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Cardiac biomarkers of disordered eating as a function of diagnostic subtypes

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ABSTRACT

Objective: The purpose of this study was to identify cardiac biomarkers of disordered eating as a function of diagnostic subtype as assessed via self-report inventory.
Method: Mean heart rate (HR), systolic and diastolic blood pressure, mean R wave amplitude (mV), mean T wave amplitude (mV), QTc interval (*sec*), Tpeak-Tend interval prolongation (sec), QTc interval prolongation (sec), QRS prolongation (sec), and spectral indicators of cardiac dysfunction (LF/HF spectral ratio, HF spectral power) were assessed via electrocardiography among women with no eating disorder symptoms (n = 32), subclinical eating disorder symptoms (n = 92), anorexia nervosa (n = 7), bulimia nervosa (n = 89), binge eating disorder (BED: n = 20), and other specified feeding and eating disorders (OSFED: n = 19).
Results: MANOVA results showed statistically significant group differences. Follow-up tests revealed significantly decreased mean R wave amplitude among participants with self-indicated clinical (bulimia nervosa, binge eating disorder) and subclinical forms of disordered eating compared to asymptomatic controls.
Discussion: Results suggest decreased mean R wave amplitude is a promising cardiac biomarker of disordered eating.

1. Introduction

Self-report of eating disorder symptomatology is often inaccurate in diagnostic, treatment, and research contexts (McCabe et al., 2000; Meyer et al., 2009; Starzomska and Tadeusiewicz, 2016). Self-reported symptoms may be underestimated due to treatment ambivalence, shame, stigma, fears of hospitalization, and demand characteristics (McCabe et al., 2000; Meyer et al., 2009; Starzomska and Tadeusiewicz, 2016). Biomarkers which consistently and effectively delineate asymptomatic, subclinical, and clinical eating disorder groups are critical for diagnostic, treatment, and research purposes.

In acknowledgement of the urgent need for increased objectivity and precision in psychiatric diagnoses, the National Institute of Mental Health created the Research Domain Criteria Project (RDoC: Insel, 2014). The goals of RDoC are to identify clinically actionable biomarkers to improve diagnostic accuracy, to increase efficiency in identifying high risk populations, and to provide objective indicators of treatment outcomes and research efficacy (Insel, 2014). Recent findings indicate clinical and subclinical eating disorder populations experience measurable cardiac changes which co-vary systematically with disorder-related symptoms (Green et al., 2016; Green et al., 2017; Jáuregui-Garrido and Jáuregui-Lobera, 2012; Panagiotopoulos et al., 2000; Ülger et al., 2006). This evidence suggests cardiac indices may serve as reliable biomarkers of eating disorder symptoms.

Cardiac changes in patients with eating disorders have been linked to disorder-precipitated electrolyte imbalances (Casiero and Frishman, 2006; Himmerich et al., 2010), hypovolemia, neuroendocrine dysregulation, shifts in cardiac autonomic regulation, and structural changes in cardiac tissue associated with energy imbalance and body mass changes (Green et al., 2017; Jáuregui-Garrido and Jáuregui-Lobera, 2012; Panagiotopoulos et al., 2000; Ülger et al., 2006). Previous studies have identified QTc interval prolongation, QRS interval prolongation, PR interval prolongation, decreased mean T wave amplitude, Tpeak-Tend (Tp-e) interval prolongation, cardiac autonomic dysfunction (increased vagal tone, decreased sympathetic tone), and decreased mean R wave amplitude as potential cardiac biomarkers of disordered eating

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(Green et al., 2016; Green et al., 2017; Green et al., 2018; Isner et al., 1979; Jáuregui-Garrido and Jáuregui-Lobera, 2012; Panagiotopoulos et al., 2000; Swenne and Larsson, 1999; Ülger et al., 2006; Vargas Upequi and Gómez, 2015). The function and significance of each biomarker is discussed briefly below.

1.1. QTc interval prolongation

QTc interval prolongation has the most comprehensive support as a cardiac biomarker for disordered eating, especially among patients with anorexia nervosa (Jáuregui-Garrido and Jáuregui-Lobera, 2012). QTc interval prolongation indicates atypical myocardial repolarization; it is linked to ventricular tachycardia, a potentially lethal cardiac arrhythmia (Jáuregui-Garrido and Jáuregui-Lobera, 2012). QTc interval prolongation is correlated with rapid weight loss and low Body Mass Index (BMI: Swenne and Larsson, 1999).

1.2. Decreased mean R wave amplitude

Decreased mean R wave amplitude is increasingly recognized as an important cardiac biomarker of disordered eating. Decreased mean R wave amplitude is associated with decreased electromotive force generation during ventricle depolarization and is linked to an increased risk of myocardial infarct and ventricular arrhythmia in non-eating disorder populations (Madias, 2008; Sun et al., 2013). It is also linked to adverse cardiac events and sudden cardiac death in eating disorder populations (Gottdiener et al., 1978; Isner et al., 1979). Decreased mean R wave amplitude is associated with binge behaviors, purge behaviors, extreme dietary restriction, low body weight, electrolyte disturbances, rapid weight loss, hypovolemia, and hypothyroidism; these pathophysiological states co-occur with eating disorders (Green et al., 2016; Jáuregui-Garrido and Jáuregui-Lobera, 2012; Madias, 2008; Ülger et al., 2006). The marker has been documented among patients with bulimia nervosa and subclinical levels of binge and purge behaviors (Green et al., 2016; Green et al., 2017; Green et al., 2018). Decreased mean R wave amplitude is also demonstrated among patients with anorexia nervosa (Panagiotopoulos et al., 2000; Ülger et al., 2006); it has not been previously investigated among patients with binge eating disorder or other specified feeding and eating disorder (OSFED).

1.3. Tp-e interval prolongation

Tp-e interval prolongation reflects aberrant ventricular repolarization; the time interval of repolarization is prolonged (Watanabe et al., 2004). Tp-e interval prolongation is linked to increased risk for sudden cardiac death (Panikkath et al., 2011), especially when it co-occurs with QTc interval prolongation (Castro Hevia et al., 2006). Since QTc interval prolongation is a common clinical occurrence among patients with anorexia nervosa, Tp-e interval prolongation is an important cardiac biomarker to examine in eating disorder populations (Jáuregui-Garrido and Jáuregui-Lobera, 2012).

