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Cardiac biomarkers of disordered eating: A case for decreased mean R wave amplitude

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ABSTRACT

The purpose of this study was to identify cardiac biomarkers of disordered eating. Mean R wave amplitude (mV), mean T wave amplitude (mV), QRS interval (sec), QTc interval (sec), and Tpeak-Tend interval (sec) were assessed via electrocardiography among women with clinical (n = 53) and subclinical (n = 56) eating disorder symptoms versus asymptomatic controls (n = 32). QRS and QTc intervals were significantly longer and mean T and R wave amplitudes significantly lower among women with clinical symptoms compared to asymptomatic controls. QTc interval length was significantly longer and mean R wave amplitude was significantly lower among women with subclinical symptoms versus asymptomatic controls. Decreased mean R wave amplitude yielded a comparable effect size as QTc when differentiating between asymptomatic and subclinical groups and a larger effect size than QTc when differentiating between asymptomatic and clinical groups, representing a promising clinical biomarker.

1. Introduction

The National Institute of Mental Health (NIMH) launched the Research Domain Criteria Project (RDoC) to identify "clinically actionable biomarkers for psychiatric disorders" in order to provide reliable and valid biological indicators to 1) improve diagnostic accuracy, 2) more effectively identify and target high risk groups for intervention, and 3) systematically assess treatment outcomes (Insel, 2014, pg. 395). Existing research indicates clinical and subclinical eating disorder populations exhibit disorder-related cardiac changes which escalate with symptom progression and ameliorate with effective treatment (Green et al., 2017; Green et al., 2016; Jáuregui-Garrido and Jáuregui-Lobera, 2012; Panagiotopoulos et al., 2000; Ülger et al., 2006). Preliminary findings suggest cardiac biomarkers represent promising diagnostic indicators of symptom severity and treatment response.

Biomarkers which distinguish asymptomatic, subclinical, and clinical eating disorder populations are important for diagnostic, research, and treatment purposes. In the diagnostic realm, eating disorder patients often inaccurately report symptoms, height, or weight due to poor insight or treatment ambivalence (McCabe et al., 2000). A biomarker which reliably denotes symptom severity would provide an objective indicator with significant diagnostic utility. In the research realm, demand characteristics lead to inaccurate self-reporting of symptoms (McCambridge et al., 2012). Reliable biomarkers may represent better indicators of treatment and prevention outcomes in clinical trials compared to self-report methodology.

In the treatment realm, biomarkers which fluctuate systematically with symptom progression could serve as clinical indicators of recovery status and treatment prognosis. Promising biomarkers should be easily assessed with relatively low costs in order to be of maximal clinical utility. Cardiac biomarkers assessed via brief electrocardiography meet these criteria. Also in the treatment realm, research on cardiac biomarkers may inform cardiac-related care for eating disorder patients. Subtle cardiac changes occur early in eating disorder progression (Green et al., 2016) and vary systematically with symptom changes (Green et al., 2017; Ülger et al., 2006). Disorder-related cardiac changes become more pronounced as symptoms worsen. Adverse cardiac events are among the leading causes of mortality and morbidity among eating disorder patients. Increased understanding of disorder-related cardiac biomarkers is essential for good clinical care (Jáuregui-Garrido and Jáuregui-Lobera, 2012; Takimoto et al., 2008).

Taken together, findings suggest cardiac biomarkers show great potential among eating disorder populations. These considerations highlight the importance of identifying which cardiac biomarkers most reliably differentiate eating disorder symptoms. Several candidate electrocardiograph (ECG) biomarkers have received support including QTc interval prolongation, QRS interval prolongation, decreased mean T wave amplitude, Tpeak-Tend (Tp-e) interval prolongation, and

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decreased mean R wave amplitude (Green et al., 2016; 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 significance of each biomarker is discussed briefly below.

1.1. QRS interval prolongation

QRS interval prolongation is characterized by QRS interval widening and reflects slowed conduction of electrical impulses though the ventricular myocardium. QRS interval prolongation is linked to elevated risk for sudden cardiac death among non-eating disorder patients (Bode-Schnurbus et al., 2003; Kurl et al., 2012) and is associated with starvation (Ellis, 1946). Patients with anorexia nervosa display QRS interval prolongation which remits with weight restoration (Vargas Upequi and Gómez, 2015).

