DEVICES

Positive Psychotherapy to Improve Autonomic Function and Mood in ICD Patients (PAM-ICD): Rationale and Design of an RCT Currently Underway

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Background: *Improving mental and physical health of patients with implantable cardioverter defibrillators (ICD) is critical because this group is at high risk for ventricular arrhythmias and sudden death and depressed or anxious cardiovascular disease (CVD) patients appear to be at even higher risk for mortality compared to nondepressed or nonanxious CVD patients. Further, autonomic dysfunction is present in these patients, and negative emotions and arrhythmias form a downward spiral further worsening mood, well-being, and cardiovascular health. Much research demonstrates that positive emotion is related to health benefits, improved physiology, and increased survival.*

Methods and Results: *This is a two-arm randomized controlled trial aiming to recruit 60 adult ICD patients comparing 12 individually delivered, weekly sessions of: (1) a positive emotion-focused cognitive-behavioral therapy (Quality of Life Therapy [QOLT]), and (2) Heart Healthy Education. Autonomic functioning, heart rhythm indices, and psychosocial health are measured at baseline, 3 months, and 9 months. The first goal is feasibility and acceptability, with the primary outcome being arrhythmic event frequency data.*

Conclusion: *This study is designed to test whether QOLT produces changes in mood, quality of life/well-being, autonomic function, and arrhythmic and ICD therapy event rates. This feasibility trial is a foundational step for the next trial of QOLT to help determine whether a 3-month QOLT trial can reduce arrhythmias occurrences among ICD patients, and examine a mechanism of autonomic functioning. This study may help to develop and implement new medical or psychological therapies for ICD patients. (PACE 2016; 39:458–470)*

implantable cardioverter defibrillator (ICD), autonomic function, quality of life, positive emotion, behavioral medicine, psychological treatment

Introduction

Approximately 50% of all cardiovascular disease deaths are sudden and unexpected. The incidence of sudden death in the United States ranges from 200,000 to 450,000 annually.[1] The implantable cardioverter defibrillator (ICD) is used in patients at risk for ventricular arrhythmias and sudden death. Implant rates have increased 10-fold from 1990 to 2008,[1,2] with the most recent 2013 estimate of monthly implant rate at 12,500 per month.[3] Many ICD patients experience depression and anxiety (up to 63% experience anxiety, and 41% experience depression[4]), and reduced quality of life (QOL).[5,6]

Mental stress and negative emotions can provoke ischemia, arrhythmias, and sudden death among patients with coronary artery disease, ventricular fibrillation, atrial fibrillation, congestive heart failure, and ICDs.[7–19] By contrast, positive emotions and well-being have been shown to (1) protect against risk of coronary heart disease (CHD),[20–22] (2) be inversely related to cardiovascular death[22,23] and mortality,[22,24] (3) promote

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recovery and reduce rehospitalization,[25–28] and (4) improve mental health and social functioning among ICD patients.[29]

Positive emotion is also associated with several physiological pathways and biomarkers of cardiovascular disease (CVD), such as cortisol and the hypothalamus-pituitary-adrenal (HPA) axis; blood pressure, heart rate, and hemodynamic response; and markers of the inflammatory processes.[30] Up to 20% of life-threatening arrhythmias or sudden death are precipitated by an intense emotion, positive or negative in nature (e.g., earthquake, sporting event, World Trade Center Attack),[11,30,31] an effect replicated in ICD patients after controlling for traditional arrhythmic risk factors and medications.[9,10] In a recent study examining positivity and heart functioning, happiness was associated with a 40% reduction in the odds of a 24-hour risk of life-threatening arrhythmic events in patients with long QT syndrome, with stress having an opposite effect.[17] This is one of the first investigations to indicate the protective effect that positive emotion may have on arrhythmias. The fact that this is one of the first also highlights that the bulk of research on emotion and heart function is still focused on the role of *negative* emotion/distress rather than the *positive* spectrum of the emotional experience.

Several studies have demonstrated associations between emotion and autonomic function, arrhythmias, and cardiac events[7–9,15–19]; however, thus far studies have not yet demonstrated the mechanism by which emotion and arrhythmias are connected. Autonomic function is one mechanism that is hypothesized to link emotion to arrhythmias. Markers of diminished parasympathetic activity are associated with both ventricular arrhythmias and sudden death, and with depression and anxiety.[5,6,9,10,15,16,32–34] Patients with ICDs are particularly susceptible to emotion-triggered arrhythmias, sudden death, and ICD shocks.[11,30,31] Thus, ICD patients may directly benefit from a treatment that improves mood, autonomic functioning, and arrhythmias.

