Hidalgo et al., 2006; Alexander et al., 2009). Additionally, we did not carefully capture medication use, which, despite the overall good health of the sample, may influence levels of inflammation. Finally, our study was not specifically powered to detect mediation. Mediation effects can be difficult to find in small samples, and thus the results from our model should be considered preliminary (Fritz and MacKinnon, 2007).

In conclusion, HRV has been linked to a variety of psychological and physical illnesses (Thayer and Sternberg, 2006), including depression, anxiety disorders, and all-cause mortality (Tsuji et al., 1994; Gorman and Sloan, 2000). Our findings suggest that HRV may also play a role in fatigue experienced in the aftermath of cancer treatment. Given the prevalence and persistence of this symptom in the growing population of cancer survivors, future work should continue to explore the role of HRV as a correlate and potential contributor to this debilitating symptom.

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Conflict of interest statement

The authors report no conflicts of interest.

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