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Associations Between Positive Emotional Well-Being and Stress-Induced Myocardial:

Ischemia Well-being scores predict exercise-induced ischemia

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Abstract

Objective—Depressive symptoms have been associated with myocardial ischemia induced by mental (MSIMI) and exercise (ESIMI) stress in clinically stable ischemic heart disease (IHD) patients, but the association between positive emotions and inducible ischemia is less well characterized. The objective of this study was to examine the associations between ratings of well-being and stress-induced ischemia.

Methods—Subjects were adult patients with documented IHD underwent mental and exercise stress testing for the Responses of Myocardial Ischemia to Escitalopram Treatment (REMIT) trial. The General Well-Being Schedule (GWBS), with higher scores reflecting greater subjective well-being, and the Center for Epidemiologic Studies Depression Scale (CES-D) were obtained from the REMIT participants. Echocardiography was used to measure ischemic responses to mental stress and Bruce protocol treadmill exercise testing. Data were analyzed using logistic regression adjusting for age, sex, resting left-ventricular ejection fraction (LVEF), and resting wall motion score index, as well as health-related behaviors.

Results—GWBS scores were obtained for 210 individuals, with MSIMI present in 92 (43.8%) and ESIMI present in 64 (30.5%). There was a significant inverse correlation between GWBS-PE (Positive Emotion subscale) scores and probability of ESIMI (OR = 0.55 (95%CI 0.36 - 0.83), p

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All other authors have reported that they have no relationships relevant to the contents of this paper to disclose.

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= .005). This association persisted after additional control for CESD subscales measuring negative and positive emotions and for variables reflecting health-related behaviors. A similar inverse correlation between GWBS-PE and MSIMI was observed, but did not reach statistical significance (OR = 0.81 (95%CI 0.54 – 1.20), $p = .28$).

Conclusion—This is, to our knowledge, the first study demonstrating that greater levels of self-reported positive emotions are associated with a lower likelihood of ESIMI among patients with known IHD. Our results highlight the important interface functions of the central nervous and cardiovascular systems and underscore areas for future investigation.

Keywords

General well-being schedule; General well-being scale; positive emotions; exercise induced ischemia; mental stress induced ischemia; coronary heart disease

Introduction

Negative emotions and the parallel psychiatric diagnoses, namely depression, are shown to predict the development of cardiovascular disease and increased mortality.¹⁻³ One limitation of commonly used measures of distress, such as the Beck Depression Inventory and Patient Health Questionnaire-9,⁴ is they do not adequately assess the experience of positive emotion, another dimension of emotional functioning with implications for cardiovascular health.

Several studies have shown that high scores on measures of positive emotions are associated with a lower probability of early mortality,⁵ the development of cardiovascular disease,⁵⁻⁷ and subsequent cardiovascular events among individuals with cardiovascular disease.^{8,9} Many of these findings include controls for negative emotion or psychiatric disease,^{5,7,8,10,11} demonstrating that positive emotion appears to be an independent predictor of disease development and progression. This underscores the importance of assessing both positive and negative emotions in studies investigating the influence of psychological factors on cardiovascular health

The General Well-being Schedule (GWBS) is a measure of various aspects of negative and positive emotional being and has been shown to be a predictor of health outcomes, including incident cardiovascular disease.⁷ Among the domains of well-being comprising the GWBS, there is a subscale, GWBS-Positive Emotions (GWBS-PE), that assesses individual differences in the experience of both positive and negative emotion using a bipolar scale. Given the evidence documenting the importance of both positive and negative emotions to health, a measure that integrates that information into a single scale may confer advantages in the prediction of health outcomes.

One way of documenting the possible effects of well-being on ischemic heart disease (IHD) prognosis is via its association with intermediate biomarkers of adverse risk. Traditionally, inducible ischemia via exercise stress testing (ESIMI) is used as a risk indicator in IHD patients since it predicts a two-fold increase risk of mortality.¹² Mental stress-induced myocardial ischemia (MSIMI) is emerging as a reliable risk indicator in the IHD population

with one pooled analysis of 5 studies showing that MSIMI was associated with a twofold increased risk of a combined end point of cardiovascular events or total mortality.¹³ There are data supporting the association between negative emotions and inducible ischemia, as the severity of depressive symptoms has been linked to higher rates of MSIMI^{14,15} and ESIMI.¹⁴ Positive emotion measured by the Center for Epidemiologic Studies Depression Scale (CES-D) positive emotion subscale was associated with a lower rate of ESIMI.¹⁴ However, this analysis did not control for negative emotion, making it difficult to draw conclusions regarding the relative contribution of positive and negative emotion to that association.