1.2. QTc interval prolongation

QTc interval prolongation reflects aberrant myocardial repolarization and is associated with ventricular tachycardia, a life-threatening cardiac arrhythmia (Jáuregui-Garrido and Jáuregui-Lobera, 2012). QTc prolongation has received the most extensive empirical support as a cardiac biomarker differentiating patients with disordered eating and asymptomatic controls (Jáuregui-Garrido and Jáuregui-Lobera, 2012). QTc prolongation has been linked to electrolyte abnormalities, low body mass index (BMI), and rapid weight loss. QTc prolongation occurs in patients with low BMI or rapid weight loss even in the absence of electrolyte abnormalities (Swenne and Larsson, 1999).

1.3. Tp-e interval prolongation

Tp-e interval prolongation is associated with atypical ventricular repolarization and is predictive of sudden cardiac death among non-eating disorder populations (Panikkath et al., 2011). Tp-e interval prolongation is more likely to predict sudden cardiac death when co-occurring alongside comorbid QTc interval prolongation (Castro Hevia et al., 2006). Eating disorder patients frequently demonstrate both of these markers (Jáuregui-Garrido and Jáuregui-Lobera, 2012).

1.4. Decreased mean T wave amplitude

Decreased mean T wave amplitude is associated with atypical ventricular repolarization. The marker is linked to starvation, protein energy malnutrition (Ellis, 1946; Kumar et al., 2015), hypokalemia (Diercks et al., 2004), excessive exercise, weight loss, and low weight (Swenne and Larsson, 1999). Patients with anorexia nervosa display significant reductions in mean T wave amplitude which remits with weight restoration (Vargas Upequi and Gómez, 2015).

1.5. Decreased mean R wave amplitude

Decreased mean R wave amplitude is linked to decreased electromotive force generation during depolarization of the ventricles; it is a risk indicator for ventricular arrhythmia and myocardial infarct (Madias, 2008; Sun et al., 2013). Mean R wave amplitude worsens with protein-energy malnutrition and improves with weight restoration (Gottdiener et al., 1978). Isner et al. (1979) identified decreased mean R wave amplitude as a predictor of sudden and unexpected cardiac death among patients who lost massive amounts of weight over a short period of time via a liquid-protein-modified fast diet. Pre- and post-diet ECGs were available for a percentage of the patients prior to sudden cardiac death; results indicated a significant 23–50% decrease (average 38%) in mean R wave amplitude from pre- to post-diet. Decreased mean R wave amplitude was associated with postmortem structural abnormalities including significantly reduced heart size, thinning of the ventricular myocardium, and increased lipofuscin or “wear and tear” pigment in myocardial fibers.

Ülger et al. (2006) showed significantly decreased mean R wave amplitude among women with anorexia nervosa; decreased mean R wave amplitude was related to other cardiac risk indices, including QT interval prolongation, decreased left ventricular mass, and bradycardia. Panagiotopoulous et al. (2000) demonstrated decreased mean R wave amplitude among women with anorexia nervosa. Green et al. (2016) demonstrated decreased mean R wave amplitude among women with bulimia nervosa and subclinical levels of binge/purge behaviors. Regression analyses revealed binge and purge frequency, most notably laxative abuse as a purge method, predicted the marker. Green et al. (2017) examined mean R wave amplitude among women with clinical and subclinical eating disorder symptoms pre-, post-, and 2-months after a dissonance-based eating disorder intervention program. Findings showed mean R wave amplitude significantly increased as eating disorder symptoms improved at post-intervention and 2-month follow-up.

1.6. Present study

The purpose of this study was to identify cardiac biomarkers of disordered eating. Mean R wave amplitude (mV), mean T wave amplitude (mV), QRS interval (sec), QTc interval (sec), and Tpeak-Tend interval (sec) were assessed via electrocardiography among women with clinical ($n = 53$) and subclinical ($n = 56$) eating disorder symptoms versus asymptomatic controls ($n = 32$). A one-way (group: asymptomatic, subclinical, clinical) MANOVA was used to investigate mean differences in BMI, eating disorder symptoms, and cardiac indices as a function of group. Based on previous research, we predicted mean QRS interval length, QTc interval length, and Tp-e interval length would be significantly longer and mean R wave and T wave amplitude significantly lower among clinical and subclinical compared to asymptomatic groups (Hypothesis 1). We further predicted mean R wave amplitude would show the largest effect size differentiating groups, establishing mean R wave amplitude as a promising biomarker of disordered eating (Hypothesis 2).