Cognitive behavior therapy (CBT), which focuses on symptom reduction of negative emotions, has been the standard for nonpharmacologic treatment of depression and anxiety disorders. CBT has improved depression symptoms and autonomic functioning in ICD patients, but has not reduced the frequency of arrhythmias[35–38] or ICD shock. However, these studies did not examine shock burden, only time to first shock.[37,38] A limitation of focusing on shock as an outcome is the relative rarity of the event, and the lack of understanding of the mechanism by which arrhythmia-requiring shock to terminate occurs. Reducing frequency of arrhythmias has greater clinical implications for health than delaying the time to first shock. Furthermore, these previous CBT studies may have been too narrowly focused on the reduction of negative emotions. Studies indicate that positive emotion may influence autonomic function by heightened parasympathetic activity and accelerating cardiovascular recovery following a negative emotion or stressor.[20,24,25,29,39–44]

Quality of Life Therapy (QOLT) combines CBT and positive psychology techniques and has been empirically validated to improve positive emotion, QOL, and to reduce negative emotion.[45–48] A paradigm shift toward enhancing positive emotions may provide a beneficial effect on reducing arrhythmia burden.

Study Objectives

The purpose of this paper is to present the positive psychotherapy to improve autonomic function and mood in ICD patients (PAM-ICD) trial, a clinical randomized controlled trial (RCT) which was designed to test the feasibility and acceptability of a nonpharmacological QOLT intervention among a sample of cardiac patients with ICDs. The PAM-ICD trial is currently funded by the National Heart, Lung, and Blood Institute of the National Institutes of Health (R34 HL107733). This paper discusses the design of the PAM-ICD RCT trial, discussing the research strategy in detail. The aims of the PAM-ICD Trial subscribe to the R34 mechanism—piloting a project with a plan for an R01 study. The study aims are to:

1. Examine the feasibility and acceptability of a 3-month positive-emotion-focused therapy (QOLT)[46] modified for ICD patients.
2. Obtain estimates of effect size for QOLT compared to a contact-control group (Heart Healthy Education [HHE]) on the changes in arrhythmia frequency and biomarkers of autonomic function, across time (baseline, 3 months, and 9 months).
3. Obtain estimates of effect size for QOLT compared to a contact-control group (HHE) on the changes in emotion, mood, and well-being and QOL, across time (baseline, 3 months, and 9 months).

Method

Study Design

The PAM-ICD Trial is a two-group, RCT design (planned N = 60 ICD patients; 30 per group) comparing two, 12-week, individually delivered interventions: (1) "experimental" intervention (QOLT); and (2) "control" group utilizing a contact-control, HHE intervention. Assessments are conducted at baseline, end of intervention (week 12), and at 9 months (6 months, postintervention completion).

The design was chosen as the best method for answering the questions central to the study. The contact control group was chosen because it will: (1) allow us to control for the amount of contact and attention given to all participants; (2) enable all the participants to receive some benefit from the study; (3) limit attrition and differential dropout rates because all participants will be engaged throughout the study; (4) provide improvement to previous studies' methodological weakness. In addition, it attempts to equalize subject burden between conditions, reducing chance of differential dropout.

All study procedures were approved by the MUSC's Institutional Review Board (Protocol #: Pro00028869) and NHLBI. The study is registered at ClinicalTrials.gov (Identifier: NCT02088619). The study is currently in the recruitment phase.

Sample Size and Power Calculations

While a primary aim of this application is feasibility and acceptability of QOLT, a second important aim is to obtain an estimate of the effect size of a 3-month QOLT intervention on the event rate change in the frequencies of ventricular arrhythmia episodes, that will serve as the basis for a future adequately powered R01 RCT. Published studies of CBT interventions among ICD patients have not previously examined the effect on arrhythmia frequency, but have examined shock frequency,[37,38] with one underway examining time to first shock.[49] Published findings to date are all underpowered.[50] However, there have been several clinical trials examining ICD programming that have measured the incidence of ventricular arrhythmia episodes, including the PainFREE Rx I trial,[51] which measured 1,100 episodes over 12 months in 220 study participants. Several other studies[52,53] have also measured similar but variant forms of arrhythmias in other populations. Our study population of interest shares many characteristics of the sample within the Wathen[51] study, and we used those frequency counts as the basis for our power and sample size estimation.

While the actual event rate reduction from the QOLT intervention is a focus of this study, our goal is to achieve a 20% reduction in rates, which would likely be clinically significant (Personal Communication, JJ Goldberger, February 5, 2010; AE Buxton, October 5, 2010) in the number of arrhythmia episodes in the QOLT group versus the HHE group. Based on our total sample of 60 (30 in each group), our power to detect significance at this clinically significant 20% reduction will be very low (17% power for a two-tailed test at $\alpha = 0.05$). However, if we can achieve that level of reduction in a future R01 with a follow-up period of 2 years, and assuming a 20% attrition rate, we would be able to achieve 80% power for a two-tailed test at $\alpha = 0.05$ with an initial sample before attrition of approximately 160 participants. With 60 participants, if we were to achieve a large (50%) reduction in ventricular arrhythmia episodes, we would also achieve 80% power for a two-tailed test at $\alpha = 0.05$. A *major study aim in this R34 is to provide a valid effect size estimate of our innovative intervention*.