In the current study, we investigated the association between the GWBS Positive Emotions subscale (GWBS-PE), a bipolar measure of positive and negative emotion, and inducible ischemia in response to both mental and exercise stress in patients with clinically stable IHD. In addition, we adjusted for the individual effects of positive and negative emotions. Further, we explored whether various health behaviors are possible mechanisms linking positive emotions to health outcomes. We hypothesized that higher levels of positive emotion, independent of negative emotion, would predict lower rates of ESIMI and MSIMI.

Methods

Study Design

Study participants were males and females 21 years of age or older recruited systematically for the REMIT study from the Duke University Health System department of cardiology outpatient clinics.¹⁶ All participants had documented IHD, as defined by angiographic finding of coronary artery stenosis > 70%, history of myocardial infarction, or status post revascularization procedures (i.e. coronary artery bypass grafting, or stenting). For complete details of the REMIT trial intervention, see the published methodology.¹⁶ Because the GWBS was not added to the REMIT protocol until after recruitment had begun, scores are only available from 210 (67.7%) REMIT participants.

During two separate visits, participants underwent interviews and psychometric testing, followed by mental and exercise stress testing protocols. Stress testing was conducted at the Duke Cardiac Diagnostic Unit in the morning between 8am and 11am following a period of beta-blocker washout of 24-48 hours. Three mental stress tasks (mental arithmetic, mirror trace, and anger recall) were administered in sequence, with a rest period of 6 minutes between tests. Approximately 20 minutes following mental stress testing, the patients completed treadmill exercise stress testing using the standard Bruce protocol,¹⁷ and testing was terminated according to the American College of Sports Medicine guidelines. Baseline and stress echocardiography was performed in the left-lateral position, with images captured during the final 3 minutes of each rest period and during the mental stress tasks. Images were acquired with a 3 MHz transducer in the harmonic imaging mode with a Phillips iE33 system (Bothell, WA) in the parasternal long- and short-axis views and apical 4- and 2-chamber views. Left ventricular ejection fraction (LVEF) is calculated from a 3 to 5 beat loop, and wall motion assessments are determined from 30 to 40 frames of systole from one cardiac cycle. Two experienced, blinded and independent raters performed echocardiographic readings of baseline and post-intervention images after the 6-week endpoint assessments using the American Society of Echocardiography 16-segment model.

¹⁸ Each segment was graded and scored as normal (1 = normal or hyperdynamic, score) or abnormal (2 = hypokinetic, 3 = akinetic, 4 = dyskinetic, or 5 =aneurysmal) wall motion. A wall motion score index (WMSI) was calculated as the sum of the segmental wall motion scores divided by the total number of the scored segments.

Inducible ischemia (both ESIMI and MSIMI) was defined as, compared to rest, the development of 1 or more ischemic markers during stress, including new or worsened wall motion abnormality (WMA); reduction of LVEF by 8% or more; or ST segment deviation (2 consecutive leads for 3 consecutive beats).

Participants were administered a battery of psychological assessments including the GWBS and the CES-D. The GWBS is an 18-item scale comprised of six subsets assessing various aspects of well-being and distress (depressed mood, anxiety, general health, vitality, emotional self-control, and a sense of positive well-being [GWBS-PE]), and has been demonstrated to be stable over time.¹⁹ For the purpose of the present study, we will focus on the three item GWBS-PE subscale as it will allow us to model individual differences in the propensity to experience negative and positive emotion measured on a bipolar scale. A representative item from that scale is “How have you been feeling in general?” with six response options ranging from “In very low spirits” to “In excellent spirits”. We chose this scale because the content reflected positive emotion in contrast to other facets of well being (i.e. self-control or general health). Also, the bipolar nature of each item of the scale had appeal as it integrates information about positive and negative emotion into a single scale.

The CES-D is a 20-item questionnaire in which patients report on the frequency of depressive symptoms experienced in the past 2 weeks using a 4-point Likert scale (range from “Rarely” to “All of the time”). Factor analytic studies suggest that the items can be meaningfully summarized as four unipolar subscales including a four item scale that measures individual differences in the experience of positive emotion (e.g. I was happy) and a seven item scale that measures individual differences in the experience of negative emotion (e.g. I was depressed).^{20,21} A study of IHD patients reported a moderate, inverse association between those two scales.²² We chose the CES-D subscales in order to test whether any associations between GWBS-PE and inducible ischemia are due to individual differences in the experience of positive emotions, negative emotions or both.