2. Methods

2.1. Participants

Participants were recruited from 2 Midwestern cities and 5 surrounding suburban communities. Participants were recruited via advertisements posted in 2 local newspapers, on the websites of the National Eating Disorder Association and the Academy for Eating Disorders, on the social media websites *Facebook* and *Instagram*, on the online posting board *Craigslist*, and via fliers posted in 101 retail locations. Letters containing fliers were also sent to health practitioners, behavioral health practitioners, nutritionists, and to sorority houses in the identified communities. Fliers were posted in the women's restrooms of 6 large urban high schools, across the campus of a three small Midwestern liberal arts colleges and a large Midwestern University; the study was announced in select classes in the Department of Health and Human Physiology at a large Midwestern university, and an announcement regarding the study appeared on an e-mail listserv of a large Midwestern university.

An on-line screening was administered via *Qualtrics* to determine participant eligibility. The on-line screening consisted of a demographic questionnaire and the Questionnaire for Eating Disorder Diagnoses (Q-EDD: Mintz et al., 1997). Eligible participants included women between the ages of 14–34 who indicated no disordered eating (asymptomatic group) according to Q-EDD scoring criteria, women who endorsed a high level of body dissatisfaction and binge or purge behaviors at subthreshold levels but did not meet diagnostic criteria for an eating disorder according to Q-EDD scoring criteria (subclinical group), and

women who met 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).

Eligibility was limited to women ages 14–34 to control for the effects of estrogens on cardiovascular function; the protocol required that all female participants be postpubescent and premenopausal. This was verified via self-report. Pregnant women were excluded from the sample due to the effects of pregnancy on cardiovascular function. Participants with binge eating disorder were excluded from the sample because existing research indicates cardiac risk indices differ significantly in this subgroup compared to other eating disorder groups (Friedrich et al., 2006).

Prior to admittance into the study, participants completed an online screening consisting of a demographic questionnaire, questions to determine study eligibility, and the Questionnaire for Eating Disorder Diagnoses (Q-EDD: Mintz et al., 1997) to determine ED group status (asymptomatic, subclinical, clinical). 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. An a priori power analysis indicated researchers should admit 30 participants per group to ensure adequate statistical power based on the anticipated effect sizes.

Participants' ages ranged from 14 to 34 years ($M = 23.38$, $SD = 4.77$). The racial and ethnic composition of the sample was 84.4% Caucasian, 2.1% African American, 6.3% Asian American, 1.0% Latina American, 1.0% Biracial, 1.0% Multiracial, and 1.0% International. 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)

The Questionnaire for Eating Disorder Diagnoses (Q-EDD: Mintz et al., 1997) was used to assign participants to diagnostic groups. The Q-EDD is a self-report questionnaire used to assess level of eating disorder symptomatology. The Q-EDD (Mintz et al., 1997) operationalizes diagnostic criteria for eating disorder diagnoses according to the Diagnostic and Statistical Manual of Mental Disorders, 4th edition, Text Revision (DSM-IV-TR: American Psychiatric Association, 2000); scoring criteria were adapted in the present study to fit criteria specified by DSM-5 (American Psychiatric Association, 2013).

Participants were assigned to the clinical group if they met DSM-5 diagnostic criteria for an eating disorder (American Psychiatric Association, 2013). Subclinical group designation was determined in accordance with Q-EDD scoring criteria for symptomatic classification (Mintz et al., 1997). Specifically, participants were assigned to the subclinical group if they endorsed excessive dietary restriction (i.e., 24 h fasting), laxative use, diuretic use, dieting, maladaptive exercise, or binge behaviors at subthreshold levels and a high level of weight/shape preoccupation and body dissatisfaction on the Q-EDD (Mintz et al., 1997). Participants were assigned to the asymptomatic group if they received asymptomatic classification according to the scoring criteria outlined by Mintz et al. (1997). Participants in this group did not endorse binge behaviors or purge behaviors in the form of self-induced vomiting, laxative use, diuretic use, fasting, chew/spit behaviors, dietary restriction, or maladaptive exercise for weight-related reasons.

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

2.2.2. Eating Disorder Examination-Questionnaire (EDE-Q 6.0)

The Eating Disorder Examination-Questionnaire 6.0 (EDE-Q 6.0: Fairburn and Beglin, 2008) was used to examine eating disorder symptom levels among the 3 groups (asymptomatic, subclinical, clinical) in the present study. The EDE-Q 6.0 is a 28-item self-report assessment of ED symptoms adapted from the Eating Disorder Examination (EDE: Cooper et al., 1989); it consists of the 4 following subscales: Restraint, Weight Concern, Eating Concern, and Shape Concern. Participants are asked to assess dietary restraint, weight concern, eating concern, and shape concern over the past 28 days on a 7-point Likert scale ranging from 0 (*no days*) to 6 (*every day*). Subscale scores are mean scores derived by averaging subscale items. A global ED score is obtained by averaging subscale scores. Higher scores indicate higher levels of eating disorder pathology.

