Heart Rate Variability as a Marker of Distress and Recovery: The Effect of Brief Supportive Expressive Group Therapy With Mindfulness in Cancer Patients

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Abstract

Objectives. We aimed to investigate the effects of brief supportive expressive group therapy with mindfulness for cancer patients and to assess the utility of heart rate variability (HRV) as a biomarker of distress and treatment effect. *Methods.* A total of 28 female patients with nonmetastatic cancer at a university hospital in South Korea received a 4-week modified group therapy for distress reduction. The BESTMIND (Brief Expression and Support Therapy with Mindfulness) program consisted of supportive–expressive group therapy and mindfulness-based stress reduction. The subjective outcomes of distress, anger, sleep quality, and sense of well-being and the physiological outcome of HRV were assessed before and after the program. *Results.* After the program, patients showed significantly reduced distress, perceived stress, anger, and sleep disturbance and increased quality of life. No significant change was observed in the degree of mindfulness. A significantly increased SD in the normal beat-to-beat intervals and normalized high-frequency (HF 0.15-0.4 Hz) power from spectral analysis were observed after treatment. According to the correlation analyses, HF power correlated with depression scores, and normalized HF power was associated with depression, anxiety, perceived stress, and anger at baseline. The pretreatment and posttreatment comparison indicated that an increase in HF power was associated with a decrease in anger. *Conclusions.* These results suggest the effectiveness of this modified group-based program for distress reduction and also provide preliminary evidence for the use of HRV as a biomarker of distress and recovery. HF power from HRV variables may serve as a quantitative biomarker of the treatment response of distress management, including anger.

Keywords

cancer, distress management, heart rate variability, anger, marker

Introduction

Cancer and its treatment often induce psychological distress and physical dysfunctions.[1] Previous studies have demonstrated that tumor-promoting factors, the effects of surgery or anticancer treatment, and distress can also affect cardiac autonomic functioning and modulate the autonomic nervous system (ANS) in patients with cancer.[2] Heart rate variability (HRV) is one of the objective and noninvasive measures of ANS regulation. HRV is a quantified analysis of the beat-to-beat variation in R-R interval and represents an interaction between sympathetic and parasympathetic control in the central and peripheral nervous systems.[3] Altered and dysfunctional ANS has been reported in patients with cancer, and patients with cancer had lower HRV than healthy controls.[4]

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Integrative treatment to reduce the distress associated with cancer has been considered a key component of supportive care for patients with cancer. For example, supportive-expressive group therapy (SEGT) is a psychotherapeutic intervention originally developed for patients with metastatic breast cancer.[5] It is now available as a brief program of 12 weekly sessions that focuses on the development of strategies to express painful emotions and enrich social support and individual resources.[5] The SEGT helps participants work through fears about dying and loss of roles; the participants in the SEGT have opportunities to review their lives, enhance their sense of control, and address the meaning of the cancer.[6] SEGT is psychosocially effective for patients with breast cancer in terms of various outcomes, such as mood and pain.[7] Mindfulness-based stress reduction (MBSR), a meditation-based program designed by Kabat-Zinn[8] to relieve emotional and physical stress, has also been shown to be an effective intervention for reducing stress and mood-related symptoms and for improving psychosocial coping in patients with cancer.[9] Nijjar et al[10] reported that MBSR improved the cardiac sympathetic/parasympathetic balance, measured by HRV, of healthy volunteers. However, few interventional trials have demonstrated improvement in HRV parameters after distress management interventions for patients with cancer, though nonspecific treatment, including autogenic training,[11] massage,[12] and exercise,[13] showed positive effects, as measured by HRV.

In this study, we developed a BESTMIND (Brief Expression and Support Therapy with Mindfulness) program for patients with cancer. It is a group therapy combining SEGT and MBSR that we modified to a 4-week, brief program to provide a feasible and applicable intervention overcoming time commitment and enhancing cost efficacy.[14] We hypothesized that this program would ameliorate psychological distress and, thus, improve HRV parameters in patients with cancer. The aim of our study was to investigate the effects of a BESTMIND program and examine associations between the psychological distress and HRV parameters after the treatment.