Patients were also asked to provide information about various health related behaviors including smoking, exercise and BMI. Smoking status was determined by self-report and grouped into current smokers and former/never smokers. Exercise status data was collected via self-report survey of the number of episodes in the last week of mild (minimal effort), moderate (not exhausting) or strenuous (heart beats rapidly) exercise. The sum of these three indicators was used as a measure of exercise frequency. BMI was calculated as weight (kg)/ (height in m)² from data that was gathered from the electronic medical record.

Statistical Analysis

Logistic regression models were used to examine the associations between GWBS-PE scores and MSIMI and ESIMI, adjusting for age, sex, resting LVEF, and resting WMSI (Model I). Subsequent models were refitted to provide additional control for negative

emotion (CESD-NE) scores (Model II), positive emotion (CESD-PE) scores (Model III), and a final model that controlled for both the CESD-NE and CESD-PE scores (Model IV).

We also refitted Model I with inclusion of the health-related behaviors previously described (smoking, exercise and BMI) as individual co-variables in the multivariate analysis. The purpose of this analysis was to see if the association between GWBS-PE and inducible ischemia could be accounted for by any of those health behaviors. Missing data for health behaviors was handled via listwise exclusion.

In all analyses, the GWBS-PE was scaled to its interquartile range so that the OR from the logistic models compared the risk of an individual at the 75th percentile of the predictor with an individual at the 25th percentile. SAS version 9.1 was used for the analysis (SAS Inc, Cary, NC). A p-value of less than .05 was considered statistically significant.

Results

Descriptive statistics were calculated and reported for all independent and dependent variables for the sample (Table 1). GWBS scores were obtained from 210 individuals. Valid data for scoring the presence or absence of MSIMI was available for all patients, whereas data on ESIMI was only available in 198 patients. Thus, the primary analyses are based on a sample size of 210 for MSIMI and 198 for ESIMI. There were no adverse events secondary to stress testing. Data on BMI and exercise habits was only available for 201 and 175 individuals, respectively. There were 170 patients with complete health behavior and MSIMI data and 163 patients with complete health behavior and ESIMI data.

GWBS-PE scores ranged from 1 to 15 with a mean of 10.07(SD = 3.05), and the Cronbach's alpha for the scale was 0.85. GWBS-PE scores were positively associated with CESD-PE scores ($r = .55$, $p < .001$) and negatively associated with CESD-NE scores ($r = -.66$, $p < .001$). Consistent with a previous study of IHD patients,²² CESD-PE and CESD-NE scores were significantly and inversely correlated ($r = -.50$, $p < .001$), and the Cronbach's alpha for the scales was 0.69, and 0.82, respectively.

MSIMI was present in 92 (43.8%) and ESIMI was present in 64 (30.48%). The rates of MSIMI and ESIMI were highly similar to those of the complete sample of 310 patients (43.5% and 33.8%, respectively) and tended to co-occur (Cramer's $V = 0.35$, $p < .001$). Adjusted analysis showed a significant negative association between GWBS-PE scores and probability of ESIMI (OR = 0.55 (95%CI 0.36 - 0.83), $p = .005$) (Table 2). There was not a significant association between GWBS-PE scores and probability of MSIMI (OR = 0.81 (95%CI 0.54 - 1.20), $p = .28$) (Table 2). The results were essentially the same when refitting this model in the sample of patients that reached target heart rate ($N = 154$) during exercise testing (OR = 0.53 (95%CI 0.34 - 0.84), $p = .007$).

The association between the GWBS-PE and ESIMI remained significant after additional control for CESD-NE scores (OR = .45 (95%CI 0.25-0.81), $p = .008$) and CESD-PE scores (OR = .60 (95%CI 0.37-0.972), $p = .038$) (Table 3). The association between GWBS-PE scores and ESIMI was attenuated and no longer statistically significant after adjusting for

both the CESD-NE and CESD-PE subscales (OR = 0.49 (95%CI 0.26-0.90), $p = .07$) (Table 3).