The EDE-Q 6.0 is an updated version of its 36-item predecessor, the Eating Disorder Examination-Questionnaire (Fairburn and Beglin, 1994); the 22-items assessing eating disorder pathology on the 4 subscales are assessed similarly on both instruments, with only slight wording changes (Aardoom et al., 2012). The EDE is recognized as the highest standard of assessment instruments in ED research; the EDE-Q shows high convergent validity with EDE subscales (Mond et al., 2004). Cronbach's α coefficients were high in a community sample which included women with eating disorder symptoms (Aardoom et al., 2012).

2.2.3. ECG data

ECG data were recorded via a 3-lead ECG with a lead II chest configuration. The ECG signal was acquired via a MP35 BIOPAC psychophysiological data acquisition system with a sampling rate of 1000 Hz. A sampling rate of 100 to 500 Hz is sufficient for human studies, but higher sampling rates are optimal (Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology, 1996). Hardware setup included an ECG100C amplifier with a 35 Hz LPN filter and a 0.5 Hz HP filter. Data were analyzed via PowerLab LabChart 7 software for Microsoft Windows. Experimenters observed ECG strips during data collection and marked artifacts in the strip as they occurred. Artifacts were evaluated during ECG analysis. All strips were trimmed to the first 300 s of artifact-free data for subsequent statistical analysis; 5 min and 30 s of ECG data were collected to allow for subsequent trimming.

In PowerLab LabChart 7, the ECG settings are at the preset detection and analysis settings for human participants. The data source is Channel 1 (0.05–35 Hz) using the whole channel. For detection, typical QRS width is 80 ms and R waves are at least 300 ms apart. For analysis, the pre-P baseline is at 120 ms, maximum PR is at 240 ms, maximum RT is at 400 ms, and ST height is at 120 ms from alignment. QTc is corrected with Bazett's formula.

The heart rate variability (HRV) settings are also at the preset human participant detection settings. The data source is Channel 1 (0.05–35 Hz) using the whole channel. Analysis settings have histogram bin width at 10 ms, pRR threshold at 50 ms, and SDARR averaging 300 s. Ectopic beats have been included in the analysis. RR interval is set at 800–1200 ms with complexity between 1 and 1.5. For spectrum, maximum frequency is 0.5 Hz with number of frequencies at 500. VLF is set at 0–0.04 Hz, LF at 0.04–0.15 Hz, and HF at 0.15–0.45 Hz.

2.3. Procedure

Participants were instructed to avoid the intake of food, coffee, and nicotine for 3 h, and to abstain from vigorous physical exercise for 24 h prior to their research appointments. If signs of acute physical illness and accompanying fever developed within 48 h of the appointment, participants were instructed to reschedule due to the effects of

Table 1
Descriptive statistics as a function of condition: age, BMI, HR, systolic and diastolic blood pressure, Eating Disorder Symptoms (EDE-Q), QRS interval length, QTc interval length, Tp-e interval length, R Amplitude and T Amplitude as a function of condition .

ED Group	Asymptomatic		Subclinical		Clinical	
	M	*SD*	*M*	*SD*	*M*	*SD*
Age	24.50	4.93	22.94	4.73	23.32	4.73
BMI	23.63	5.26	26.95	6.83	26.57	7.87
HR	66.72	10.18	75.10	46.40	67.05	14.31
Systolic BP	107.00	10.12	113.68	9.49	109.52	6.97
Diastolic BP	62.94	8.55	66.05	9.76	65.59	7.61
EDE-Q	0.83	0.84	2.96	1.02	3.36	1.18
QRS interval length	0.07	0.01	0.07	0.01	0.08	0.01
QTc interval length	0.39	0.02	0.40	0.02	0.40	0.02
Tp-e interval length	0.06	0.01	0.06	0.01	0.06	0.01
R Amplitude	1.43	0.52	1.20	0.40	1.11	0.34
T Amplitude	0.40	0.13	0.36	0.12	0.34	0.12

Note. BMI: body mass index; HR: heart rate; Systolic BP: Systolic blood pressure; Diastolic BP: Diastolic blood pressure; EDE-Q: Eating Disorder Examination – Questionnaire 6.0 (Fairburn and Beglin, 1994).

