STUDY TITLE: The Care After Life-threatening Medical Events (CALME) pilot study: An investigation of heart rate variability biofeedback training

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1. Study Purpose and Rationale

Posttraumatic stress disorder (PTSD) is characterized in part by an imbalance of the autonomic nervous system, including diminished parasympathetic activity[1, 2] and heightened sympathetic activity.[3] Diminished parasympathetic activity is indicated by low heart rate variability (HRV), which itself is a risk factor for worsened cardiovascular health. Patients with low HRV have more frequent ventricular arrhythmias,[4] develop atherosclerosis more rapidly,[5] show lower ejection fraction,[4] and have a three-fold increase in risk of cardiac mortality relative to people with higher HRV.[6]

HRV biofeedback is a technique that combines slow paced breathing with the use of accurate, moment-to-moment physiological monitoring.[7] The goal is to make internal cardiac information available to people in order to help them learn how to increase the beat-to-beat variability in their heart's activity and thereby increase parasympathetic activity. Apart from active interventions such as exercise training that reliably increase HRV but that may be inappropriate for many cardiac patients,[8] HRV biofeedback is an easy-to-implement technique allows people to monitor and then ultimately alter their parasympathetic activity.

A growing body of research shows that HRV biofeedback training not only increases HRV but also reduces symptoms of stress and anxiety with a large standardized effect size in a meta-analysis of 24 studies.[9] The intervention is believed to restore autonomic balance by increasing activity in the vagus nerve, which underlies activation of the parasympathetic branch of the autonomic nervous system. Pilot studies have revealed that HRV training specifically reduces PTSD symptoms in traumatized people[10] and reduces anxiety in cardiac patients.[11] These intervention findings are in line with the reliable correlational finding that higher HRV has been associated with lower negative affect, even after controlling for respiration rate, demographic characteristics, exercise, smoking, and medications that affect cardiac activity.[12] Critically, in a randomized controlled study, HRV biofeedback training using the same hardware and smartphone app as in the present study has been shown to lower resting heart rate by over 5 beats per minute and increase HRV by over 30%.[13]

Research is needed to determine whether HRV training has beneficial consequences for mental and cardiovascular health in patients who have experienced serious cardiac events. Cardiac arrest survivors, in particular, may benefit from such an intervention because many of them experience clinically significant psychological distress after their medical event.[14] An important research question for this population concerns the best ways to maximize the efficacy of HRV training on fear outcomes. The currently predominant version of HRV training was developed two decades years ago by Paul Lehrer and colleagues.[7] It involves identifying for each individual the respiratory rate at which their variability in beat-to-beat heart rate (HR) is maximized. For many people, this rate tends to be approximately 0.1 Hz (i.e., breaths per second), which amounts to 6 breaths/minute. Participants then practice breathing at this rate with the goal of improving their post-training resting state HRV. It has been proposed that the training achieves its dampening effects on fear, stress, and anxiety by enhancing the baroreflex and increasing vagal afferent traffic to frontal cortical brain regions associated with affective regulation.[15]

Distressed cardiac patients may be especially motivated to learn to influence their own heart activity in order to improve their own HRV, reduce their cardiovascular risk, and lessen their symptoms of psychological distress. Therefore, it may be wise to harness this motivation in the service of helping these patients *deliberately learn* to alter their own autonomic activity rather than simply breathing at a rate that *automatically* improves HRV without any learning process. As noted by Robert Gatchel, biofeedback "is based on the fundamental learning principle that people learn to perform a particular response when they receive feedback or information about the consequences of that response, and then make the appropriate compensatory behavior adjustments" (p. 197).[16] By providing patients with an external (e.g., visual) form of feedback about their otherwise largely

inaccessible autonomic physiology (i.e., vagus nerve activity), we will conduct a feasibility study of HRV biofeedback training with the goal of increasing HRV and reducing anxiety symptoms.

The purpose of this pilot study is to examine the feasibility of enrolling 10 participants and assessing their satisfaction with HRV biofeedback training. The data collected from participants as part of this feasibility pilot will influence the decision to submit an R01 grant in 2021 to conduct a large-scale randomized intervention using the methods in this pilot.

2. Study Design

We will recruit 10 participants who each recently survived a cardiac arrest and who are either 1) participating in a separate ongoing longitudinal study (Cardiac Arrest Neuropsychological Outcomes Evaluation [CANOE]; IRB Protocol #: AAAR8497) or 2) on a mailing list to receive information from the Sudden Cardiac Arrest Foundation (SCAF), a community of cardiac arrest survivors, their families, and other advocates. They will complete a brief set of screening questions to determine eligibility. They will complete three "Video Visits" that will be conducted by study staff who will meet with the participant via the Zoom application associated with Columbia University Irving Medical Center, 1) an enrollment video visit within 72 months since their cardiac arrest, 2) a baseline/pre-intervention video visit approximately a week after the enrollment video visit (once participant confirms receiving study materials), and 3) a post-intervention video visit 3 weeks after the pre-intervention video visit. The first video visit will last approximately 45 minutes, the second video visit will last approximately 60 minutes and the third video visit will last approximately 30 minutes.

