Protocol for Proposed Pilot Study: The Reducing Exercise Sensitivity with Exposure Training (RESET) Study

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1. Study Purpose and Rationale

Cardiac Rehabilitation (CR), an evidence-based, multi-disciplinary, standard of care program delivered in clinic- and/or home-based settings, has been shown to improve morbidity and mortality rates in Acute Coronary Syndrome (ACS) patients.[1] Accordingly, CR is recognized as a Class I, Level A recommendation for secondary prevention by the American Heart Association (AHA) and American College of Cardiology (ACC).[2] Despite its well-established effectiveness and safety, less than 30% of eligible cardiac patients participate in and adhere to CR programs in the United States.[3] One potential, unexplored patient-level mechanism underlying poor participation in CR programs is fear of exercise.

Fear of exercise may be prominent among ACS patients due to the presence of physical disease states that can exacerbate uncertainty about bodily sensations.[4] For instance, patients may perceive physical sensations experienced during exercise (e.g., increased heart rate, shortness of breath, fatigue) as dangerous, intolerable, or similar to sensations experienced or attributed to their ACS, resulting in a fear of exercise sensations (e.g., exercise sensitivity).[5] As a result, patients may avoid situations and activities, such as cardiac rehab and physical activity, that prompt these physical sensations or terminate activities at the first sign of discomfort.[4-6] Novel programs that target patient-level fears related to exercise sensations (e.g., exercise sensitivity) during the first-year post-discharge (the time window patients are eligible for CR) may be needed to improve CR enrollment (i.e., attendance at first CR visit), participation (i.e., overall number of CR visits) and physical activity levels.

In our prior studies of ACS patients, we found indicators of exercise sensitivity to be a strong predictor of nonadherence to physical activity. When we asked about physical activity, ACS patients reported avoiding physical activity because they were afraid of experiencing rapid heart rate.[7] A recent study demonstrated that more than 40% of cardiac patients attending CR reported fears about exercise and that these fears were associated with poorer clinical presentation at CR admission.[6] Another study found that cardiac patients not attending CR reported higher levels of kinesiophobia (i.e., fear of movement) and exercise avoidance relative to their peers attending CR, suggesting that the most fearful patients may avoid CR attendance.[8] Accordingly, fear of exercise may prevent eligible cardiac patients from attending and/or adhering to the CR programs and physical activity guidelines prescribed by their treating clinicians.

To our knowledge, no intervention has been developed specifically to reduce exercise sensitivity in ACS survivors; a vulnerable population that is extremely sedentary, fails to meet physical activity guidelines, and with the most to gain from CR participation.[2,9,10] Thus, we will develop a *de novo* protocol for a reducing exercise sensitivity with exposure training (RESET) intervention. We will model RESET on Anxiety Sensitivity Amelioration Training (ASAT).[11] ASAT combines psychoeducation about the acute effects of interoceptive anxiety on the body, with behavioral exercises that are postulated to promote habituation to threatening interoceptive cues. These behavioral exercises (e.g., breathing into a paper bag to experience high CO2 concentration) involve repeated exposure to internal bodily cues that commonly cause distress, also known as interoceptive exposure.[12] The ASAT is delivered by video, and interoceptive exposure exercises are expected to be practiced at home-independent from monitoring.

To develop our RESET intervention, we will modify the protocol of the aforementioned ASAT to target exercise sensitivity (vs. anxiety sensitivity) in ACS patients (vs. healthy adults), as well as use structured physical activity (vs. breathing into a paper bag) as a form of interoceptive exposure in home-based and community settings (Stage 1A: Intervention Development). We will then use an iterative human-centered design process to optimize the patient experience and maximize feasibility (Stage 1B: Feasibility). The purpose of this pilot study is to determine the feasibility (e.g., recruitment, adherence, fidelity), acceptability, and appropriateness of a RESET intervention in ACS patients. We will also explore pre- to post-intervention changes in exercise sensitivity and physical activity levels.