cytokines on cardiac autonomic balance. Participants were placed in a supine posture for a 10-min equilibration period; a blood pressure cuff with heart rate monitor was secured to the left arm. Blood pressure and heart rate indices were checked at two 5-min intervals to assess cardiac equilibration. Participants were prepared for electrocardiography (ECG) during this equilibration period. 3 self-adhesive electrodes were secured using a lead II chest configuration; ECG lead wires were attached and a sample (~5 s) ECG recording was obtained to check signal quality. Immediately after the 10-min equilibration period, participants were instructed to remain silent and still while the ECG recording was obtained. At the conclusion of the recording, each participant's height and weight was assessed in the laboratory. Participants were debriefed and compensated $40 in exchange for their participation.

3. Results

Table 1 summarizes descriptive statistics for age, BMI, eating disorder symptoms, and cardiac indices as a function of condition. A one-way MANOVA was conducted to examine differences as a function of ED group. Results were statistically significant, *Pillai's Trace* = 0.61, $F(14, 266) = 8.35$, $p < 0.001$, $\text{eta}^2_p = 0.31$, observed power = 1.00.

A series of one way analyses of variance (ANOVAS) were conducted to interpret statistically significant MANOVA results. Table 2 summarizes the ANOVA results. As predicted, there were statistically significant mean group differences in eating disorder symptoms, QRS interval length, QTc interval length, and mean R wave amplitude. There were marginally significant ($p < 0.10$) mean group differences in BMI, Tp-e interval, and mean T wave amplitude.

Table 2
One way ANOVA summary table: eating disorder symptoms and cardiac risk factors as a function of eating disorder diagnostic group ($N = 141$).

Measure	Sum of Squares	*df*	*Mean Square*	*F*	*Partial* η^2	Observed power
BMI	245.99	2, 138	123.00	2.56ˆ	0.04	0.50
EDE-Q	137.67	2, 138	68.83	62.68***	0.48	1.00
QRS Interval	0.001	2, 138	0.001	3.93*	0.05	0.70
QTc interval	0.003	2, 138	0.002	3.51*	0.05	0.65
Tp-e interval	0.000	2, 138	0.000	2.61ˆ	0.04	0.51
R Amplitude	2.02	2, 138	1.01	5.95**	0.08	0.87
T Amplitude	0.08	2, 138	0.04	2.80ˆ	0.04	0.54

Note. EDE-Q: Eating Disorder Examination – Questionnaire 6.0 (Fairburn and Beglin, 1994).
ˆ $p \leq 0.10$ (marginally significant) ˆˆ $p = 0.05$ (marginally significant).
* $p < 0.05$.
** $p < 0.01$.
*** $p < 0.001$. QRS, QTc, Tp-e intervals measured in seconds. R Amplitude and T amplitude measured in mV.

Contrast tests were conducted to interpret statistically significant ANOVA results. Based on Levene's test, equal variances were assumed for all variables except eating disorder symptomatology. Table 3 summarizes contrast test results. As predicted, mean R wave amplitude was significantly lower in clinical and subclinical compared to asymptomatic groups; T wave amplitude was significantly lower in clinical compared to asymptomatic groups. QTc, QRS, and Tp-e intervals were significantly longer in clinical compared to asymptomatic groups; QTc interval was significantly longer in subclinical compared to asymptomatic groups. There was not an adequate cell size to examine differences in cardiac biomarkers as a function of eating disorder diagnostic subtypes (e.g., anorexia nervosa, bulimia nervosa, etc.). However, descriptive statistics for cardiac biomarkers as a function of eating disorder diagnostic subtypes are provided in Table 4 for the interested reader.

Secondary analyses were conducted to examine binge and purge frequency in the past 28 days as predictors of QTc and decreased mean R wave amplitude. Specifically, frequency of binging, self-induced vomiting, laxative use, and excessive exercise for weight-control purposes (as indicated on the Q-EDD; Mintz et al., 1997) were evaluated as predictors of QTc and decreased mean R wave amplitude. See Table 5 for regression results. Findings indicate binge frequency was a significant predictor of QTc prolongation and decreased mean R wave amplitude.