Study Procedures

Participant Selection, Recruitment, and Randomization

Patients receiving specialized ICD care at the academic medical center are being recruited for the study through the cardiology and electrophysiology clinics. Potential participants will be identified by: (1) the patient's institutional healthcare providers; and/or (2) attendance to regularly scheduled clinic appointments. Currently, ICD patients do not receive routine psychosocial or psychotherapeutic treatment as part of their standard care at MUSC. We will aim to recruit at least 50% women and 25% minorities.

Patients are *eligible for inclusion* in the study if they meet the following inclusion criteria: (1) adult men and women (≥18 years of age) who have received an ICD for primary or secondary prevention of sudden cardiac death (SCD). All patients will have systolic left ventricular dysfunction due to coronary disease or nonischemic cardiomyopathy. There is no requirement for time since implant. (2) Scoring ≥5 on the Hospital Anxiety and Depression Scale (HADS)[54] on either the anxiety or depression scale. (3) Patients will be able to read and write English. (4) Commit to the 3-month QOLT/HHE program and three assessments over a 9-month duration.

Patients are *ineligible for participation* if any of the following exclusion criteria: (1) >5% atrial or ventricular pacing. (2) Sinus node dysfunction. (3) Persistent and permanent atrial fibrillation (AF) (history of paroxysmal AF will be allowed). (4) Long QT syndrome, and other channelopathies (e.g., Brugada syndrome, Wolff-Parkinson-White syndrome [WPW]). (5) Hypertrophic cardiomyopathy. (6) Neurocognitive or cognitive impairments based on observation and/or difficulty with informed consent. (7) Severe psychopathology that warrants intensive treatment, documented in medical record, by provider, or observed upon screening and consent processes. (8) Participation in another research trial. (9) Currently being enrolled in psychological or psychiatric treatment (counseling, therapy, etc.). (10) Current psychotropic and cardiac medication prescriptions and usage need to be stable (i.e., no change in type or dosage) for 3 months prior to study enrollment.

Medications will be continuously monitored, since cardiac and psychotropic medications can influence autonomic tone. While not initially or formally identified as an exclusion criteria, patients on antiarrhythmic medications, as well as patients with ventricular assist devices (VAD) or those who are likely to receive a VAD or heart transplant in the next 9 months (duration of study participation), will be excluded. Our center is a VAD Center of Excellence, and therefore, while not considered initially in establishing eligibility criteria, this situation has come up. Due to not being able to measure Heart Rate Variability (HRV), they are excluded.

Recruitment. Inclusion and exclusion criteria and the potential participant's medical history are extensively reviewed by the multidisciplinary research team (psychology, cardiology). During recruitment, a member of the research team will explain the study, assess interest, and conduct a brief screen for eligibility, specifically related to the psychological and medical eligibility criteria (e.g., psychopathology, medications, cardiac diagnoses). As part of the inclusion criteria the patient will need to score ≥5 on the HADS on either the depression scale or the anxiety scale, which is a self-report survey completed at screening. Scores of at least 5 on either scale express a level of symptoms that likely impair some area of functioning.[55–59] The requirement of symptoms of anxiety or depression for inclusion into the study is to enable improvement in mood and autonomic function. Therapy cannot be expected to enhance mood and well-being if participants are already feeling good. Additionally, since negative mood is related to autonomic dysfunction, full effect of the intervention is again not possible if participants are starting the intervention physically and/or mentally healthy. If eligible for the study, written informed consent and HIPAA authorization are obtained from the participant and baseline assessment scheduled. Included in consent is permission for the research team to contact their general practitioner and/or cardiologist regarding medication, general health status, and provide information about the study. The investigator will communicate extensively with the patient's cardiologist to seek reinforcement regarding the benefits of patient participation.

Intervention commencement initially was not to begin until after a series of individualized prerequisites were met; however, due to slow recruitment and difficulties participants were having arriving at appointments (e.g., due to significant travel distances), we have changed the flow minimally. Originally planned as (a) screening, (b) informed consent, (c) baseline assessment, (d) randomization, (e) first intervention session; as separate steps; steps (b)–(e) have now been combined into one visit. Baseline assessment remains in two parts, and thus, randomization and first intervention session are combined into the second part of the assessment (upon the return of Holter monitor and questionnaires). Since this change, we have seen positive response from participants and a reduction in attrition from baseline assessment to start of intervention.

Randomization. Participants are randomized to one of two treatment groups, stratified by indication for ICD (primary vs secondary prevention), and age (< or ≥65 years old). We assume that most patients will be taking a β-blocker, which will be controlled using statistical procedures rather than stratifying during randomization, along with time since implant.