2. Study Design

An overview of the RESET pilot study design, including visits and research activity, is presented in Table 1. We will recruit **30** participants who survived an ACS event in the past 12 months. Participants will be contacted by research personnel via phone call to review the study, obtain verbal consent, and complete a brief set of screening questions to determine eligibility (Phone or Zoom Call Visit 1). Phone Call Visit 2 will include completion of ***baseline questionnaires*** and a ***cardiac rehabilitation interview***. Phone Call Visit 2 can occur

Table 1. Overview of Study Design			
Visit Type	**Research Activity**	**Duration**	**Mode**
Phone (or Zoom) Call Visit 1	1. Participant consent and enrollment	15-30 mins	Phone Zoom
Phone Call Visit 2	1. Pre-Intervention Preparation a. Baseline Questionnaires b. Cardiac Rehabilitation Interview	 20 mins 30 mins	Phone
Video Visit 1	1. Intervention Setup	60-90 mins	Zoom
Video Visit 2	1. Intervention visit a. Psychoeducation b. Interoceptive exposure c. Interoceptive counseling	 30 mins 15 mins 10-20 mins	Zoom
Video Visit 3	1. Intervention visit a. Interoceptive exposure b. Interoceptive counseling	 15 mins 10-20 mins	Zoom
Video Visit 3 Continued	1. Post intervention visit a. Post-intervention questionnaires	 20 mins	 Zoom or Phone
Phone Call 3	2. Exit Interview	30-45 mins	Phone

at the time of enrollment (Phone Call Visit 1) or within 1-2 weeks after enrollment based on participant preference. The ***intervention setup video visit*** (Video Visit 1) will include download of the Fitbit app and setup of the Fitbit Inspire HR device, setup of the home environment, and a brief practice session to familiarize participants with the intervention visits, which will include psychoeducation, a brief, low-to-moderate intensity physical activity session (e.g., gradual six-minute walk [G6MW]), and interoceptive counseling. Participants will be guided in setting up their walking course as well as positioning their device with Zoom so that study staff can monitor them as they walk. If the participant's home-environment is not conducive for proper monitoring of the G6MW, or they are uncomfortable displaying their home environment, they will be given the opportunity to complete the physical activity session by walking in place.

The RESET ***intervention visits*** (Video Visits 2-3) will include psychoeducation (in Video Visit 2 only), a brief, low-to-moderate intensity physical activity session (e.g., gradual six-minute walk [G6MW]), and interoceptive counseling. Each RESET intervention visit will occur once or twice per week based on participant preference. All video visits will be conducted with research personnel via Zoom, an encrypted, HIPAA compliant, web-based, video-conferencing application.

At the end of Video Visit 3, participants will be asked to complete ***post-intervention questionnaires***. The post-intervention questionnaires will include the same set of baseline questionnaires plus additional surveys to rate the acceptability, appropriateness, and feasibility of the intervention sessions. Lastly, to elicit feedback on the RESET design and assess the participant's perceived barriers and facilitators to participating in the pilot study, the participant will also be asked to complete a 30-minute semi-structured ***exit interview***, which will be completed on the telephone and will be audio recorded using the Zoom platform on a separate device with participants on speaker phone with research personnel.

3. Study Procedures

Eligibility Criteria: A total of 30 acute coronary syndrome (ACS) patients who report at least some fear of exercise will be offered an opportunity to enroll in the RESET study.

Patients will be included if they meet the following inclusion/exclusion criteria:

Inclusion Criteria:

- Age 18 years or older
- Speak and read English
- A diagnosis of ACS based on ICD10 codes in the electronic health record within the past 12 months. ACS events will be defined according to American Heart Association/American College of Cardiology criteria as either non-ST-elevation myocardial infarction (NSTEMI), ST-elevation myocardial infarction (STEMI), or unstable angina (UA).[2]
    - Corresponding ICD10 codes for criteria above: I20.__ (i.e., I20.0, I20.9), I21.__ (i.e., I21.3, I21.4, I21.02, I21.29, I21.9), Z95.__ (i.e., Z95.1, Z95.5), Z98.61