Upon obtaining verbal consent, the first video visit includes demographic and partner/caregiver questionnaires, download of the smartphone app (Elite HRV), and selection of appropriate chest strap size for the heart rate monitor for the participant.

The second video visit consists of attachment of the heart rate monitor (Polar H10), setup of the smartphone app (Elite HRV), completion of questionnaires (cardiac-related interoceptive fear, trait anxiety, and trait negative affect), a short baseline resting state breathing task, and a training in how to do the intervention using the heart rate monitor together with the smartphone app. Since the equipment is unobtrusive and handled exclusively by the participant, this visit is easily conducted remotely. The hardware device (Polar H10 heart rate monitor) measures HR and HRV, and the app (Elite HRV) receives data wirelessly via a Bluetooth connection. During the second video visit, a heart rate monitor chest strap will be attached around the torso along the bottom of the rib cage of each participant to measure interbeat intervals in order to compute heart rate (HR) and heart rate variability (HRV). Participants will complete a paradigm in which they breathe at a set frequency (e.g., one breath lasting 10 seconds) while they watch their real-time heart rate on a visual display on the Elite HRV app. Participants will be told that the goal of the training is to increase the amount of variation in their heart rate between one heartbeat and the next heartbeat. Participants will have the advantage of seeing real-time HR feedback as a means to guide their success at maximizing HRV with each breath as the training progresses over time. Detailed procedures are provided to the IRB in separate documents entitled "CALME_HardwareAndAppInstructions_IPHONE.pptx" and "CALME_HardwareAndAppInstructions_Android.pptx."

The third video visit consists of attachment of the heart rate monitor (Polar H10), a short baseline resting state breathing task, and completion of the self-report measures of cardiac-related interoceptive fear, trait anxiety, and trait negative affect. Within-in person changes in these measures will be computed as a preliminary test of the intervention's efficacy.

<u>Measures</u>

Cardiac-related interoceptive fear is measured with the four cardiac-related items from the Anxiety Sensitivity Index-3.[17] Trait anxiety is measured using the State-Trait Anxiety Inventory.[18] Cognitive and somatic facets of trait anxiety are measured with the State-Trait Inventory of Cognitive and Somatic Anxiety (STICSA).[18] Facets of trait affect are measured with the Positive and Negative Affect Schedule (PANAS)[19]. Those measures above are administered at both the pre- and post-training video visits. Additionally, at the post-training video visit only, participants complete the following standalone self-report items: 1) "How

pleasant did it feel to pay attention to your heart's activity during the training sessions at home?" (scale of 1, *very unpleasant*, to 5, *very pleasant*); 2) "How successful were you in increasing the variability in your heart activity by the end of the training sessions at home?" (scale of 1, *not at all successful*, to 5, *very successful*). Also at the third video visit, intervention usability is measured with the System Usability Scale, [20] and intervention acceptability, feasibility, and appropriateness are measured with the three validated four-item scales.[21] Additionally, we assess demographic information and partner and caregiver status.

3. Study procedures

Recruitment/First Video Visit (45 Minutes)

For participants already enrolled in the CANOE Study:
Participants already enrolled in the CANOE Study who have indicated they are willing to hear about additional research opportunities and who meet initial study criteria will be contacted by telephone by the study team. Those who are interested in learning more about the study will undergo consent using a verbal information sheet for screening. Those who agree to be screened will answer a brief set of questions to determine study eligibility. Those who meet inclusion and exclusion criteria will be scheduled for the first Zoom Video Visit during which the informed consent process for participation in the overall study will take place. Those who provide verbal consent, answer baseline demographics and a brief partner/caregiver questionnaire, and successfully install the Elite HRV App on their smartphone will continue with the second Video Visit as outlined below (once they confirm receiving the Polar H10 heart rate monitor in the mail). Participants will receive a PayCard in the mail following this visit onto which compensation will be loaded for this and future sessions.
For non-CANOE cardiac arrest survivors who respond to our study flyer online:
Cardiac arrest survivors who view the CALME study flyer online and who choose to view the online eligibility assessment that is included on the flyer will be directed to a brief study description on a Columbia University Qualtrics website. Those who agree to be screened will answer a brief set of questions to determine study eligibility via this secure website. Those who meet inclusion and exclusion criteria will be asked at the conclusion of the survey to provide their contact information (first name, last name, email address, and phone number) for the study team to send them the study materials. Those who provide their contact information will be contacted by phone and if necessary, will be asked a brief set of questions to confirm study eligibility. Those who are verified to meet inclusion and exclusion criteria will be scheduled for the first Zoom Video Visit during which the informed consent process for participation in the overall study will take place. Those who provide verbal consent, answer baseline demographics and a brief partner/caregiver questionnaire, and successfully install the Elite HRV App on their smartphone will continue with the second Video Visit as outlined below (once they confirm receiving the Polar H10 heart rate monitor in the mail). Participants will receive a PayCard in the mail following this visit onto which compensation will be loaded for this and future sessions.