1.4. Decreased mean T wave amplitude

Decreased mean T wave amplitude is linked to atypical ventricular repolarization. It is associated with protein energy malnutrition, overexercise, rapid weight loss, low body weight, hypokalemia, and extreme calorie deficits (Ellis, 1946; Kumar et al., 2015; Swenne and Larsson, 1999). Individuals with anorexia nervosa develop significant reductions in mean T wave amplitude which correct with healthy weight restoration (Vargas Upequi and Gómez, 2015).

1.5. Cardiac autonomic dysfunction

Cardiac autonomic dysfunction reflects aberrant cardiac input from a relative imbalance in the sympathetic and parasympathetic autonomic inputs to the cardiac system. Cardiac autonomic dysfunction is linked to ventricular arrhythmias and myocardial infarction (Ng, 2016). In patients with anorexia nervosa and bulimia nervosa, autonomic dysfunction presents as vagal hyperactivity and reduced sympathetic tone (Cong et al., 2004; Faris et al., 2006; Green et al., 2009). Hypervagal tone has been linked to binge and purge behaviors, bradycardia, and ventricular tachycardia (Faris et al., 2006).

1.6. Cardiac biomarkers by eating disorder subtype

The indices noted above show empirical support as potential cardiac biomarkers of disordered eating; however, few of the markers have been examined as a function of eating disorder diagnostic subtype. This is important because aberrant behaviors which constitute different diagnostic subtypes may lead to differing pathophysiological cardiac states. For example, Panagiotopoulos et al. (2000) found evidence of decreased mean R wave amplitude among patients with anorexia nervosa but not among patients with bulimia nervosa (though it should be noted there was a very small sample size for the latter group).

Similarly, several previous research studies indicate the nature of cardiac autonomic dysfunction may vary by diagnostic subtype. Specifically, patients with anorexia nervosa and bulimia nervosa demonstrate cardiac autonomic dysfunction in the form of hypervagal tone while patients with binge eating disorder show cardiac autonomic dysfunction in the form of increased sympathetic tone (Godfrey et al., 2019; Messerli-Bürgy et al., 2010). If cardiac markers are to be identified as reliable indicators of eating disorder symptomatology, it is important to understand how these markers vary as a function of diagnostic subtype.

Conversely, it may be helpful to understand if certain cardiac biomarkers overlap between various diagnostic subtypes. Given the fluidity of eating disorder diagnoses across patients' diagnostic trajectories and existing studies which suggest some shared etiologies across subtypes, shared cardiac biomarkers may exist across subtypes. Shared markers may actually have more utility than differential markers if they are uniformly present across several diagnostic subtypes and serve as a reliable indicator of severity.

Previous research on cardiac biomarkers of disordered eating is limited in several ways. First, the sample sizes of many of these previous studies are small, leaving inadequate statistical power to detect differences in cardiac biomarkers as a function of diagnostic subtype. Second, previous research has not included all diagnostic subtypes in a single comparative study, resulting in an inability to understand how cardiac-related biomarkers may vary in their comparative sensitivity (i.e., their ability to differentiate between asymptomatic, subclinical, and clinical groups). Table 1 provides a summary of the sample sizes and diagnostic composition of previous studies. Third, previous research has not compared multiple cardiac biomarkers simultaneously in order to determine relative effect sizes, leaving it difficult to ascertain the most reliable and sensitive cardiac biomarkers. The collective information specified above is essential if cardiac biomarkers are to be used to enhance eating disorder diagnostic, treatment, and research practices. This information is also critical to better understand subtype-specific cardiac changes which may signal subsequent cardiac-related risks as well as whether shared cardiac biomarkers exist across subtypes.

Finally, previous research has not focused extensively on subclinical groups. Previous research indicates eating disorders exist on a continuum and intervention approaches are more effective if symptoms, and their concomitant health changes, are identified early. If cardiac biomarkers do exist at subclinical levels of disordered eating, it is important to identify these markers in order to provide early screening and *se*condary prevention services prior to the development of a clinical disorder. Existing research indicates early detection and intervention is essential to improving treatment outcomes; understanding cardiac

Table 1
Sample sizes by eating disorder diagnostic group for cited cardiac studies and the current study.

Study	Asymp	Sub	Clinical					Other
			AN	BN	EDNOS	OSFED	BED	Diagnosis not specified in study
Gottdiener et al. (1978) *N* = 11			11					
Isner et al. (1979) *N* = 17								17[b]
Swenne and Larsson (1999) *N* = 96	38							58[a]
Panagiotopoulos et al. (2000) *N* = 97			62	9	26			
Cong et al. (2004) N = 25	11		6	8				
Ülger et al. (2006) *N* = 23	12		11					
Messerli-Bürgy et al. (2010) *N* = 38	13[c]			12			13	
Green et al. (2016) *N* = 52	20	20		12				
Green et al. (2017) *N* = 47		25	1	18	3			
Green et al. (2018) *N* = 82		29	1	29		10	13	
Godfrey et al. (2019) *N* = 28		13[d]					13	
Current Study *N* = 259	32	92	7	89		19	20	

Note. Asymp: asymptomatic (no eating disorder symptoms); Sub: subclinical (subclinical levels of eating disorder symptoms); AN: anorexia nervosa; BN: bulimia nervosa; EDNOS: eating disorder not otherwise specified (DSM-IV diagnosis); OSFED: otherwise specified feeding and eating disorder (DSM-5 diagnosis); BED: binge eating disorder.

[a] Participants with eating disorder symptoms similar to anorexia nervosa or EDNOS restrictive type, but diagnosis was not a part of this study.

[b] Patients who died suddenly/unexpectedly after use of liquid-protein-modified-fast diet.

[c] Participants with obesity but without binge eating behavior.

[d] Participants did not meet DSM-5 BED criteria but were not asymptomatic.

biomarkers among subclinical populations can assist in this effort.