Methods

Participants

Participants were recruited from the Cancer Center of Seoul National University Bundang Hospital (SNUBH) in South Korea from October 2012 to January 2014 using advertisements at the hospital. Because of the higher prevalence of distress in female than in male patients with cancer[15] and gender differences on HRV,[16] we included only female patients in this study. Patients were initially screened by clinical interview or chart review following inclusion criteria: (1) female, (2) diagnosis of nonmetastatic cancer, (3) completion of coadjuvant chemotherapy (except hormone therapy), and (4) desire to reduce subjective distress.

Informed consent was obtained from all participants. The exclusion criteria were as follows: (1) obvious intellectual impairment, (2) history of a psychotic disorder, (3) suicide risk, (4) any changes in medications during the program, and (5) history of cardiovascular diseases. Initially, 67 eligible patients were contacted, and 38 participants were enrolled in the study. Among them, 1 participant refused the baseline assessment for no apparent reason, and 9 participants dropped out because of personal time restrictions (5), aggravation of physical status (3), and lack of necessity (1). Ultimately, 28 participants completed this study.

Study Procedure

This study is an open-label, single-arm pre-post comparison design. The BESTMIND consisted of 3-hour weekly sessions for 4 weeks combining 2 hours of SEGT and 1 hour of MBSR per session. The efficacy of SEGT and MBSR were examined in previous research on stress management for patients with cancer.[17] We ran 6 therapy groups, including a total of 38 female patients with nonmetastatic cancer. Two psychiatrists and 1 psychologist ran the brief group therapy sessions. In the SEGT part, therapy was focused on expressing painful emotion and enriching social support for the participants. In the MBSR part, participants were trained using breathing awareness, body scanning, and walking by a facilitator trained in the Kabat-Zinn MBSR program. Participants were assessed twice: the baseline assessment was performed before participation in the program, and the follow-up assessment was performed after the last session of the program. Sociodemographic and clinical (status of cancer, cancer treatment, current medications, and body mass index [BMI]) data were collected at baseline. The study protocol was approved by the institutional review board of SNUBH (No. B-1209/170-004).

Psychological Measurements

The Korean version of the Hospital Anxiety and Depression Scale,[18] which we used to evaluate psychological distress in patients with cancer, is composed of anxiety and depression subscales. Both subscales contain 7 items, and total scores on each subscale range from 0 to 21. Higher scores reflect higher levels of distress. The Cronbach's α for this measure was .90.

The level of perceived stress was measured with the Perceived Stress Scale (PSS),[19] which consists of 10 items rated on a 5-point Likert scale. Total scores range from 0 to 40, with higher scores reflecting greater stress. The internal consistency was α =.76.

The State-Trait Anger Scale (STAS)[20] is a self-report questionnaire assessing the intensity of state and trait anger. Each subscale consists of 10 items rated on a 4-point Likert scale. Trait anger refers to a stable personality trait that underpins an individual's anger or rage responses. State

anger refers to feelings of anger at the time the scale is completed. The Cronbach's α for the state items was .92, and it was .88 for the trait items.

Sleep quality and quantity were evaluated with the Pittsburgh Sleep Quality Index (PSQI),[21] which consists of 18 items divided into 7 subscales. Total PSQI scores ≥5 indicates a clinically significant sleep disturbance. The internal consistency was α =.84 for our sample.

To assess quality of life (QoL), we used the Functional Assessment of Cancer Therapy–General (FACTG),[22] a 27-item self-report questionnaire that relies on a 5-point Likert scale. It comprises 4 domains: physical well-being, social/family well-being, emotional well-being, and functional well-being. Higher scores indicate greater well-being. The Cronbach's α for the total scale was .89 in this study.

The Mindfulness Attention Awareness Scale (MAAS)[23] was used to investigate the mediating role of mindfulness. This is a 15-item scale that measures the tendency to be attentive and aware of current life experiences. MAAS scores range from 1 to 6, and higher scores indicate greater mindfulness. The internal consistency was α =.74, in the acceptable range.