Overview of the Intervention

Both of the treatment conditions are 12 sessions and are delivered as individual therapy. The goal is 45–60-minute sessions for both groups, and for sessions to occur weekly. This study is examining feasibility and dosing of treatment, and therefore, accounting for illness and various daily hassles, duration of intervention will be stopped at 18 weeks, regardless of whether participants have completed all 12 sessions. If a participant cannot attend or misses a session, a make-up session is arranged. Sessions were originally planned to be in-person; however, due to our population and catchment area (regional medical center) we have extended to a blend of in-person and phone sessions to facilitate recruitment and retention. Rates of phone and in-person sessions are tracked and compared between intervention groups.

QOLT Intervention

QOLT combines cognitive, behavioral, and positive psychology techniques and has been empirically validated to improve positive emotion, QOL, and reduce negative emotion.[45–48,60] QOLT is considered one of seven empirically validated approaches in the field of positive psychology, and composed of intervention techniques considered promising in the field of positive psychology.[47] QOLT treatment has three foci now recognized as the three elements of happiness: (1) increased life satisfaction, (2) increased positive emotion, and (3) reduced negative emotional experience.[61] Key resiliency factors are positive emotion, cognitive flexibility, life meaning, social support, and active coping strategies.[62] QOLT has been validated among clinically depressed community volunteers,[60] lung transplant recipients and caregivers,[45,48] end-stage renal disease awaiting transplant,[63,64] hepatitis C patients awaiting liver transplantation, and in children with obsessive

compulsive disorder (OCD) and their mothers.[65] All of these studies have demonstrated QOLT, in an individually delivered format, is more effective than supportive therapy or a control group in enhancing mood, QOL, life satisfaction, and reducing negative symptoms.

Participants receive a workbook of content discussed, homework assignments, and worksheets. Each session consists of: (1) review of the previous week's content and homework; (2) didactic content of new material and/or techniques; (3) relaxation exercises; and (4) time for discussion about the new content, homework assignment, and barriers to completion. Participants are taught several cognitive and behavioral techniques for boosting their satisfaction and happiness.

The intervention focuses on QOL areas that are most pertinent to ICD patients. For example, play (e.g., recreational activities, physical activity) is an area of attention as distressed ICD patients tend to limit pleasurable activities. The area of relationships also receives attention and significant loved ones will be invited to participate in these sessions. Participants are taught skills for improving self-esteem and other positive emotions—essential happiness beliefs such as learned optimism, finding meaning, the need for self-care and renewal on a daily basis, and service to others. Specific techniques that are taught include relaxation techniques, self-monitoring and cognitive restructuring, activity scheduling, and problem-solving and goal setting. In addition, as in other behavioral interventions for health promotion, QOLT includes a daily habit of health-promoting behaviors (e.g., exercise, treatment compliance) and relapse prevention and maintenance for distress.[66]

HHE Contact Control

Serving as a contact control condition, the participants randomized to this intervention match the QOLT intervention in terms of number of sessions. Duration is also attempted to be matched, with sessions ranging from 30 to 60 minutes (duration of sessions is recorded and will be examined across the two interventions). Each session will include education provided in the form of written materials/handouts, presentations, and/or films (video/digital video discs [DVD]), and time for discussion. Content will address a variety of health and lifestyle issues related to cardiovascular health, disease prevention, and progression. Didactic topics may include nutrition, smoking cessation, physical activity, stress management, well-being, social support, and sleep. Sessions do not include any therapeutic techniques or any form of instruction beyond the didactic material for that session.

Participant Retention, Differential Dropout, and Follow-Up

To reduce likelihood of differential dropout between the two conditions, we have included several features. First, by utilizing a contact control group (HHE), all participants have regular contact with project staff, as well as receiving education materials. Therefore, both groups are receiving beneficial treatment they might not have if not enrolled in the study. Previous trials conducted by Serber et al. (HL092340) and Marcus et al. demonstrate no differential dropout rate between intervention and contact control "wellness" groups.[67,68] Second, participants complete and return baseline psychosocial measures in-person prior to randomization for study participation. After baseline assessment has been completed, participants are provided with information about randomization, the study, and their intervention assignment. These steps increase the likelihood of only randomizing individuals who will comply with the study. Finally, all participants receive frequent telephone, email, and/or mail reminders of upcoming and missed sessions and assessments. "Completers" are defined as those attending at least 75% of the QOLT/HHE sessions over the 3-month period. To maximize adherence, we provide monetary incentives (i.e., gift cards to local popular stores) for their time in completing the assessments and intervention. Retention and attrition are closely recorded for feasibility and acceptability of the intervention and trial design.

Assessment

Participants complete all assessments on the same schedule (see Table I for Schedule of Study Measures), irrespective of intervention arm. Assessments are conducted at baseline prior to randomization, 3 months (end of intervention), and 9 months. Assessments include: medical record review including ICD interrogation/device reports, 24-hour Holter monitor recording, interview, and a self-report questionnaire packet to collect QOL and psychosocial information. The packet of questionnaires take approximately 30 minutes to complete. A 6-month assessment includes only their ICD interrogation for event rates and the HADS. If at any time, during assessments or intervention, immediate, individual psychological services are warranted (e.g., suicidal ideation, extreme behavior), an appropriate referral will be made. All data for assessments are collected in one session. The 24-hour Holter recorder will be placed by trained hospital staff. Project staff conducting assessments and entering data will be blinded to which intervention participant has been assigned.