Secondary analyses were conducted to examine pathophysiological predictors of decreased mean R wave amplitude. Cardiac autonomic dysfunction expressed as decreased sympathetic tone and hypervagal tone has previously been identified as a candidate mechanism linked to decreased mean R wave amplitude (Green et al., 2016; Madias, 2008). A simple linear regression was conducted to examine heart rate, high frequency spectral power (an ECG indicator of vagal tone), and low frequency/high frequency spectral ration (an ECG indicator of sympathetic tone) as predictors of decreased mean R wave amplitude. Heart rate was included in the regression equation because it is an additional indicator of sympatho-vagal balance. Regression results were not statistically significant, $F(3, 95) = 0.15$, $p > 0.05$, $R = 0.07$, explaining 0.5% of the variance in mean R wave amplitude.

4. Discussion

Findings showed mean T wave amplitude, mean R wave amplitude, QTc interval length and QRS interval length differed significantly among clinical versus asymptomatic groups. These indices may have value in differentiating clinical eating disorder populations from asymptomatic groups. Mean R wave amplitude and QTc interval also differentiated between asymptomatic and subclinical groups, suggesting these biomarkers are more sensitive indicators of symptom level. Effect size estimates indicate mean R wave amplitude shows a comparable effect size to QTc when differentiating subclinical from asymptomatic groups and a larger effect size when differentiating clinical from asymptomatic groups. Results suggest decreased mean R wave amplitude holds considerable promise as a reliable cardiac biomarker of eating disorder symptom levels.

Implications of this finding are numerous. Elucidating cardiac indicators of eating disorders aligns well with the current National Institute of Mental Health (NIMH) initiative to identify biomarkers of psychiatric illness. Reliable biomarkers are needed in the diagnostic, research, and treatment realms. Results suggest mean R wave amplitude is a reliable indicator of eating disorder symptom severity. In this capacity, the marker could be used to improve diagnostic accuracy, more effectively identify and target high risk groups for intervention, and be an unbiased indicator of treatment outcomes. The marker could be used to supplement self-reported information to improve diagnostic,

Table 3
Posthoc tests for BMI, EDE-Q, and cardiac risk indices as a function of ED diagnostic status.

Variable	*t*(df)	Mean Difference	*Std. Error*	95% CI	Cohen's *d*
BMI					
A–S	−2.16(138)*	−3.13	1.54	−6.96, 0.33	−0.54
A–C	−1.89(138)ˆ	−2.93	1.55	−6.61, 0.75	−0.44
S–C	0.29(138)	0.38	1.33	−2.77, 3.53	0.05
EDE-Q					
A–S	−10.58(75.47)***	−2.13	0.20	−2.61, −1.65	−2.28
A–C	−11.52(80.80)***	−2.53	0.22	−3.05, −2.00	−2.47
S–C	−1.89(102.89)ˆ	−0.40	0.21	−0.90, 0.10	−0.36
QRS Interval					
A–S	−1.12(138)	−0.003	0.003	−0.009, 0.002	0.00
A–C	−2.70(138)**	−0.008	0.003	−0.013, −0.002	−1.00
S–C	−1.90(138)ˆ	−0.005	0.002	−0.009, 0.000	−1.00
QTc Interval					
A–S	−2.21(138)*	−0.010	0.005	−0.02, −0.00	−0.50
A–C	−2.53(318)*	−0.012	0.005	−0.02, −0.003	−0.50
S–C	−0.40(138)	−0.002	0.004	−0.01, 0.006	0.00
Tp-e Interval					
A–S	−1.71(138)ˆ	−0.003	0.002	−0.006, 0.000	0.00
A–C	0.11(138)	0.000	0.002	−0.003, 0.004	0.00
S–C	2.10(138)*	−0.003	0.001	−0.006, 0.000	0.00
R Amp					
A–S	2.47(138)*	0.23	0.09	0.05, 0.41	0.50
A–C	3.43(138)***	0.32	0.09	0.13, 0.50	0.73
S–C	1.14(138)	0.09	0.08	−0.07, 0.25	0.24
T Amp					
A–S	1.55(138)	0.04	0.03	−0.01, 0.10	0.32
A–C	2.37(138)*	0.07	0.03	0.01, 0.12	0.48
S–C	0.97(138)	0.02	0.02	−0.07, 0.02	0.17

Note. A: Asymptomatic Group. S: Subclinical Group. C: Clinical Group.
ˆ $p \leq 0.10$ (marginally significant) ˆˆ $p = 0.05$ (marginally significant).
* $p < 0.05$.
** $p < 0.01$.
*** $p \leq 0.001$. QRS, QTc, Tp-e intervals measured in seconds. R Amplitude and T amplitude measured in mV.

Table 4
Descriptive statistics for cardiac biomarkers as a function of eating disorder diagnostic subtype ($N = 141$).