Coping style was assessed using the Korean Cancer Coping Questionnaire, which has been validated for Korean patients.[24] It includes 23 items rated on a 4-point Likert scale, with higher scores indicating a tendency to adopt positive coping styles. The Cronbach's α was .93 in our study.

HRV Measurements

We obtained high-resolution (1000 Hz) electrocardiograms (ECGs) for 8 minutes using the Synamps 2 amplifier (Compumedics, Melbourne, Australia). The participants did not drink caffeine/alcohol and smoke for at least 8 hours prior to the examination, and ECG recordings were processed 1 hour after the last session of the program. Further analysis of the time- and frequency-domain parameters of HRV were performed using analysis software (Telescan and Complexity, version 2.0; Laxtha, Daejeon, Korea). In the time domain, the following statistical parameters were calculated: the normal-to-normal R-R interval (NN), SD of the NN (SDNN), root mean square of the differences in successive NNs (RMSSD), and HRV index (Total NNs/Height of histogram of all NNs). Parametric autoregression was performed on the power spectral domain analysis. The power of low-frequency (LF; 0.04-0.15Hz) and high-frequency (HF; 0.15-0.4 Hz) bands in absolute and normalized (divided by LF + HF) units and the LF/HF ratio were determined. Normalized HF and LF power have the advantage of reducing the effect of total power differences.[25]

Statistical Analysis

Pearson's χ^2 test or Fisher's exact test was used to analyze baseline demographic and clinical variables as well as all categorical variables; *t*-tests were used for continuous variables. HRV parameters were log-transformed because of a skewed distribution. Paired *t*-tests were used to compare the pretreatment and posttreatment data.

Our primary hypothesis was that higher levels of psychological distress would be related to lower HRV. Changes in these variables were tested for correlation after the intervention. First, partial correlations between baseline psychological data and HRV parameters were investigated, with age and BMI as covariates.[16] Second, we examined the relationship between changes caused by intervention in HRV (Δ = Post − Pre) and psychological state (Δ) using multiple linear regressions with stepwise selection. *P* values <.05 were considered significant. All analyses were conducted using IBM SPSS Statistics version 18 (IBM Corp, Armonk, NY).

Results

Demographic and Clinical Variables

In total, 38 participants were recruited, and 28 participants completed the program. The mean age of the 28 participants was 50.6 years, and 85% of participants had breast cancer (Table 1).

Psychological Variables

The results of the paired *t*-tests are presented in Table 2.

HRV Parameters

Because 5 participants refused to take ECG for posttreatment HRV because of time constraints, the pretreatment and posttreatment HRV data of 23 participants were collected and analyzed (Table 3).

Partial Correlation Analysis and Multiple Linear Regressions

The primary analyses examined the relationship between HRV parameters and psychological stress at baseline after controlling for age and BMI. Normalized LF power was significantly correlated with psychological variables (HADS-anxiety: $r = 0.471$, $P = .017$; HADS-depression: $r = 0.543$, $P = .005$; PSS: $r = 0.400$, $P = .048$; STAS-state: $r = 0.554$, $P = .004$) and negatively correlated with well-being (FACTG total: $r = −0.658$, $P < .001$). HF power was significantly correlated with distress (HADS-depression: $r = −0.573$, $P = .003$) and with well-being (FACTG total: $r = 0.412$, $P = .041$). Normalized HF power was significantly correlated with stress-related variables (for HADS-anxiety: $r = −0.471$, $P = .017$; HADS-depression: $r = −0.543$, $P = .005$; PSS: $r = −0.400$, $P = .048$; STAS-state: $r = −0.554$, $P = .004$) and with well-being (FACTG total: $r = 0.658$, $P < .001$). The LF/HF ratio was significantly

Table 1. Demographic and Clinical Characteristics of the Participants at Baseline.