2nd (Pre-Intervention) Video Visit (60 minutes)

Members of the study team will introduce participants to the heart rate monitor they received by mail and train them in its proper application. Participants put on the heart rate monitor and wear it for the duration of the session. Participants are also introduced to the Elite HRV app (previously installed in the 1st Video Visit). The experimenters assist participants in the app setting on their smartphones and pair the heart rate monitor via Bluetooth with the app. They complete the pre-intervention questionnaires to assess cardiac-related interoceptive fear, trait anxiety, and positive and negative trait affect. A two-minute resting-state reading is recorded using the "Elite HRV" app while participants sit in a comfortable, relaxed, and well-supported position with their feet flat on the floor. They then complete a single HRV biofeedback training session (see details below). Participants are trained in how to export the data on the app to an email with the form of The*CALMEStudy+###@gmail.com* where *###* is a study ID that pertains only to the participant in question and does not include any identifying information. HRV data are exported once via the app at the end of this session. Participants are made aware that they will be compensated for this session on their PayCard.

HRV Biofeedback Training (15 at-home sessions; 10 minutes each)

Participants are asked to complete the HRV biofeedback training with the heart rate monitor and app once per day for 10 minutes each time (at least 5 minutes) for at least 5 days each week. They are encouraged to practice the training before bedtime because it has been shown to improve HRV during sleep when practiced at that time. However, they are told that they can do the training at any time of day that works well for them.

Participants begin each session by applying water to the electrode strip on the Polar H10 heart rate monitor, clipping the transmitter portion of the device to its strap, and then attaching the strap around their torso over the lower portion of their ribcage. They sit in a comfortable, relaxed, and well supported position. They open the Elite HRV app on their smartphone (iPhone or Android) and verify that it has connected successfully to the heart rate monitor via Bluetooth. Participants select the "Open Reading" option in the app. After a brief stabilization period of several seconds, the training task begins. Participants see the following on the screen: 1) a breathing pacing stimulus: a circle that continually expands for 5 seconds and then contracts for 5 seconds, 2) a numerical readout of current heart rate, 3) a numerical readout of their current heart rate variability, 4) a visual representation of their increasing and decreasing heart rate over the last minute, 5) a running tally of the time elapsed in the training session. Participants are instructed to breathe in as the circle expands, and breathe out as the circle shrinks. They are told to watch as a line shows their heart rate going up and down. Participants are instructed that their goal is to try to make large, slow changes in heart rate that follow the pace of their slow breathing instead of the smaller, faster changes in heart rate that occur when they are not doing the training exercise. When the timer indicates that 10 minutes have passed (or at least 5 minutes), then participants end the training session. Detailed instructions are provided to participants with these instructions, and all the steps are also covered with the experimenters present during the second video visit.

Participants are asked to select the option to export their data using the Elite HRV app after each session. The transmitted data come to the specified email address (see above) as a zipped directory. The name of that zipped directory includes only the participant's study ID and does not contain any identifiable information. The directory includes a separate text file for each recording session (i.e., each training session) with only the date and times of the recording in the file name. Each text file contains only a list of numeric values that represent the intervals elapsed in milliseconds between consecutive heartbeats during the recording.

3rd (Post-Intervention) Video Visit (30 minutes)

The post-training procedures are identical to the pre-training procedures except for the following elements. First, participants do not need to re-download the Elite HRV app, and participants are not re-trained in the use of the heart rate monitor and app because they are already familiar with them. Second, the participants will not complete the HRV Biofeedback training task (they will only complete the resting state task). Third, the self-report items about participants' perceptions of the intervention are administered only at the post-training visit. Fourth, the session concludes with a short debriefing in which participants have a chance to share any feedback about completing the intervention and about the study in general. Fifth, participants will delete the study account in the Elite HRV App from their phones so that the study will not continue to receive their data following study completion.