Table I.

Schedule of Study Measures

Measure	Baseline	Weekly (0–3 Months)	3 Months	6 Months	9 Months
Hospital Anxiety and Depression Scale (HADS)	Screener			√	
Demographics	√				
Medical history	√				
ICD history	√				
Psychosocial history	√				
Intervention process measures		√	√		
Clinical electrophysiologic variables	√		√	√	√
Psychological well-being measures	√		√		√
Quality of life measures	√		√		√
Heart rate variability	√		√		√

ICD = implantable cardioverter defibrillator.

Sociodemographic and Medical History Data

These data are collected from patients' medical charts. Medical information includes: current cardiac diagnosis, disease duration, previous CVD and ICD history, past cardiac procedures, comorbid illness, and current medications. We gather baseline measures of cardiac functioning, including left ventricular ejection fraction (LVEF, %), systolic and diastolic blood pressure.

Measurement of Ventricular Arrhythmias

Ventricular arrhythmia burden is not often the focus of studies, as shocks have received a majority of the attention since the development of ICDs as they are associated with the most prominent symptoms; however, it is clear that frequency of arrhythmias is an index of deteriorating cardiac health and impairs survival.[69] Arrhythmias' versus shock's impact on the heart has yielded inconsistent evidence of which is the contributor to mortality, and while the debate has not been resolved, it is generally accepted that more shocks is synonymous with more arrhythmias, and overall "sicker hearts."[70–72] As this debate continues, a common conception is that greater arrhythmia burden is suggestive of greater ICD therapies delivered and higher mortality risk. This study focuses on arrhythmia burden, the beginning of this trajectory, and allows for measurement feasibility in this proposal.

Arrhythmias

Arrhythmia frequencies are collected from: (1) the ICD, and (2) 24-hour Holter monitor recording at baseline, 3 months, and 9 months. The ICD stores a record of the percent of heartbeats that are paced and sensed, and ventricular tachyarrhythmias causing ICD discharge, as well as nonsustained episodes. The ICD is interrogated every 3–6 months in the clinic or via home monitoring, with every attempt for participants to have their ICD interrogated every 3 months (previous standard of care), allowing determination of arrhythmia frequency and ICD therapies. For patients who only have their devices interrogated in clinic (usually every 6 months to 1 year), full and detailed Arrhythmia Logbooks from their devices are obtained at these clinic visits to facilitate examining frequencies of arrhythmias and ICD therapies across the study participation period. ICD detection criteria will be examined and taken into account when examining event data. All participants are treated by one institution's electrophysiologists, and therefore have general comparability as their practices are similar at the one institution.[52,73] Although a majority of episodes of ventricular tachycardia (VT) are brief, asymptomatic, and do not warrant treatment themselves, data from the CAST trial indicate that episodes of VT > 100 beats/min have adverse prognostic significance, and in the absence of antiarrhythmic agents such as flecainide, greater frequency and faster rate do not correlate with increased mortality in post-myocardial infarction (MI) patients.[74] Data reported from the MUSTT trial of patients with CHD, LVEF ≥ 40%, and spontaneous nonsustained VT indicate that longer episodes (≥6 beats) are associated with increased risk of cardiac arrest or sudden death. The mean rate of episodes does not relate to SCD risk but all patients had cycle length <500 ms.

Arrhythmia outcomes will be in the form of a continuous variable of the number of occurrences, whether they occurred in the same episode (same 24 hours) or on different days. Baseline counts will be summed from the previous 3 months prior to commencing the intervention (months –3 to 0),

3-month data (postintervention) will sum counts of the 3 months during the intervention (months 0–3), and the 6-month follow-up data will be counts of the previous 3 months (months 3–6). At the 9-month assessment, counts will be of the previous 3 months (months 6–9), and of the past 6 months since the end of the intervention (months 3–9). We will also explore differences in rates of tachycardia (100–149, 150–200, and >200 beats/min), but total arrhythmia frequencies will be the sum of Nonsustained ventricular tachycardia (NSVT) detected on the Holter (≥6 beats, at >120 beats/min) plus arrhythmias detected by the ICD. We will also analyze arrhythmia characteristics, including morphology (polymorphic vs uniform).

ICD Therapies

All therapies (antitachycardia pacing [ATP], shocks) delivered by the ICD will also be counted in the same manner as arrhythmias. This will serve as an exploratory outcome.