Variables	Participants (n = 28)
Age (years)[a]	50.61 ± 9.01
Body mass index (kg/m^2)	22.56 ± 2.84
Marital status[b]	
Married	27 (96.4)
Divorce/Separated	1 (3.6)
Educational level[b]	
High school	15 (53.6)
≥University	13 (46.4)
Type of cancer (number)	
Breast	24 (85.7)
Colon	3 (10.7)
Cervical	1 (3.6)
Stage[b]	
0	2 (7.1)
1	13 (46.46)
2	7 (25.0)
3	6 (21.4)
4	0 (0.0)
Chemotherapy (yes)[b]	19 (67.9)
Radiotherapy (yes)[b]	18 (64.3)
Current medications	
No	21 (75.0)
Yes	
Antidepressants	5 (17.9)
Antihypertensive drugs	1 (3.6)
Antidiabetic drugs	1 (3.6)
Antihypercholesterolemic drugs	2 (7.1)
Hormonal therapy (yes)[b]	14 (50.0)
Time since diagnosis until the study entry (days)[a]	385.2 ± 479.8

[a]Data given as mean ± SD.
[b]Data given as number (%).

correlated with psychological variables (HADS-anxiety: $r = 0.474$, $P = .017$; HADS-depression: $r = 0.565$, $P = .003$; PSS: $r = 0.548$, $P = .005$; STAS-state: $r = 0.447$, $P = .025$) and negatively correlated with well-being (FACTG total: $r = -0.657$, $P < .001$). RMSSD was correlated with sleep disturbances (PSQI: $r = -0.418$, $P = .038$).

Second, analyses of the relationship between changes in HRV and psychological data, before and after treatment (Δ) were performed using multiple linear regressions, with stepwise selection (Δ HRV parameters as dependent variables, Δ psychological data, psychological and HRV variables at baseline, age, and BMI as independent variables). Results are presented in Table 4.

Discussion

This study investigated the effects of a BESTMIND program for female patients with cancer suffering

from psychological distress. We observed significant improvement in psychological factors, including depression, distress, anger, insomnia, and QoL after the program. HRV parameters, including SDNN and normalized HF, were increased in participants. More important, there were negative correlations between HF power and depression and between normalized HF power and distress in the form of depression, anxiety, perceived stress, and anger at baseline. Furthermore, HF power and normalized HF power were both positively associated with QoL. The LF/HF ratio was positively correlated with cancer participants' anger and negatively correlated with sense of well-being. In the context of the intervention, mean changes in normalized LF and normalized HF power were related to changes in sleep disturbances, and changes in HF power were related to changes in anger and sleep before and after the intervention.

Previous studies have shown that SEGT and MBSR have positive effects on mood disturbance, emotional adaptation, and maladaptive coping behaviors in patients with cancer.[26,27] Our results suggest the clinical usefulness of this relatively short-term, group-based therapy, which includes strategies from SEGT and MBSR, for female patients with cancer. In this study, MAAS scores of the participants did not significantly change after the intervention was completed. This was likely because the total time for the mindfulness practice was shorter than that of conventional MBSR and because the MAAS measures only one aspect of mindfulness, leaving other aspects that may be affected by MBSR unaddressed.[28] Future studies with multifaceted measures of mindfulness could overcome these weaknesses.

Because vagal activity tends to be impaired in patients with cancer, the SDNN and RMSSD were lower in our sample than those in healthy people.[4] This difference may be explained by tumor progress and cancer treatment. Research has demonstrated that emotional stress also reduces HRV[29]; however, despite the high level of stress associated with the disease, this relationship has not been directly investigated in patients with cancer. A recent review[2] noted that fatigue and depression had a strong impact on vagal attenuation in patients with breast cancer, but there have been few investigations of associations between HRV and more specific psychological dimensions. Our correlation analyses on baseline data indicated that HF power (absolute or normalized) was negatively related to scores for distress and positively correlated with QoL. HRV has been considered a marker of emotional awareness and self-regulation in healthy people,[30] and it may be an index of the central autonomic network that controls psychophysiological resources during emotional regulation processes.[31] Decreased HRV, which reflects a hypoactive vagal system, is related to cognitive and affective dysregulation, both of which are significant risk factors for depression.[31] Specifically, HF power is mediated primarily by parasympathetic (vagal) influences. During mental stress,