Recognizing that the effects of positive emotions on inducible ischemia may be accounted for by health-related behaviors, we attempted to incorporate these into our analysis. The GWBS-PE scores were higher among non-smokers ($M = 10.26$, $SE = .23$) compared to current smokers ($M = 9.03$, $SE = .53$), and this difference was significant ($p = .036$). Higher GWBS-PE scores tended to be associated with a lower BMI ($r = -.11$, $p = .11$) and greater exercise frequency ($r = .11$, $p = .18$), but those associations were not statistically significant. We refitted Model 1 in the sample with complete data on all three health behavior measures and ESIMI (i.e., $n = 163$). The association between the GWBS-PE and ESIMI in this subgroup was significant (OR = .51 (95%CI 0.32-0.81), $p = .004$) and was similar in magnitude to that seen in the total sample ($N = 193$). This association remained significant after further adjustment for smoking, exercise, and BMI (OR = .50 (95%CI 0.31-0.80), $p = .004$) (Table 4). A comparison of the ORs between the two models suggests that adjusting for health behaviors had little effect on the GWBS-PE/ESIMI association.

Discussion

The major purpose of this study was to examine associations of GWBS-PE to MSIMI and ESIMI in patients with stable IHD. Our findings indicate that patients who reported higher levels of positive emotion showed a lower probability of ESIMI. This association persisted even when controlling for negative emotion and important health behaviors (smoking, BMI, and reported exercise). There was also an inverse association between positive emotions and probability of MSIMI, but this association was not statistically significant.

The association between GWBS-PE and ESIMI survived adjustment for CESD-NE (Model II) and CESD-PE (Model III), suggesting the association of positive emotional well-being with ESIMI was independent of the individual experience of both positive and negative emotions captured by CESD. Intuitively, this makes sense, as individuals who score low on a measure of negative emotions may vary greatly in their frequency and intensity of positive emotions. Furthermore, there was a trend to indicate that the GWBS-PE may be a better predictor of ESIMI than a combination of the CESD-PE and CESD-NE subscales, suggesting that GWBS captures those aspects of well-being that are important for coronary health. For example, a post-hoc item analysis of the GWBS-PE scale showed a particularly strong association between ESIMI and an item reflecting engagement in one's environment ("Has your daily life been full of things that are interesting to you?"). A related construct, trait curiosity, has been shown to predict mortality in aging adults,²³ and in patients with cardiac disease.²⁴ This content domain does not appear to be captured by the CESD. If this variance captures important health information, then measures integrating trait positive and negative emotion on a single scale may prove to be stronger correlates of health outcomes than measures of either trait alone.

GWBS-PE scores were higher among non-smokers and were associated with a lower BMI and more frequent exercise. However, controlling for those factors did not impact the association between GWBS-PE and ESIMI suggesting that those health behaviors were not

playing a significant role in the GWBS-PE and ESIMI association. It is also possible that the effect of positive emotion on inducible ischemia is mediated by the cumulative effect of health behaviors that are not fully captured by our measures of smoking, BMI, and exercise levels. Other mechanisms whereby positive emotions might influence coronary health include lower levels of inflammation,²⁵ and neuroendocrine^{26,27} and autonomic function.²⁶

The work of Fredrickson and colleagues suggests that positive emotions speed recovery of cardiovascular function following mental stress.^{28,29} This is of particular relevance to the current study since mental stress testing preceded exercise stress testing. A recent study demonstrated that IHD patients had shortened exercise durations when exercise stress followed a mental stress protocol, suggesting that mental stress might alter exercise capacity.³⁰ This might be expected to have less impact on individuals who show better recovery to mental stress; that is, patients who have a greater capacity to cultivate positive emotions. There was a trend in our sample for lower levels of positive emotion to be associated with a higher rate of MSIMI, which was tested prior to exercise stress testing. The adverse effect of mental stress might have influenced the cardiovascular responses to subsequent physical exercise and thus ESIMI rates.

The association between GWBS and ESIMI does not imply a casual role for well-being on cardiovascular health. It is possible that causation operates in the opposite direction, meaning that ischemia causes lower well-being scores. If true, this could be indicative of a neurovascular disease state that predisposes to less positive emotion,³¹ for which inducible ischemia would be an interesting biomarker because patients are not cognitively aware of their stress testing results. This association has not been studied to our knowledge.