1.7. Present study

The purpose of this study was to identify cardiac biomarkers of disordered eating as a function of diagnostic group assessed via a self-report diagnostic assessment. Mean R wave amplitude (mV), Tpeak-Tend interval prolongation (sec), QTc interval prolongation (sec), mean T wave amplitude (mV), and spectral indicators of cardiac autonomic dysfunction (LF/HF spectral power ratio, HF spectral power) were assessed via electrocardiography (ECG) among women with no eating disorder symptoms (n = 32), subclinical eating disorder symptoms (n = 92), anorexia nervosa (n = 7), bulimia nervosa (n = 89), binge eating disorder (BED: n = 20), or other specified feeding and eating disorders (OSFED: n = 19).

2. Method

2.1. Participants

Participants (N = 259) were recruited from 2 Midwestern cities and 5 surrounding suburban communities as part of an ongoing research agenda evaluating cardiac biomarkers in populations with disordered eating. Subsets of the present sample (n = 141) were included in previous papers (see Green et al., 2016; Green et al., 2017; Green et al., 2018); the present study reflects the first from this ongoing program of research with an adequate sample size to evaluate cardiac biomarkers among diagnostic subtypes.

The following participant recruitment mechanisms were used with the aim of increasing participant diversity and community involvement. Advertisements were placed in 2 local newspapers, online (including the websites for the National Eating Disorder Association and Academy for Eating Disorders, as well as *Facebook*, *Instagram*, and *Craigslist*), and on campus radio stations for a small Midwestern liberal arts college and a large Midwestern university. Fliers were posted in retail locations, community bulletin boards, high schools, and across the campuses of local colleges/universities. Additionally, letters containing fliers were sent to health practitioners, behavioral health practitioners, nutritionists, summer camps, high school athletic trainers, high school nurses, community cultural centers, and sorority houses in the identified communities.

An on-line screening was administered via *Qualtrics* to determine participant eligibility. The on-line screening consisted of a demographic questionnaire, questions to determine study eligibility, and the Questionnaire for Eating Disorder Diagnoses (Q-EDD: Mintz et al., 1997). Eligible participants included women who indicated no disordered eating (asymptomatic group) according to Q-EDD (Mintz et al., 1997) scoring criteria, women who endorsed subthreshold levels of disordered eating according to Q-EDD scoring criteria (subclinical group), and women who met probable diagnostic criteria for an eating disorder according to the Diagnostic and Statistical Manual of Mental Disorders, 5th Edition (DSM-5: American Psychiatric Association, 2013) as assessed by Q-EDD scoring criteria adapted for DSM-5 (American Psychiatric Association, 2013).

Eligibility was limited to women ages 14–35 to control for the effects of estrogens on cardiovascular function; the protocol required that all female participants be postpubescent and premenopausal. Menstrual status was verified via two self-report items included in the demographic questionnaire. The first item asked participants to verify postpubescent and premenopausal status; the second item asked participants to indicate whether they missed three consecutive menstrual periods over the past 3 months. One 38-year-old participant was allowed to participate (a protocol deviation was granted) once premenopausal status was verified. Pregnant women were excluded from the sample due to the effects of pregnancy on cardiovascular function. The screening took approximately 20 min to complete; women were entered into a drawing to win 1 of 2 $25 gift certificates to *Amazon.com* in exchange for their participation in the screening.

Participants' ages ranged from 14 to 38 years (M = 23.95, SD = 5.08). The racial and ethnic composition of the sample was 84.6% Anglo American/Caucasian, 4.2% Hispanic/Latina American, 3.7% Asian American/Pacific Islander, 2.3% African American, 2.3% Biracial, 0.9% International, 0.9% other, 0.5% Native American, and 0.5% Multiracial. All participants were treated in accordance with the APA Ethical Standards and Code of Conduct (American Psychological Association, 2010). The research protocol was approved by two Institutional Review Boards.

2.2. Materials

2.2.1. Questionnaire for eating disorder diagnoses (Q-EDD)

To assign diagnostic groups, the Q-EDD was utilized (Mintz et al., 1997). Q-EDD scoring criteria were adapted for DSM-5 (American Psychiatric Association, 2013). Participants received a probable

diagnosis of anorexia nervosa, bulimia nervosa, OSFED, or binge eating disorder if they met DSM-5 diagnostic criteria for these disorders. Consistent with Q-EDD scoring criteria (Mintz et al., 1997), participants received a subclinical designation if they endorsed high body dissatisfaction and subthreshold symptoms of binge behaviors, laxative use, diuretic use, dieting for weight loss purposes, chew/spit behaviors, fasting for 24 h, or maladaptive exercise for the purposes of counteracting weight gain. Also consistent with Q-EDD scoring criteria (Mintz et al., 1997), participants received an asymptomatic designation if they did not endorse any of the above behaviors.

Compared to the Revised Bulimia Test (BULIT-R: Thelen et al., 1991) and the Eating Attitudes Test (EAT: Garner and Garfinkel, 1979), the Q-EDD has strong convergent validity in community and undergraduate samples (Mintz et al., 1997). The Q-EDD had a 98% diagnostic accuracy when compared to eating disorder diagnoses made by the Structured Clinical Interview for Axis I DSM-IV Disorders (SCID) for Module H (Eating Disorders: First et al., 2002) among clinical populations (Mintz et al., 1997). Test-retest reliability statistics for one- to three-month follow- up were = 0.64 for eating disordered and non-eating-disorder groups (Mintz et al., 1997).

The Q-EDD has been used to determine DSM-5 diagnostic subtypes in similar studies of cardiac biomarkers (see Green et al., 2016; Green et al., 2017). Some evidence of convergent validity with another reliable and valid self-report assessment of eating disorder symptoms is indicated in those studies. For example, Green et al. (2016) found EDE-Q global scores varied in the predicted systematic manner according to Q-EDD diagnostic distinctions adapted for DSM 5 (asymptomatic [M = 0.89, SD = 0.79], subclinical [M = 2.88, SD = 1.02], and clinical [M = 4.20, SD = 1.10]). These data provide preliminary evidence of convergent validity between the Q-EDD (adapted for DSM-5) and the EDE-Q (Fairburn and Beglin, 2008).