Table 2. Paired Sample *t*-Test of Psychological Variables Before and After the Treatment (n = 28).[a]

Variables	Baseline	After the Treatment	*t*-Value	P Value
Hospital Anxiety and Depression Scale (total)	31.71 ± 5.55	27.04 ± 4.74	4.34	<.001
Anxiety	16.25 ± 3.43	13.75 ± 2.62	4.36	<.001
Depression	15.54 ± 3.05	13.29 ± 2.94	3.44	.002
Perceived Stress Scale	20.75 ± 5.23	16.93 ± 4.96	4.17	<.001
State-Trait Anger Scale	36.69 ± 10.12	32.00 ± 8.98	3.12	.005
State	15.91 ± 6.33	12.60 ± 3.11	4.07	<.001
Trait	20.78 ± 5.91	19.39 ± 4.38	1.64	.112
Pittsburgh Sleep Quality Index	8.74 ± 5.00	7.30 ± 4.30	2.57	.016
Mindfulness Attention Awareness Scale	28.75 ± 9.10	26.64 ± 6.66	1.26	.219
Cancer Coping Questionnaire	50.14 ± 8.61	53.50 ± 9.14	−2.02	.053
Functional Assessment of Cancer Therapy General (total)	53.43 ± 15.17	61.25 ± 16.61	−3.21	.003
Physical well-being	14.93 ± 6.09	16.75 ± 6.94	−1.80	.084
Social/Family well-being	10.57 ± 3.90	11.46 ± 5.41	−1.22	.232
Emotional well-being	14.14 ± 5.54	16.50 ± 5.38	−2.93	.007
Functional well-being	13.89 ± 4.87	16.89 ± 5.17	−3.21	.003

[a]Data are given as mean ± SD.

Table 3. Paired Sample *t*-Test of Heart Rate Variability Parameters Before and After the Treatment (n = 23).[a]

Variables	Baseline	After the Treatment	*t* Value	P Value
Time domain				
RR intervals (ms)	852.1 ± 137.0	891.5 ± 143.4	−2.17	.041
SDNN (ms)	33.42 ± 14.08	37.39 ± 17.62	−2.31	.031
RMSSD (ms)	27.56 ± 19.92	28.37 ± 21.32	−0.44	.667
Frequency domain				
TP, $\ln(ms^2)$	6.46 ± 0.86	6.51 ± 0.85	−0.44	.662
VLF, $\ln(ms^2)$	5.51 ± 0.90	5.47 ± 0.73	0.27	.790
LF, $\ln(ms^2)$	4.96 ± 1.49	4.70 ± 1.19	1.39	.179
Normalized LF (ν)	56.84 ± 22.43	42.26 ± 19.87	2.69	.014
HF, $\ln(ms^2)$	4.77 ± 1.21	5.05 ± 1.60	−1.43	.167
Normalized HF (ν)	43.16 ± 22.43	57.74 ± 19.87	−2.69	.014
LF/HF ratio	2.99 ± 4.99	1.07 ± 1.20	1.83	.080

Abbreviations: SDNN, SD of normal beat to beat intervals; RMSSD, root mean square successive difference; TP, total power; VLF, very-low-frequency power; LF, low-frequency power; HF, high-frequency power.
[a]Data given as mean ± SD.

Table 4. Multiple Linear Regression Analysis Predicting Post-Pre Changes (Δ) in Variables of Heart Rate Variability by Δ Psychological Variable (n = 23).