A limitation of this study is that GWBS scores were obtained from only 210 of the 310 patients that underwent mental stress testing. This smaller sample size reduced our power to detect certain effect sizes and might account for the non-significant association between GWBS-PE and MSIMI. Assuming a sample size of 310, we estimate that would have had approximately .70 power to reliably detect an effect size of the magnitude seen in our study (i.e. OR = .81). A sample size of approximately 400 would be needed for .80 power. Thus, larger samples sizes may be necessary to clarify an association between GWBS-PE and MSIMI.

It is also important to recognize that females tend to have higher depression scores and higher rates of isolated MSIMI.¹⁴ Unfortunately, our sample of females in the final cohort was small (N=36), which is a weakness of this study and prevented the differential analysis of the affects of gender on our results.

Conclusions

Positive emotion is important to medical disease, even when controlling for the effect of negative emotions. Our findings may have practical implications for future interventions in IHD patients and suggest that researchers and clinicians could target cultivating positive emotions, in addition to the normalization of psychological disease states, in order to improve outcomes.

The GWBS may be a particularly useful measure of positive emotion when compared with other measures because it integrates information related to the experience of both negative and positive emotion on a single scale. Inducible ischemia may be a useful biomarker for documenting the effects of emotion on medical disease. Exercise stress testing is already a very common diagnostic test in clinical practice. Future studies of the effects of interventions targeted at enhancing positive emotion may consider using this as a marker of treatment effectiveness.

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Highlights

- Well-being scores, including measures of positive emotion, predict lower rates of exercise-stress induced myocardial ischemia in a cohort of patients with ischemic heart disease.
- This relationship persists when controlling for negative emotion.
- This relationship persists when controlling for traditional health-related behaviors that are associated with ischemic heart disease.

Table 1

Patient characteristics

Baseline Characteristics	N = 210
Age, yrs	62.61(10.87)
Race, white	166(79.05)
Women	36(17.14)
BMI, kg/m ²	28.96(5.12)
Current smoker	32(15.24)
Exercise Frequency	5.24(3.47)
Resting LVEF	56.66(9.54)
Resting WMSI	1.19(.38)
MSIMI	92(43.81)
ESIMI	64(32.32)
GWBS-PE	10.07(3.05)
CESD-PE	13.80(2.54)
CESD-NE	9.73(3.40)

Values are mean (SD) for continuous variables, n (%) for categorical variables.

BMI=body mass index; LVEF= left ventricular ejection fraction; WMSI = wall motion score index; MSIMI = Mental stress induced myocardial ischemia; ESIMI = Exercise induced myocardial ischemia; GWBS-PE = General Well Being Scale-Positive Emotions; CESD-PE = Center for Epidemiological Studies-Depression-Positive Emotion scale; CESD-NE = Center for Epidemiological Studies-Depression-Negative Emotion scale.

Table 2

Primary adjusted models examining GWBS-PE scores as a predictor of ESIMI and MSIMI

	ESIMI		MSIMI	
Predictor	OR (95% CI)	P value	OR (95% CI)	P value
Age	1.03 (1.00-1.06)	.06	1.01 (0.98-1.04)	.43
Sex (Male)	0.73 (0.33-1.60)	.43	0.52 (0.25-1.12)	.096
Resting LVEF	1.01 (0.96-1.05)	.83	0.99 (0.95-1.03)	.59
Resting WMSI	1.67 (0.56-4.95)	.36	4.77 (1.56-14.6)	.006
GWBS-PE	0.55 (0.36-0.83)	.005	0.81 (0.54-1.20)	.28

Table 3

Association between GWBS-PE and probability of ESIMI (N = 198)

Model	Odds Ratio	95% Confidence Interval	P-value
Model I	0.55	0.36 - 0.83	.005
Model II	0.45	0.25-0.81	.008
Model III	0.60	0.37-0.97	.038
Model IV	0.49	0.26-0.90	.07

Model I: Standard covariates (Age, sex, resting ejection fraction, resting WMSI)

Model II: Standard covariates and CESD-NE

Model III: Standard covariates and CESD-PE

Model IV: Standard covariates and CESD-NE and CESD-PE

Table 4

Association between GWBS-PE and ESIMI with adjustment for health behaviors (N = 163)

Adjustment	Odds Ratio	95% Confidence Interval	p - value
Standard covariates *	0.51	0.29 - 0.90	.02
Standard covariates and health behaviors **	0.51	0.29 - 0.91	.02

* Age, sex, resting ejection fraction and resting WMSI

** smoking status, bmi, and exercise