Measurement of Autonomic Function

Autonomic dysfunction is the common element in arrhythmias and negative emotion and mood; therefore, obtaining an effect size for change in autonomic function, specifically high frequency (HF)-HRV, an index of parasympathetic activity, will be the primary interest among HRV variables in this R34. HRV is a widely accepted index of measuring autonomic balance.[71,72,75] There are a number of ways that HRV can be analyzed and no consensus exists as to which method is superior. The *JACC* review suggests that several methods can be considered complementary to each other.[76] As noted in the consensus statement of *JACC*,[77] heart rate turbulence (HRT) is an indirect index of baroreflex sensitivity, and has been found appropriate in risk stratification after acute myocardial infarction, risk prediction, and monitoring of disease progression in heart failure, as well as in several other pathologies. T-wave alternans (TWA) appears to be a useful marker of risk for arrhythmias according to the consensus statement of the International Society for Holter and Noninvasive Electrocardiology published in *JACC*.[77] TWA has received a great deal of attention for risk stratification of sudden cardiac death and as an arrhythmia marker, particularly in ICD patients. The combination of TWA with HRT taken from ambulatory electrocardiograms (ECG)s is also being examined in a current NHLBI trial, REFINE-ICD (NCT00673842). Both sympathetic and parasympathetic branches of autonomic functioning affect TWA, along with various other cardiovascular measures, underscoring the link between TWA and arrhythmogenesis.[78]

Linear HRV

Linear and nonlinear HRV and HRT will be measured for best estimates of autonomic function. These will be calculated from data obtained by the 24-hour Holter recordings and analyses. HRV is an indicator of regulation of the heart by the autonomic nervous system. HRV is commonly analyzed in time and frequency domains. Most time domain indices reflect the overall autonomic modulation of heart rate. The frequency domain method involves power spectral analyses of HRV; the HF components have been shown to be due to parasympathetic modulation (of primary interest) and the low frequency (LF) components have been shown to be due to sympathetic and parasympathetic modulation of the heart rate. HRV analyses will be performed in accordance with the recommendations from the Task Force of the ESC/NASPE,[79] using the recommended time-domain variables: standard deviation of all normal RR intervals, the standard deviation of the average normal RR intervals, and root mean square of successive RR interval differences (RMSSD). RMSSD is highly correlated and a stable index of respiratory sinus arrhythmia (RSA).[80] Heart rate oscillations at HF also reflect RSA and are considered a marker of cardiac parasympathetic activity.[81–83] We will examine HF, LF, and LF/HF ratio.

Heart Rate Turbulence (HRT)

HRT describes the biphasic reaction of acceleration and deceleration of the sinus rhythm in response to a premature ventricular beat.[84] It is an indicator of baroreflex sensitivity. The baroreflex response is believed to reflect the capability of the regulatory system to increase vagal activity in response to changing blood pressure.[85] HRT will also be collected from a 24-hour Holter monitor based on calculations from the International Society for Holter and Noninvasive Electrophysiology Consensus standards of measurement, published in JACC.[86] Two numerical descriptors will be estimated: turbulence onset (TO), reflecting the initial phase of sinus rhythm acceleration, and turbulence slope (TS), describing the deceleration phase. TO is the difference between the mean cycle length of the first two beats following the post-premature ventricular contraction pause (R + 1, R + 2) and the two beats preceding premature ventricular contraction (R − 1, R − 2) as a percentage of preceding cycle lengths: TO = 100 * (R + 1, R + 2) − (R − 1, R − 2)/(R − 1, R − 2), where TO < 0% is normal.[87] TS is the steepest slope of linear regression lines for sequences of five consecutive post-premature ventricular contraction intervals for up to 20 beats. Normal

TS = 2.5 mm/RR.87. When using both HRT parameters simultaneously, participants can be classified as having two HRT parameters normal, one parameter abnormal, or two abnormal.[88]

T-Wave Alternans (TWA)

TWA, defined as a beat-to-beat fluctuation in ST-segment or T-wave morphology, has emerged as a useful electrocardiographic marker of risk for cardiovascular mortality and SCD. TWA will be obtained from analyzing the 24-hour Holter monitor recordings based on consensus guidelines.[89]

Psychological Well-Being Measures

Psychological measures are given at the three assessments to determine whether QOLT has direct effects on improving psychological well-being and QOL from baseline to 3- and 9- month assessment compared to HHE.

Screening

The HADS is used as a screening measure for eligibility in the study, and is also administered at 6 months after initiating the intervention. It measures depression and anxiety in hospital and outpatient settings, and is particularly useful for medical populations.[54] The HADS is valid and reliable, and in a variety of populations, including ICD patients.[58,90] Part of the inclusion criteria is scoring ≥ 5 on the HADS on either the depression or the anxiety scale; those scoring at least 5 on either scale are still expressing a level of symptoms that are likely impairing some area of functioning, while still enabling improvement via intervention.[58,59,91] ICD studies yielded mean HADS subscale scores (M $\pm$ standard deviation) $2.24 \pm 2.52 - 5.9 \pm 4.65$, as well as prevalence rates of scores >8 estimated at 25–53% for depression and anxiety, respectively.[55–57]