Variables		Frequency Domain			
		ΔVLF, $\ln(ms^2)$	ΔNormalized LF (ν)	ΔHF, $\ln(ms^2)$	ΔNormalized HF (ν)
Δ Hospital Anxiety and Depression Scale: anxiety	β Coefficient, P value	—	−3.651, .170	—	3.661, .165
Δ Hospital Anxiety and Depression Scale: depression	β coefficient, P value	—	2.129, .315	—	−2.171, .300
Δ Perceived Stress Scale	β coefficient, P value	0.042, .187	1.822, .097	—	−1.812, .095
Δ State-Trait Anger Scale: state	β coefficient, P value	0.096, .043	3.274, .066	−0.123, .024	−3.263, .064
Δ State-Trait Anger Scale: trait	β coefficient, P value	−0.069, .108	2.033, .137	—	−2.029, .134
Δ Pittsburgh Sleep Quality Index	β coefficient, P value	—	−4.666, .027	0.167, .014	4.667, .026

Abbreviations: VLF, very-low-frequency power; LF, low-frequency power; HF, high-frequency power.

the ANS balance shifts toward parasympathetic withdrawal, and there is a consensus that decreased HF power is associated with psychological stress.[32] Our results are consistent with these previous studies and imply the usefulness of HRV as an adjuvant marker of QoL as well as distress in patients with cancer. However, the results on cancer populations remain limited, and additional research is needed to link psychological factors and HRV parameters.

There have been only a limited number of interventional studies investigating the role of HRV in patients with cancer. Fernandez-Lao et al[12] found increased SDNN, RMSSD, and HF power after a single session of massage in breast cancer survivors. Minowa and Koitabashi[11] reported increased HF power after autogenic training and relaxation in patients with breast cancer. Fong et al[13] reported transient improvements in HRV, increased HF power, and decreased LF power during Tai Chi and Qigong among patients with nasopharyngeal cancer. However, other pilot studies have described contrasting results on HRV variables after mindfulness art therapy[33] and relaxation[34] in cancer patients. We observed increased SDNN and normalized HF power after the 4-week intervention. Further regression analyses showed that a decrease in anger state after the intervention was related to an increase in HF power after adjusting covariates. To the best of our knowledge, this is the first study to show the effect of brief group therapy for stress reduction on HRV in patients with cancer and associated psychological difficulties, including anger regulation and dissatisfaction with QoL. Patients with cancer can suffer from difficulty coping with and expressing painful emotion. Spiegel et al,[5] who developed SEGT, demonstrated that the expression of painful emotion might correlate with the survival rates of patients with cancer. Our intervention was focused primarily on the expression of painful emotions such as anxiety and anger, and participants reported a reduction in anxiety and anger after the program, reflecting the effect of expressive therapy on emotional adaptation. In this study, decrease in anger was related to increase in HF power on pre-post comparison. The HF-HRV is a relatively unbiased index of parasympathetic (vagal) activity.[25] In contrast, the LF-HRV has been considered to be an index of sympathetic/parasympathetic activity because it is dually mediated.[25] Therefore, the HF power component was used as the main index of vagal activity, which is especially important given that painful emotion (eg, anger) leads to parasympathetic withdrawal.[35] Indeed, a previous study reported an association between angry rumination and low levels of vagal activity in adolescents.[36] Kop et al[37] also reported that negative mood was associated with HF-HRV in healthy individuals. Our results add support to evidence of the connection between the HF-HRV and anger control in patients with cancer and suggest that HF-HRV may be an index of the success of treatment targeting the emotional (anger) control of patients with cancer.

This exploratory study produced suggestive results, but several limitations should be noted. The statistical power of our study may have been compromised by the modest sample size and absence of a control group; therefore, the results should be interpreted with caution. Additionally, the findings cannot be generalized to male patients and other areas.

Conclusion

In summary, the BESTMIND program ameliorated stress and HRV by increasing SDNN and normalized HF power in female patients with cancer. Moreover, improvement in HF power and decrease in anger were correlated after the intervention. This implies that HRV may be an easily measurable, safe, and clinically meaningful marker of the psychological state and well-being of patients with cancer. Additionally, HRV has the additional advantage of enabling repeated measures within the same participant, which is important for assessing acute ANS responses to psychological interventions as well as for understanding the emotional valence associated with such interventions. The results of this study may have clinical implications related to the efficacy of BESTMIND for Korean female patients with cancer and to the use of HRV as a psychophysiological marker of stress and amelioration thereof in patients with cancer.

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