2.2.2. Eating disorder examination-questionnaire 6.0 (EDE-Q)

The Eating Disorder Examination-Questionnaire 6.0 was used (EDE-Q: Fairburn and Beglin, 2008) to assess eating disorder symptoms across diagnostic groups. The EDE-Q is a 28-item self-report assessment of eating disorder symptoms derived from the Eating Disorder Examination (EDE: Fairburn and Beglin, 1994). The EDE-Q assesses the frequency and duration of dietary restraint, weight concern, eating concern, and shape concern over the past 28 days. Several items are scored on a 7-point Likert scale ranging from 0 (*no days*) to 6 (*every day*). The EDE-Q consists of the 4 following subscales: Restraint, Weight Concern, Eating Concern, and Shape Concern. A global disordered eating symptomology score is calculated by the mean of the averaged subscale scores. Lower scores indicate lower levels of eating disorder pathology. The EDE-Q demonstrates strong convergent validity with the EDE in previous research (Mond et al., 2004). Cronbach's α coefficients in the present sample were as follows: α = 0.85 (Restraint), α = 0.84 (Eating Concern), α = 0.90 (Shape Concern), α = 0.79 (Weight Concern), and α = 0.90 (Global).

2.2.3. Electrocardiography (ECG)

A lead II chest configuration was used to record ECG data. BIOPAC MP35/36 psychophysiological data acquisition systems were used to collect ECG signal at a 1000 Hz sampling rate. A lower sampling rate (ranging from 100 to 500 Hz) is adequate for human research, but higher sampling rates are ideal (Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology, 1996). The laboratory hardware included an ECG100C amplifier with a 35 Hz LPN filter and a .5 Hz HP filter.

Previous research indicates 5 min of ECG data is required for heart rate variability (HRV) spectral analyses (Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology, 1996). A total of 5 min and 30 s of ECG data were collected to allow for artifact trimming. Artifacts were flagged by experimenters during data collection. All ECG strips were trimmed to the first 300 s of artifact-free data for subsequent analysis.

ECG and HRV indices were analyzed via PowerLab LabChart 7 for Microsoft Windows. The ECG settings were at the preset detection and analysis settings for human participants. The data source was Channel 1 (0.05–35 Hz) using the whole channel. For detection, typical QRS width was set at 80 ms and R waves were at least 300 ms apart. For analysis, the pre-P baseline was at 120 ms, maximum PR was at 240 ms, maximum RT was at 400 ms, and ST height was at 120 ms from alignment. On a case to case basis, if these settings were too conservative, the pre-P baseline was increased to 150 ms and maximum PR was increased to 270 ms on the recommendation of LabChart technical support engineers. QTc was corrected with Bazett's formula.

The HRV settings were also at the preset human participant detection settings. The data source was Channel 1 (0.05–35 Hz) using the whole channel. Analysis settings had histogram bin width at 10 ms, pRR threshold at 50 ms, and SDARR averaging 300 s. All ectopic beats (i.e., beats in which the RR interval or waveform morphology fell outside of normal human physiology) were included in the analysis. Ectopic beats were selected for inclusion because atypical beat patterns are common among patients with disordered eating. RR interval was set at 800–1200 ms with complexity between 1 and 1.5. For spectral analysis, maximum frequency was set at 0.5 Hz with number of frequencies at 500. LF spectral power ranged from 0.04–0.15 Hz. HF spectral power ranged from 0.15–0.45 Hz.

2.3. Procedure

To control for the effects of extraneous variables on cardiac function, participants were asked to refrain from the consumption of food, beverages (except water), and nicotine for a minimum of 3 h prior to their cardiac assessments. Participants were also asked to refrain from intense physical exercise for 24 h prior to data collection. Participants were asked to reschedule their cardiac assessments if suffering from a fever or other indicators of acute physical illness within 48 h of data collection in order to control for the effects of cytokines on cardiac function.

The cardiac assessment protocol placed participants in a supine posture for a 10-min equilibration period while a blood pressure cuff with heart rate measuring capabilities was attached to the left arm. Heart rate and blood pressure measurements were taken at the 0-min, 5-min, and 10-min mark to verify cardiac equilibrium. During the equilibration period, participants were prepared for ECG; 3 self-adhesive electrodes were placed in a lead II chest configuration. After the lead wires were attached, a brief sample recording (~5 s) was collected to check ECG signal quality. Immediately following the 10-min equilibrium period, the ECG recording was obtained while participants were instructed to remain quiet and still in a supine posture. After the recording period, the experimenter measured participants' height and weight. Participants were then debriefed and compensated $40 in Amazon gift cards in exchange for their participation.

2.4. Statistical analysis

A one-way (group: asymptomatic, subclinical, anorexia nervosa, bulimia nervosa, BED, OSFED) MANOVA was used to investigate mean differences in BMI, eating disorder symptoms, and cardiac indices as a function of group. One-way ANOVAs and contrast tests were used to interpret MANOVA findings. Based on previous research, we predicted patients with anorexia nervosa and bulimia nervosa would show increased QTc interval length, decreased mean R wave amplitude, decreased mean T wave amplitude, increased HF spectral power and decreased LF/HF spectral power ratio compared to asymptomatic patients (hypothesis 1). We further predicted mean R wave amplitude would show the largest effect size differentiating asymptomatic from clinical and subclinical groups, establishing mean R wave amplitude as a promising biomarker of disordered eating (hypothesis 2). We predicted

Table 2
Descriptive statistics as a function of eating disorder diagnostic group: BMI, Eating Disorder Symptoms (EDE-Q Global score), LF/HF, HFnu, QTc Interval Length, Tp-e interval length, Mean R wave amplitude, and Mean T wave amplitude.