4. Compensation

Participants receive a Bank of America PayCard in the mail after successfully completing the initial/first video visit (45 minutes). Once they confirm receiving the PayCard with study personnel, $30 will be uploaded to the card as compensation for the first video visit. Following successful completion of the second 60-minute pre-intervention video visit, they will be compensated an additional $60 on the PayCard, and following the third and final 30-minute post-intervention video visit they will be compensated an additional $60 on the PayCard. Therefore, the total possible compensation for completing the study is $150. All compensation is loaded onto one Bank of America PayCard registered specifically to the participant.

In addition, participants will be permitted to keep the study-provided heart rate monitor (Polar H10) upon completion of the study, which has an estimated value of $70.00 when purchased as new.

5. Eligibility

For participants already enrolled in the CANOE Study:

Inclusion criteria

(1) Age 18 years or older
(2) Fluent in English
(3) A diagnosis of cardiac arrest (CA)
(4) Time elapsed since their CA is less than 72 months
(5) Previously enrolled in the protocol titled "Cardiac Arrest Neuropsychological Outcomes Evaluation" (CANOE; IRB-AAAR8497)
(6) Willing to be contacted about other studies (this applies to CANOE participants who agreed to be contacted about future research opportunities either during the initial consent process or during a follow-up visit or phone call
(7) Elevated post-traumatic stress disorder (PTSD) symptom total scores on the 17-item Post-Traumatic Stress Disorder Checklist (PCL) of 30 or higher (i.e., greater than the median in a prior sample of cardiac arrest survivors) or elevated PCL-5 scores of 30 or higher or Acute Stress Disorder Scale (ASDS) scores of 34 or higher
(8) Owns either an iPhone or Android smartphone in order to run the app involved in the intervention

Exclusion criteria

(1) Breathing difficulty that does not allow participant to complete the intervention
(2) Inability to comply with the protocol (either self-selected or indicated during screening that s/he could not complete all requested tasks). This includes, but is not limited to, patients with a level of cognitive impairment indicative of dementia and patients with current alcohol or substance abuse, patients with severe visual impairment, patients with severe auditory impairment, and patients with severe mental illness (e.g., schizophrenia).

For non-CANOE cardiac arrest survivors who respond to our study flyer online:

Inclusion criteria

(1) Age 18 years or older
(2) Fluent in English
(3) A self-reported diagnosis of cardiac arrest (CA)
(4) Time elapsed since their CA is less than 72 months
(5) Elevated PCL-5 scores of 30 or higher
(6) Owns either an iPhone or Android smartphone in order to run the app involved in the intervention

Exclusion criteria

(1) Breathing difficulty that does not allow participant to complete the intervention
(2) Inability to comply with the protocol (either self-selected or indicated during screening that s/he could not complete all requested tasks). This includes, but is not limited to, patients with a level of cognitive impairment indicative of dementia, patients with current alcohol or substance problems, patients with severe visual impairment, patients with severe auditory impairment, and patients with severe mental illness (e.g., schizophrenia).

6. Risks

There are minimal risks involved with completing the HRV training and the questions about emotions and state anxiety. The questions asked and the thoughts evoked during the course of this research study pose minimal risk of psychological discomfort, and some participants may wish to skip any question or

questionnaire that they choose. Participants will be made aware of these risks, and will be assured they can terminate their participation in the study at any time without penalty.

The study staff that will be conducting the video visits of the HRV pilot includes a trained psychologist and emotion scientist who will be able to provide on-the-spot assistance or assist in referring participants to a mental health professional, if they experience any distressing thoughts or feelings during their participation in this pilot study.

Risk of Breach of Confidentiality: A risk of taking part in this study includes the possibility of a loss of confidentiality. The study team has outlined the plans to protect participant confidentiality in the Privacy and Data Security section of RASCAL.

7. Benefits

There is no direct benefit to participation. Participants may begin to learn some stress reduction skills that could help them to relax or improve their HRV, which may be beneficial for mental or physical health. Additionally, the pilot study will contribute to scientific knowledge about stress, emotion, and HRV training.

8. Alternatives

The alternative is not to participate in the study.

9. Data and Safety Monitoring

As this study presents minimal risk to participants, data and safety monitoring will be conducted by the study staff as directed by the principal investigator. Thus, there is no plan for a Data Safety and Monitoring Board (DSMB). Investigators and research assistants will meet weekly to discuss any issues or concerns with the study, in particular, whether there were any unexpected complaints about the study procedures or questionnaires, or whether there were any breaches in data confidentiality (which will be reported to the IRB as required by policy). If unexpected complaints about the procedures or questionnaires are generated, then the study may be stopped or altered prior to recruiting the full sample.

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