Outcome Measures

Other psychological outcome measures include ICD-specific, positive and negative emotions and mood, and QOL. These measures are administered at baseline, 3 months after initiating the intervention, and again at 9 months after initiating the intervention. The Florida Shock Anxiety Scale (FSAS) assesses device-specific fears regarding experiencing a shock, applicable to those who have and have not experienced a shock.[92] It has a total score and two reliable subscales: consequences of device firing, and triggers of device firing that can be calculated. All scales have good reliability (0.74–0.91).[92] The Florida Patient Acceptance Scale (FPAS)[93] assesses patient acceptance of the ICD. The FPAS is comprised of four consistent factors: return to function, device-related distress, positive appraisal, and body image concerns. The FPAS demonstrated convergent, divergent, and predictive validity when compared to other self-report measures (e.g., SF-36).[93] The Emotions Questionnaire is used to measure happiness.[94] It provides quantitative and qualitative information about happiness/unhappiness and according to Diener[95] provides the most important qualities of well-being (i.e., frequency and intensity of affect). It has established strong validity and reliability.[94] Other measures include the Center for Epidemiologic Studies-Depression Scale (CES-D)[96] for depression, the State Trait Anxiety Inventory (STAI)[97] for state and trait anxiety, the Life Orientation Test-Revised (LOT-R)[98] for generalized expectancies (dispositional optimism), the Positive and Negative Affect Schedule (PANAS)[99] for positive and negative emotion, and the Satisfaction with Life Scale (SWLS)[100] for satisfaction with life. The Quality of Life Inventory (QOLI)[101] is a domain-based life satisfaction instrument that consists of 16 items of the 16 domains of QOL according to QOLT and with strong reliability and validity.[101] Health-related QOL will be measured by the Short-Form Health Survey-36 (SF-36)[102] for general health-related QOL, Minnesota Living with Heart Failure Questionnaire (MLHFQ)[103] for cardiac-specific QOL.

Feasibility, Acceptability, and Treatment Integrity Measures

Feasibility will be determined from recruitment and attrition data, and process variables of attendance and homework assignment completion. The latter two, along with treatment satisfaction will be used as indices of acceptability. Attendance, homework assignment completion, and treatment satisfaction will be measured on a weekly basis, and at the 3-month assessment. These measures will also serve as an indicator of treatment acceptability. We will also gather self-report data on participant and interventionalist satisfaction with the interventions, which will also be used for "acceptability" of the intervention. The Program Evaluation Survey is a project-designed survey that is included in the 3-month assessment asking the participants to evaluate their experience with the intervention in which they participated and includes quantitative and qualitative-descriptive data. Each session, we track whether sessions occurred in person or by phone. The proportion of sessions attended versus sessions required for protocol and homework completion will be used as measures of treatment fidelity. In addition, treatment fidelity is self-rated by each interventionist each session on 1–5 Likert-type scales developed for use in this study (QOLT Fidelity and HHE Fidelity).

For treatment fidelity and quality control, all sessions in both conditions will be audio taped and reviewed on a regular basis. There were 100% fidelity ratings for the initial participants in each intervention. After demonstrating high treatment fidelity, a minimum of 25% of each participant's sessions receive fidelity ratings by the principal investigator on the same QOLT and HHE Fidelity scales. Feasibility, acceptability, and treatment fidelity will be evaluated not only between intervention groups but also across mode of intervention delivery (in-person and phone).

Outcomes

Analyses

Statistical analyses have been developed to support each of the four specific aims of the project. Preliminary analyses (χ^2 tests or analysis of variance) will first be conducted to examine participant characteristics in the QOLT group versus the HHE group for comparability at baseline on various demographic, cardiovascular history, and psychosocial and behavioral characteristics. If any group differences are found, we will evaluate them and if necessary we will statistically control them in the outcome analyses.

Aim 1 will examine variables that are associated with the feasibility and acceptability of the intervention protocol, at both preintervention (recruitment, screening, and enrollment process) and postintervention (attendance, homework completion, attrition, adverse events, participant program evaluation). Some of these analyses are descriptive in nature, such as percent of participants recruited, rate of accrual, total attrition, attrition rate over time, percent accepting randomization to treatment, number of adverse events, and percent compliance with study protocols (measured by number of sessions attended). Study goals are ≥80% retention of our cohort to denote feasibility, a 75% attendance rate to demarcate delivery of a full versus a partial intervention dosage, and will also use a 75% completion rate of homework assignments in the QOLT group. These analyses will be especially useful in guiding and informing the implementation of the future R01 efficacy trial. To further investigate adherence, we will also conduct two linear mixed model longitudinal analyses over 3 monthly time points to examine the number of sessions and homework assignments completed each month, and will employ the intention-to-treat principle using all randomized participants in the analyses.