Diagnostic subtype	Anorexia *M(SD)* $n = 2$	Bulimia *M(SD)* $n = 42$	OSFED *M(SD)* $n = 9$
QRS interval	0.071(0.006)	0.077(0.012)	0.086(0.019)
QTc interval	0.405(0.008)	0.389(0.021)	0.402(0.018)
Tp-e interval	0.059(0.006)	0.061(0.007)	0.057(0.010)
R Amplitude	1.31(0.66)	1.10(0.36)	1.20(0.25)
T Amplitude	0.33(0.09)	0.35(0.12)	0.28(0.11)

Note. OSFED: Other Specified Feeding or Eating Disorder. QRS, QTc, Tp-e intervals measured in seconds. R Amplitude and T amplitude measured in mV.

Table 5
Multiple linear regression analyses: binge and purge frequency as a predictor of mean R wave amplitude and QTc ($N = 140$).

Model 1 Outcome variable	*R*	R^2	*Adjusted* R^2
Mean R Amplitude	0.28	0.08	0.05*
Predictor variables	*B*	*SEB*	*β*
Binge	−0.017	0.01	−0.25*
Vomit	−0.004	0.01	−0.05
Laxative	−0.005	0.01	−0.08
Excessive Exercise	0 0.001	0.01	0.02
Model 2 Outcome variable	*R*	R^2	*Adjusted* R^2
QTc	0.33	0.11	0.05*
Predictor variables	*B*	*SEB*	*β*
Binge	0.001	0.00	0.26**
Vomit	0.000	0.00	0.02
Laxative	−0.000	0.00	−0.00
Excessive Exercise	0.000	0.00	−0.08

ˆˆ $p < 0.10$,
* $p < 0.05$,
** $p < 0.01$. QRS, QTc, Tp-e intervals measured in seconds. R Amplitude and T amplitude measured in mV.

research, and treatment accuracy.

Assessment of mean R wave amplitude in psychiatric settings would not be overly burdensome. ECG methodology to assess this marker is quick and fairly inexpensive. Computer-assisted analysis of mean R wave amplitude is relatively straightforward. For a small investment in equipment and training, treatment and research centers could incorporate the assessment of this biomarker to more reliably evaluate symptom level and symptom progression. If clinical norms based on the marker are developed, these norms can be integrated into treatment planning decisions as indicators of disease severity. Additional research on mean R wave amplitude may demonstrate a marker threshold associated with significant weight loss or frequent binge and purge behaviors. Marker thresholds may be integrated to decide level of clinical care. Diagnostic reliability and treatment planning could be significantly enhanced by incorporating this reliable symptom biomarker alongside self-report data.

Assessment of this biomarker may be particularly important for patients who underreport symptoms due to treatment ambivalence or poor insight. It may also be important for patients who underreport symptoms levels due to their fears of disappointing therapists or family members who have invested a considerable amount of resources into their treatment. For these reasons, an objective biomarker is needed to promote best practices in the assessment of treatment outcomes.

Research implications are also highly salient. Demand characteristics inherent in clinical trials may lead to biased self-report of symptoms; reliable biomarkers can ameliorate this problem (Green et al., 2017). Assessment of decreased mean R wave amplitude represents a

method to objectively evaluate clinical outcomes for treatment and prevention trials. It may also be useful in other research contexts when an additional indicator of symptomatology that is resistant to potential self-report bias is needed.

Enhanced conceptualization of disorder-related cardiac changes in eating disorder populations is another area of application of the present findings. Previous research indicates mean R wave amplitude decreases with symptom deterioration (Isner et al., 1979), increases with symptom improvement (Green et al., 2017; Ülger et al., 2006), and is associated with increased risk for sudden cardiac death among eating disorder (Isner et al., 1979) and non-eating disorder populations (Madias, 2008). Taken together, results suggest assessing this indicator as a standard component of an eating disorder diagnostic interview could facilitate a greater number of referrals for comprehensive cardiac evaluation and intervention among at-risk patients. Since sudden cardiac death is one of the leading causes of death in eating disorder patients, this is an important aim.

Results of the present study indicate binge frequency is a predictor of decreased mean R wave amplitude and QTc prolongation. Findings suggest reductions in binge frequency may help to normalize aberrant cardiac function in eating disorder patients. Results replicate earlier findings which indicate a relationship between binge behaviors and mean R wave amplitude (Green et al., 2017; Green et al., 2016). The link between these constructs may be systematically related to pathophysiological changes driven by binge behaviors (Green et al., 2016; Mehler and Walsh, 2016). Cardiac autonomic dysfunction characterized as hypervagal tone and decreased sympathetic tone is a candidate pathophysiological mechanism (Green et al., 2016; Madias, 2008).