Group	Asymp		Sub		AN		BN		OSFED		BED	
	M (*SD*)		*M* (*SD*)		*M* (*SD*)		*M* (*SD*)		*M* (*SD*)		*M* (*SD*)	
BMI	23.63	(5.26)	27.71	(7.41)	18.50	(1.65)	27.44	(7.65)	23.02	(3.80)	35.30	(11.24)
EDEQ	0.83	(0.84)	3.23	(1.04)	3.79	(0.91)	3.82	(1.19)	4.19	(1.11)	3.47	(0.91)
LF/HF	0.75	(0.53)	1.04	(1.58)	0.72	(0.86)	1.16	(1.52)	1.33	(1.66)	3.48	(9.05)
HFnu	56.21	(15.41)	57.24	(18.43)	59.53	(18.40)	54.96	(20.58)	50.81	(16.63)	47.64	(22.05)
QTc	0.39	(0.02)	0.39	(0.02)	0.39	(0.03)	0.39	(0.02)	0.39	(0.03)	0.39	(0.02)
Tp-e Int	0.06	(0.01)	0.06	(0.01)	0.06	(0.01)	0.06	(0.01)	0.06	(0.01)	0.05	(0.01)
R Amp	1.43	(0.52)	1.19	(0.37)	1.36	(0.49)	1.16	(0.37)	1.16	(0.27)	1.06	(0.35)
T Amp	0.40	(0.13)	0.35	(0.13)	0.34	(0.14)	0.34	(0.12)	0.28	(0.11)	0.27	(0.12)

Note. Asymp: asymptomatic (no eating disorder symptoms); Sub: subclinical (subclinical levels of eating disorder symptoms); AN: anorexia nervosa; BN: bulimia nervosa; OSFED: otherwise specified feeding and eating disorder; BED: binge eating disorder; BMI: Body Mass Index; EDEQ: Eating Disorder Examination – Questionnaire 6.0 Global Score (Fairburn and Beglin, 1994); LF/HF: LF/HF spectral power ratio; HFnu: HF spectral power (normalized units); QTc: QTc interval (seconds); Tp-e Int: Tpeak-Tend interval (seconds); R Amp: mean R wave amplitude (mV); T Amp: mean T wave amplitude (mV).

patients with binge eating disorder would show decreased HF spectral power and increased LF/HF spectral power ratio compared to other groups (hypothesis 3). All other comparisons conducted in the present study were exploratory since other cardiac markers have not been extensively examined among these comparison groups.

3. Results

Table 2 summarizes descriptive statistics for BMI, EDE-Q global scores, LF/HF spectral power, HF spectral power, QTc interval length, Tpeak-Tend interval length, mean T wave amplitude, and mean R wave amplitude as a function of condition. A one-way MANOVA was conducted to examine differences as a function of diagnostic group. Results were statistically significant, *Pillai's Trace* = 0.74, $F(40,1250) = 5.41$, $p < .001$, $\text{eta}_p^2 = 0.15$, observed power = 1.00.

A series of one way analyses of variance (ANOVAS) were conducted to interpret statistically significant MANOVA results. Table 3 summarizes the ANOVA results, effect sizes, and observed power of each analysis. As predicted, there were statistically significant mean group differences in BMI, eating disorder symptoms, LF/HF spectral power ratio, mean R wave amplitude, mean T wave amplitude, and Tpeak-Tend interval length. Contrary to predictions, there were not statistically significant mean group differences in HF spectral power or QTc interval length. The largest effect sizes (see Table 3) were for mean R wave amplitude and mean T wave amplitude.

Contrast tests were conducted to interpret statistically significant ANOVA results. Based on Levene's test, equal variances were assumed for all variables except BMI and LF/HF spectral power ratio. Table 4 summarizes contrast test results, observed power, and effect sizes for statistically significant effects; Table 5 summaries these effects for findings that were not statistically significant. BMI was significantly lower in patients with anorexia nervosa as compared to bulimia nervosa, OSFED, BED, subclinical groups; BMI was lower in asymptomatic groups and OSFED groups as compared to BED and subclinical groups. BMI was significantly higher in bulimia nervosa as compared to OSFED or asymptomatic groups and in BED and subclinical groups as compared to asymptomatic groups. Eating disorder symptoms were significantly higher among participants with anorexia nervosa compared to asymptomatic groups, among participants with bulimia nervosa and OSFED compared to asymptomatic or subclinical groups, and among BED and subclinical groups compared to asymptomatic groups.

Consistent with predictions, mean R wave amplitude was significantly lower among bulimia nervosa, BED, and subclinical groups compared to the asymptomatic group. Contrary to predictions, mean R wave amplitude was not lower among participants with anorexia nervosa compared to the asymptomatic group. This null finding was likely attributable to small sample size for the anorexia nervosa group (see Table 5 for the low observed power for this comparison). Tpeak-Tend interval was significantly longer in subclinical participants as compared to participants with BED. Mean T wave amplitude was significantly lower in OSFED and BED groups as compared to the asymptomatic group. Contrary to predictions, no group differences emerged in QTc interval length or cardiac autonomic balance as a function of group. It is important to note ANOVA results for LF/HF spectral power ratio (i.e., sympathetic tone) were statistically significant but follow-up tests were not statistically significant following an adjustment for unequal variances. To our knowledge, the sample size of the present study ($N = 259$) is larger and more diagnostically diverse than any previous study, allowing a much greater ability to detect differences in cardiac biomarkers. Posthoc power analyses indicate adequate statistical power (at a threshold of 0.80) to detect statistically significant group differences for all assessed cardiac variables except HF spectral power and QTc interval length (see Tables 3, 4, and 5 for observed power estimates). The methodology allowed for effect size comparisons to specify which biomarkers are the most sensitive indicators of disordered eating and in which diagnostic subtypes (see Tables 3, 4, and 5).

Table 3
One way ANOVA summary table: eating disorder symptoms and cardiac risk factors as a function of eating disorder diagnostic group ($N = 259$).

Measure	Sum of squares	*df*	*Mean square*	*F*	*Partial* η^2	Observed power
BMI	2606.74	5, 258	521.35	9.65***	0.16	1.00
EDE-Q	236.25	5, 258	47.25	41.60***	0.45	1.00
LF/HF	114.58	5, 258	22.92	2.83*	0.05	0.83
HFnu	2059.55	5, 258	411.91	1.14	0.02	0.40
QTc	0.002	5, 258	0	0.63	0.01	0.23
Tp-e Int	0.001	5, 258	0	2.87*	0.05	0.84
R Amp	2.421	5, 258	0.48	3.19**	0.06	0.88
T Amp	0.286	5, 258	0.06	3.57**	0.07	0.92

Note. BMI: Body Mass Index; EDE-Q: Eating Disorder Examination – Questionnaire 6.0 Global Score (Fairburn and Beglin, 1994); LF/HF: LF/HF spectral power ratio, HFnu: HF spectral power (normalized units), QTc: QTc interval (seconds), Tp-e Int: Tpeak-Tend interval (seconds), R Amp: mean R wave amplitude (mV), T Amp: mean T wave amplitude (mV). $\hat{p} \leq .10$ (marginally significant) $*^{=}p = .05$ (marginally significant) $*p < .05$. $**p \leq .01$. $***p < .001$.