Aim 2 will estimate the QOLT intervention effect size with respect to arrhythmia frequency versus the effect of the HHE group. This analysis will examine the frequency count of arrhythmias in each participant for the period between the 3-month immediate posttreatment assessment and the 9-month final assessment using a Poisson regression model with a binary treatment group indicator as the predictor. We will perform a second analysis on the frequency counts during the period between baseline and the 3-month immediate posttreatment assessment to examine for early treatment effects. These analyses will employ the intention-to-treat principle to calculate treatment effects and differences using all randomized participants. Additional covariates may be included in these analyses, if the preliminary analyses indicate the need for statistical control. Additional Poisson modeling analyses will also examine the frequency count of ICD therapies (alone and combined with arrhythmia frequency) to provide a richer examination of the mechanistic and electrophysiological profile of the participants and the effects of the interventions.

Aim 3 will examine psychological improvement in well-being and QOL from baseline to 3- and 9-month assessment for QOLT versus HHE. An initial analysis of covariance (ANCOVA), using baseline measures of well-being and QOL as covariates, will examine change from baseline to the 3-month immediate posttreatment follow-up. A second longitudinal linear mixed model analysis (baseline, 3 months, 9 months) will examine for extended treatment effects and will compare within group trends over time. If indicated by preliminary analyses, additional covariates may be included in these analyses.

Aim 4 will estimate the QOLT intervention effects with respect to autonomic function as measured by HRV and HRT, and the differential effect for autonomic function when compared to the effects of the HHE group. Our primary HRV variable of interest is the HF-HRV, indicative of parasympathetic activity. Separate analyses of covariance will be conducted for each dependent variable, using baseline measurements of HRV and HRT as covariates, to examine change from baseline to the 3-month assessment. A second longitudinal linear mixed model analysis (baseline, 3 months, 9 months) will also be conducted to examine for extended treatment effects and to compare within group trends over time, with additional covariates included, if necessary, in these analyses.

Discussion

Reducing arrhythmias via a noninvasive, nonpharmacologic method that is also designed to improve well-being has tremendous potential benefit to the individual and to public health as a whole. Improving mental and physical health of ICD

patients is critical because: (1) this group is at high risk for ventricular arrhythmias and sudden death; (2) depressed or anxious CHD patients appear to be at 0 even higher risk for mortality compared to nondepressed or nonanxious CHD patients[104,105]; and (3) negative emotions and arrhythmias form a downward spiral further worsening mood, well-being, and cardiovascular health.[106,107] Unique to ICD patients is the ability to objectively and quantifiably measure arrhythmic events by the ICD, providing optimal measurement of arrhythmias. We hypothesize that a positive-emotion focused CBT (i.e., QOLT) will reduce arrhythmias. Much research demonstrates that positive emotion is related to health benefits, physiology, and increased survival.[20,21,24,25,29,41–44]

This pilot RCT is testing the feasibility and acceptability of a manualized positive-emotion focused cognitive behavioral therapy treatment program using QOLT for ICD patients. Additionally, the pilot study will examine the effects of this positive psychotherapy intervention on ventricular arrhythmias, autonomic functioning, and mood in ICD patients with left ventricular dysfunction. *Innovative aspects* of this trial include: (1) a focus on positive emotion and using a strength-based intervention focused on increasing QOL; (2) the use of several measures of autonomic function in an attempt to capture different aspects of sympathetic and parasympathetic functioning; and (3) an attempt to count frequency of arrhythmias and ICD therapies, rather than only examining time to first event. This trial makes use of the already-existing technology within ICDs to obtain primary outcome data. The effect size estimates obtained in this study will be used to inform the design of a rigorous efficacy trial of QOLT among ICD patients to test whether QOLT can reduce arrhythmias.

This study has both theoretical and clinical impact. The *theoretical significance* of this trial lies in testing the mechanistic pathway by which QOLT acts on arrhythmias (i.e., autonomic function). This will enable us to design nonpharmacologic, noninvasive treatments to reduce arrhythmias (and thereby, shocks). The *clinical significance* of the trial is that patients are receiving immediate intervention which is promoting mood and life satisfaction. Currently with anecdotal evidence only, participants are reporting tremendous positive benefit. In addition, improvements in QOL and psychological well-being may have both direct and indirect effects on physical and mental health, and may be further examined in a larger, fully powered R01 in the future.

Data from this study have the potential to provide important feasibility and pilot information to be used as the foundation for a larger trial. It may enable us to introduce a better standard of care for ICD patients, improving well-being and reducing emotion-triggered arrhythmias and ICD shocks. It may also aid in the identification of behavioral therapies that may be beneficial for patients who may be prone to emotion-triggered arrhythmias, allowing for better stratification for treatments. For example, if there is benefit, or even a demonstration of a positive effect size for the QOLT group and enhanced positive well-being on autonomic function or arrhythmia frequency, then positive psychotherapy may be worth considering as a standard adjuvant treatment to help reduce arrhythmias and improve cardiovascular function, QOL, and positive well-being.

In sum, the present trial provides a novel approach to examining relationships between positive emotion, autonomic functioning, and heart functioning. This study also makes important strides toward examining the role of positive psychology interventions and physical health outcomes. This is the first trial, to our knowledge, examining the role of a positive psychology intervention in ICD patients, and has the potential to improve care for these patients.

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