In a secondary simple regression analysis, we examined cardiac autonomic dysfunction as a potential predictor of decreased mean R wave amplitude since previous research suggests aberrant autonomic shifts attributable to protein-energy malnutrition may play a role in decreased mean R wave amplitude (Madias, 2008). This analysis was not statistically significant. That said, the potential role of cardiac autonomic dysfunction should be further examined. Spectral analysis of short-term ECG data to evaluate cardiac autonomic dysfunction via spectral heart rate variability analysis has significant error in short-term recordings (Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology, 1996). This error may obscure important findings related to the role of cardiac autonomic dysfunction in decreased mean R wave amplitude in ED populations. Future research should use longer ECG recordings (such as 24-h or 48-h recordings obtained via Holter monitor) to evaluate this potential relationship.

4.1. Limitations

There were several limitations of the present study. First, results indicated the eating disorder scores of subclinical and clinical groups did not significantly differ (though there was a trend in this direction at $p = 0.06$). Findings suggest the diagnostic classification method (i.e., Q-EDD criteria: Mintz et al., 1997) did not function reliably in the present sample. This is somewhat surprising given that this method has been used extensively to reliably classify eating disorder diagnostic status in previous research. Future research should replicate the present findings with a more reliable diagnostic classification method.

A second limitation was an inadequate sample size to evaluate biomarkers as a function of diagnostic subtype. Mean R wave amplitude may vary systematically with eating disorder diagnostic subtype based on the pathological behaviors practiced. For example, if weight loss most reliably predicts decreased mean R wave amplitude, then persons with anorexia nervosa may be at greatest risk. Alternatively, if binge frequency best predicts the marker, then patients with bulimia nervosa or anorexia nervosa binge-purge subtype may be at greatest risk. Future research should determine which groups may be at greatest risk of showing the aberrant maker and therefore, in highest need of marker assessment to ascertain symptom status and other cardiac risks. It should be noted that some may not view this gap in the literature as a limitation. If mean R wave amplitude indicates ED pathology, other diagnostic measures may be used to determine the nature of the diagnostic subtype (i.e., BMI, diagnostic interviews).

A third limitation of this body of literature is that diagnostic thresholds or clinical cutoffs have not yet been conclusively established for R wave amplitude among eating disorder populations. Data from the current and previous studies suggest mean R wave amplitude ranges from 0.98 to 1.11 mV for clinical ED populations, 1.20–1.37 mV for populations with subclinical symptoms, and 1.40–1.59 mV for asymptomatic populations (Green et al., 2016). Treatment efficacy literature suggests the marker increased in amplitude by 0.17 mV after a 4-week treatment program which decreased eating disorder symptoms among clinical and subclinical groups (Green et al., 2017). Future research should continue to identify mean R wave amplitude values among clinical, subclinical, and clinical populations and track changes in these values as a function of treatment response in order to move toward the identification of clinically meaningful diagnostic cutoffs and agreed upon clinical indicators of treatment response. Once diagnostic and clinical cutoffs are established, this marker is easily assessed in clinical settings as most computerized ECG equipment calculates the amplitude of this portion of the ECG waveform. For clinics without existing access to computerized ECG technology, this technology is relatively inexpensive (< $20,000).

Finally, candidate pathophysiological mechanisms driving the relationship between eating disorder behaviors and decreased mean R wave amplitude were not identified in the present study. Previous research indicates weight loss (Isner et al., 1979), low BMI (Ülger et al., 2006) and binge/purge behaviors (Green et al., 2016) predicted decreased mean R wave amplitude among eating disorder patients but the physiological mechanisms underlying these relationships have not been fully explained. It is important to target pathophysiological mechanisms, and their associated behavioral etiology, in order to better understand changes in mean R wave amplitude among eating disorder patients. The present findings did not provide any additional evidence on the pathophysiological mechanisms responsible for decreased mean R wave amplitude in ED populations. Future research should continue to identify potential pathophysiological mechanisms which may explain this aberrant cardiac biomarker in ED populations. Potential mechanisms include decreased left ventricular mass associated with protein-energy malnutrition (as assessed by echocardiography), ischemia, electrolyte imbalances, thyroid disturbances, estrogen depletion, or hypovolemia associated with fluid depletion (Green et al., 2016; Madias, 2008).

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.psychres.2018.12.162.

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