4. Discussion

Previous research on cardiac biomarkers of disordered eating is limited in several ways; many of these limitations were addressed in the present study. First, the sample sizes of many previous studies were small, leaving inadequate statistical power to examine cardiac

Table 4
Posthoc tests for BMI, EDE-Q, and cardiac risk indices as a function of eating disorder diagnostic status for statistically significant effects.

Variable		Mean difference	*Std. error*	95% CI		Cohen's *d*	Observed power
BMI[2]	AN-BN	−8.95***	1.023	−12.022,	−5.868	1.616	1.00
	AN-OSFED	−4.52**	1.073	−7.852,	−1.197	1.543	0.99
	AN-BED	−16.80***	2.589	−24.893,	−8.708	2.091	1.00
	AN-S	−9.21***	0.993	−12.211,	−6.211	1.716	1.00
	AN-A	−5.14***	1.120	−8.533,	−1.743	1.316	1.00
	BN-OSFED	4.42**	1.191	0.902,	7.939	0.732	0.96
	BN-BED	−7.86^	2.640	−16.044,	0.333	0.818	0.85
	BN-A	3.81*	1.234	0.202,	7.412	0.580	0.87
	OSFED-BED	−12.28***	2.659	−20.514,	−4.039	1.464	1.00
	OSFED-S	−4.69**	1.165	−8.135,	−1.237	0.796	0.98
	BED-S	7.59^	2.628	−0.574,	15.754	0.797	0.82
	BED-A	11.66**	2.679	3.387,	19.938	1.330	0.99
	S-A	4.07*	1.209	0.537,	7.608	0.635	0.92
EDE-Q[1]	AN-A	2.96***	0.445	1.684,	4.238	3.380	1.00
	BN-S	0.59**	0.158	0.137,	1.047	0.528	0.94
	BN-A	2.99***	0.220	2.361,	3.622	2.903	1.00
	OSFED-S	0.96**	0.269	0.186,	1.729	0.893	0.91
	OSFED-A	3.36***	0.309	2.471,	4.243	3.414	1.00
	BED-A	2.65***	0.304	1.773,	3.518	3.015	1.00
	S-A	2.40***	0.219	1.771,	3.028	2.539	1.00
Tp-e int[1]	BED-S	−0.006*	0.002	−0.012,	0.000	1.000	0.98
R amp[1]	BN-A	−0.269*	0.080	−0.499,	−0.038	0.598	0.77
	BED-A	−0.368*	0.111	−0.687,	−0.049	0.835	0.87
	S-A	−0.238*	0.080	−0.467,	−0.008	0.532	0.67
T amp[1]	OSFED-A	−0.121*	0.037	−0.226,	−0.015	0.997	0.94
	BED-A	−0.131**	0.036	−0.234,	−0.027	1.039	0.96

Note. A: Asymptomatic Group; S: Subclinical Group; AN: Anorexia Nervosa Group; BN: Bulimia Nervosa Group; OSFED: Otherwise Specified Feeding and Eating Disorder Group; BED: Binge Eating Disorder Group; BMI: Body Mass Index; EDE-Q: Eating Disorder Examination – Questionnaire 6.0 Global Score (Fairburn and Beglin, 1994); Tp-e Int: Tpeak-Tend interval (seconds), R Amp: mean R wave amplitude (mV), T Amp: mean T wave amplitude (mV).

[1] Based on Levene's test, equal variances were assumed and Tukey HSD was used in analysis.

[2] Based on Levene's test, equal variances were not assumed and Games-Howell was used in analysis.

^ $p \leq .10$ (marginally significant) * $= p = .05$ (marginally significant).

* $p < .05$.

** $p \leq .01$.

*** $p \leq .001$.

biomarkers as a function of diagnostic subtype. Second, previous research has not included all diagnostic subtypes in a single comparative study, resulting in an inability to understand how cardiac-related biomarkers may vary in their comparative sensitivity. Third, previous research has not simultaneously compared multiple cardiac biomarkers across groups in order to determine relative effect sizes, leaving it difficult to ascertain the most reliable and sensitive cardiac biomarkers. The present study addressed these limitations.

The current findings suggest decreased mean R wave amplitude may be a sensitive cardiac biomarker of eating disorder symptoms among patients with bulimia nervosa, BED, and subclinical forms of disordered eating. This finding replicates existing research on patients with bulimia nervosa and extends previous findings to patients with BED. Decreased mean R wave amplitude was the only cardiac biomarker to distinguish groups with bulimia nervosa and subclinical eating disorders from asymptomatic groups in the present study; both decreased mean R wave amplitude and decreased T wave amplitude distinguished patients with BED from asymptomatic patients. These findings, pending replication, are of potential notable import.

Previous research demonstrates decreased mean R wave amplitude is associated with increased cardiac risk and sudden adverse cardiac events in eating disorder and non-eating disorder populations (Isner et al., 1979; Madias, 2008). Decreased mean R wave amplitude represents atypical ventricular contraction and is linked to a host of pathophysiological states induced by disordered eating including electrolyte disturbances, hypovolemia, aberrant thyroid function, aberrant estrogen function, cardiac autonomic dysfunction, and structural atrophy of the left ventricle of the heart, leading to an increased risk for sudden adverse cardiac events (Gottdiener et al., 1978; Isner et al., 1979; Madias, 2008).

Decreased mean R wave amplitude is linked to structural changes to the left ventricle precipitated by sudden weight loss, low BMI, inconsistent energy availability, protein-energy malnutrition, binge behaviors, and purge behaviors (Gottdiener et al., 1978; Green et al., 2016; Green et al., 2017; Madias, 2008; Ülger et al., 2006). Decreased mean R wave amplitude predicted cardiac-related mortality from subsequent myocardial infarct in a sample of patients on a liquid protein diet who had lost a significant amount of weight prior to death (Isner et al., 1979). Taken together, findings suggest decreased mean R wave amplitude may be an important marker to monitor in eating disorder populations. The present results suggest the significance of this marker should be extended to patients with binge eating disorder and subclinical presentations of disordered eating. This shared presentation across diagnostic subtypes may add to the utility of this marker. However, it is important to note that all present findings are based on a self-report assessment of diagnostic status and should be interpreted with appropriate caution given that limitation.

As noted above, previous research suggests decreased mean R wave amplitude may be driven (at least in part) by electrolyte imbalance. The impact of electrolyte disturbances on cardiac signaling is well-documented in existing research; electrolyte disturbances are known to precipitate sudden ventricular arrythmias in eating disorder patients (Casiero and Frishman, 2006). Monitoring the impact of electrolyte disturbances on cardiac function via ongoing assessment of mean R wave amplitude may result in more comprehensive and reliable monitoring of cardiac risk in eating disorder patients. This is an important consideration given that individuals with low mean R wave amplitude were twice as likely to die in a long-term (average follow-up of 13.8 years) mortality study of 6440 individuals in a non-eating disorder population (Usoro et al., 2014).

Table 5
Posthoc tests for BMI, EDE-Q, and cardiac risk indices as a function of eating disorder diagnostic status (not statistically significant).

Variable		Mean difference	*Std. error*	95% CI		Cohen's *d*	Observed power
BMI[2]	BN-BED	−7.42	2.891	−16.606,	1.645	−0.818	0.98
	BN-S	−0.29	1.145	−3.594,	3.008	−0.036	0.04
	OSFED-A	−0.61	1.276	−4.403,	3.176	−0.133	0.05
	BED-S	7.13	2.860	−2.003,	16.258	0.797	0.99
EDE-Q[1]	AN-BN	0.03	0.427	−1.195,	1.256	−0.028	0.03
	AN-OSFED	−0.40	0.479	−1.772,	0.981	−0.394	0.16
	AN-BED	0.38	0.491	−1.026,	1.795	0.352	0.14
	AN-S	0.57	0.426	−0.651,	1.795	0.573	0.80
	BN-OSFED	−0.43	0.276	−1.219,	0.366	−0.323	0.38
	BN-BED	0.35	0.296	−0.496,	1.205	0.330	0.40
	OSFED-BED	0.78	0.368	−0.276,	1.837	0.709	0.56
	BED-S	0.19	0.295	−0.660,	1.034	0.246	0.25
LF/HF[1]	AN-BN	−0.450	0.597	−2.165,	1.266	−0.151	0.11
	AN-OSFED	−0.606	0.670	−2.532,	1.321	−0.275	0.10
	AN-BED	−0.769	0.687	−2.743,	1.205	−0.395	0.16
	AN-S	−0.335	0.596	−2.048,	1.377	−0.068	0.05
	AN-A	−0.025	0.633	−1.843,	1.793	0.247	0.11
	BN-OSFED	−0.156	0.386	−1.265,	0.953	−0.128	0.10
	BN-BED	−0.319	0.414	−1.510,	0.871	−0.365	0.47
	BN-S	0.114	0.234	−0.558,	0.787	0.059	0.06
	BN-A	0.425	0.316	−0.483,	1.333	0.352	0.48
	OSFED-BED	−0.163	0.514	−1.642,	1.315	−0.332	0.17
	OSFED-S	0.270	0.384	−0.834,	1.375	0.173	0.14
	OSFED-A	0.581	0.439	−0.681,	1.843	0.450	0.34
	BED-S	0.434	0.413	−0.752,	1.620	0.377	0.51
	BED-A	0.744	0.464	−0.590,	2.078	0.426	0.32
	S-A	0.311	0.314	−0.591,	1.213	0.230	0.24
R amp[1]	AN-BN	0.205	0.155	−0.240,	0.650	0.592	0.82
	AN-OSFED	0.199	0.174	−0.300,	0.699	0.685	0.39
	AN-BED	0.246	0.178	−0.266,	0.758	0.832	0.53
	AN-S	0.159	0.155	−0.285,	0.604	0.546	0.76
	AN-A	−0.069	0.164	−0.541,	0.402	0.011	0.03
	BN-OSFED	−0.006	0.100	−0.294,	0.282	0.048	0.04
	BN-BED	0.041	0.107	−0.268,	0.350	0.277	0.30
	BN-S	−0.046	0.061	−0.200,	0.129	−0.058	0.06
	OSFED-BED	0.047	0.133	−0.337,	0.430	0.271	0.13
	OSFED-S	−0.040	0.100	−0.326,	0.247	−0.116	0.09
	OSFED-A	−0.268	0.114	−0.596,	0.059	−0.670	0.64
	BED-S	−0.084	0.107	−0.394	0.221	−0.339	0.43
T amp[1]	AN-BN	−0.006	0.050	−0.151,	0.139	0.031	0.04
	AN-OSFED	0.056	0.057	−0.107,	0.219	0.518	0.24
	AN-BED	0.063	0.058	−0.103,	0.230	0.608	0.32
	AN-S	−0.011	0.050	−0.155,	0.134	−0.008	0.03
	AN-A	−0.065	0.053	−0.218,	0.089	−0.400	0.22
	BN-OSFED	0.062	0.033	−0.032,	0.156	0.514	0.75
	BN-BED	0.069	0.035	−0.031,	0.170	0.609	0.88
	BN-S	−0.005	0.020	−0.062,	0.052	−0.040	0.05
	BN-A	−0.059	0.027	−0.136,	0.018	−0.452	0.05
	OSFED-BED	0.001	0.043	−0.117,	0.132	0.112	0.05
	OSFED-S	−0.067	0.032	−0.160,	0.027	−0.547	0.05
	BED-S	−0.074	0.035	−0.174,	0.026	−0.639	0.05
	S-A	−0.054	0.027	−0.132,	0.022	−0.405	0.61

Note. A: Asymptomatic Group; S: Subclinical Group; AN: Anorexia Nervosa Group; BN: Bulimia Nervosa Group; OSFED: Otherwise Specified Feeding and Eating Disorder Group; BED: Binge Eating Disorder Group; BMI: Body Mass Index; EDE-Q: Eating Disorder Examination – Questionnaire 6.0 Global Score (Fairburn and Beglin, 1994); Tp-e Int: Tpeak-Tend interval (seconds), R Amp: mean R wave amplitude (mV), T Amp: mean T wave amplitude (mV).

[1] Based on Levene's test, equal variances were assumed and Tukey HSD was used in analysis.

[2] Based on Levene's test, equal variances were not assumed and Games-Howell was used in analysis. $\hat{p} \leq .10$ (marginally significant) $*^{=}p = .05$ (marginally significant) $*p < .05$. $**p \leq .01$. $***p \leq .001$.

The clinical utility of a biomarker is influenced directly by accessibility and cost considerations. Biomarkers with the highest clinical utility should be time-efficient, relatively inexpensive, and straightforward to assess. Decreased mean R wave amplitude can be assessed with a brief and minimally invasive ECG strip. Easy-to-learn computer software and hardware ECG programs allow behavioral health technicians to be trained to assess the marker and to facilitate a physician referral for further assessment when indicated. The assessment of decreased mean R wave amplitude as an indicator of symptom severity, treatment prognosis, and as a screening tool for subsequent medical evaluation of cardiac risk, can be implemented fairly easily in behavioral health settings with relatively few financial resources and a relatively low additional training commitment. This feasibility further enhances the potential value of this marker.

Within clinical and research realms, the biomarker may be a promising indicator of symptom status and clinical outcomes. This is consistent with previous research which indicates decreased mean R wave amplitude may be an important marker of treatment response for eating disorder intervention studies (Green et al., 2017). It also extends research on the cardiac biomarker to the binge eating disorder population. Taken together, and pending replication, results suggest this marker should be monitored alongside self-report and clinical interview data as an additional indicator of symptom status and severity in several disordered eating diagnostic subgroups.

The present findings demonstrate decreased mean T wave amplitude may serve as a cardiac biomarker among patients with binge eating disorder and OSFED diagnoses. Decreased T wave amplitude reflects aberrant ventricular repolarization and is associated with protein energy malnutrition, overexercise, rapid weight loss, low body weight, hypokalemia, and low calorie intake (Ellis, 1946; Kumar et al., 2015; Swenne and Larsson, 1999). The marker corrects with weight restoration in patients with anorexia nervosa (Vargas Upequi and Gómez, 2015). Given the low weight/energy depleted pathophysiological correlate of the marker in existing research, it was a bit surprising to see decreased mean T wave amplitude in patients with binge eating disorder. The BMIs of these patients were significantly higher in the present sample compared to asymptomatic controls and other diagnostic groups including patients with OSFED, bulimia nervosa, or anorexia nervosa. These results provide preliminary evidence that decreased mean T wave amplitude may also be present in eating disorder populations that are not weight depleted. The pathophysiological mechanism explaining the presence of this marker in binge eating disorder populations warrants further investigation.

4.1. Summary

The search for biomarkers of eating disorder symptoms has been elusive. Reliable biomarkers have significant potential utility in diagnostic, treatment, and research realms. Identifying biomarkers which indicate symptom onset, escalation, and remission in a sensitive and responsive way allows clinicians to make reliable symptom assessments and to accurately gauge treatment outcomes without the bias introduced via self-report. This is especially important in a patient population characterized by inaccurate symptom reporting due to treatment ambivalence and the shame associated with these highly stigmatized disorders. Within the research realm, biomarkers are less likely to be affected by demand characteristics and therefore, represent an integral component of a robust assessment process. This is especially important within efficacy and effectiveness research in the treatment and prevention realms where reporting bias and demand characteristics can be particularly pronounced. The present study suggests decreased mean R wave amplitude may be a promising candidate biomarker.

5. Limitations

There were several limitations in the present study. Decreased mean R wave amplitude has been established previously as a biomarker of symptoms of anorexia nervosa in previous research (Panagiotopoulos et al., 2000; Swenne and Larsson, 1999; Ülger et al., 2006); that finding was not replicated in the existing sample. Future research should incorporate a larger sample of patients with anorexia nervosa to more fully investigate this question.

It was somewhat surprising that QTc did not emerge as a cardiac biomarker in the present study. Previous research shows a strong relationship between this marker and eating disorder symptoms. It is important to note this marker has been most reliably demonstrated among eating disorder populations with low BMI. Specifically, it has been most consistently documented in patients with anorexia nervosa. Since the present sample contained a very small number of such patients, group differences in this marker may not have been as pronounced in the present sample.

The present study relied on self-report measures to assess eating disorder symptoms and used the Q-EDD (Mintz et al., 1997) to assess diagnostic subtypes. The Q-EED has been used to determine DSM-5 diagnostic subtypes in similar studies of cardiac biomarkers (see Green et al., 2016; Green et al., 2017). However, this measure has not been adapted for the assessment of DSM-5 diagnostic subtypes in other independent studies. Future research should replicate the present findings with symptom assessment methodologies outside of the self-report realm or should rely upon self-report measures validated for DSM-5 eating disorder diagnoses.

The present study did not examine physiological mechanisms undergirding group differences which may explain symptom-related changes in cardiac biomarkers. Future research should focus more readily on the physiological mechanisms which may explain cardiac changes. Viable mechanisms based on previous research indicate decreased left ventricular mass, aberrant thyroid function induced by malnutrition, electrolyte imbalance, protein-energy malnutrition, mitral valve prolapse, hypovolemia, and low body weight (Madias, 2008).

CRediT authorship contribution statement

Green, M. A.[1], Conceptualization, Methodology, Software, Validation, Formal Analysis, Resources, Writing – Original Draft, Writing – Review and Editing, Supervision, Project Administration, Funding Acquisition; Miles, L. [1], Formal Analysis, Investigation, Data Curation, Writing – Original Draft, Writing – Review and Editing, Supervision; Sage, E. [1], Investigation, Smith, J. [1], Investigation; Carlson, G. [1], Investigation; Hogan, K. [1], Investigation; Bogucki, J. [1], Investigation; Ferenzi, L. [1], Investigation; Hartman, E. [1]; Investigation; Tao, Y. [1], Investigation; Peng, Y. [1], Investigation; Roche, A.I.[3], Investigation; Bolenbaugh, M. A.[2], Investigation; Wienkes, C.[2], Investigation; Garrison, Y.[2], Supervision; Eilers, S.[4], Supervision.

Declaration of competing interest

Our research team has no potential conflicts of interest to disclose. Data sharing statement: The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

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