- Scored >1 (*sometimes*, *often*, or *very often*) on at least one item from the Aversive Cognitions about Physical Activity Scale and/or scored >1 (*some, much, or very much*) on at least one item from the Exercise Sensations Questionnaire.
- Owns either a tablet or smartphone (iPhone or Android) to conduct Zoom video visits
- Express interest in participating

Exclusion Criteria:

- Severe disabling chronic medical and/or psychiatric comorbidities determined on a case-by-case basis that prevent safe or adequate participation, such as:
    - Staged percutaneous coronary intervention (PCI) with significant remaining lesion
    - Decompensated heart failure (NYHA IV)
    - Untreated or unstable non-sustained or sustained ventricular and/or atrial arrhythmias
    - Recurrent syncope without definitive diagnosis and/or presently undergoing workup
    - Symptomatic valvular disease
    - Uncontrolled hypertension (SBP>200 mmHg or DBP>100 mmHg)
    - High level of silent ischemia (ST-segment depression ≥2 mm from baseline)
- Unable to comply with the protocol (either self-selected or indicated during screening that s/he/they could not complete all requested tasks) for reasons that include, but are not limited to, patients with a level of cognitive impairment indicative of dementia, patients with current alcohol or substance abuse, patients with a significant movement disorder that interferes with walking, and patients with severe mental illness (e.g., schizophrenia)
- Unavailable for follow-up for reasons such as terminal illness and imminent plans to leave the United States (as we have migrant or mobile patients due to their citizenship and work issues).

Study staff will confirm that the participant meets all inclusion/exclusion criteria for the study. Once consented and enrolled, the participants' EHR will be accessed, to further confirm study eligibility.

Recruitment and Enrollment (Phone or Zoom Call Visit 1): For the purpose of this study, we will recruit patients who survived an ACS event in the past 12 months. Potential participants for this pilot study will be identified in several ways: (1) referral from treating clinicians (e.g., physicians, physician assistants, physical therapists), (2) research studies at our Center where participants with ACS ICD-10 codes agreed to be contacted about future study opportunities, and (3) electronic health record data pulls of individuals hospitalized at NYPH/CUIMC in the past year, followed by physician approval to contact the patient.

After patient information is confirmed, research personnel will contact potential participants via telephone (Phone or Zoom Call Visit 1) to review the study and obtain verbal informed consent to be enrolled and screened for participation in the pilot study. The verbal consent will include details about being screened for eligibility as well as overall study participation. If the patient agrees, a member of the research team will ask a brief series of questions to assess study eligibility. Sociodemographic factors will include age, gender, race, ethnicity, height, weight, marital status, education, work history, social support, and home/mailing address. Questions will include topics such as internet access, electronic devices, home-based environment and resources, cardiac rehabilitation participation, and administration of an 18-item Exercise Sensations Questionnaire (ESQ), specifically designed for use in adults with CVD and CR-qualifying conditions[6] as well as the Aversive Cognitions about Physical Activity Scale; a four-item questionnaire to assess patient fear and avoidance of exercise.[7] If the participant has internet access, an electronic device with web-based capabilities, adequate space to conduct home-based exercise, and scores >1 on at least one fear of exercise question (from the ESQ or Aversive Cognitions about Physical Activity Scale), then the participant will be deemed eligible for the study. If the participant does not meet the eligibility criteria, the participant will be withdrawn from the study and thanked for their time.

Pre-Intervention Preparation (Phone Call Visit 2 and Video Visit 1): A member of the research team will meet with the participant on a secure phone line to conduct a series of pre-intervention preparation components, which includes a set of baseline questionnaires and a cardiac rehabilitation interview (Phone Call Visit 2 [50-60 mins]). The interview will be audio recorded using the Zoom platform on a separate device with participants on speaker

phone with research personnel. Once the questionnaire and cardiac rehabilitation interview is concluded, research personnel will meet with the participant via the Zoom Video Visit platform to conduct intervention setup (Video Visit 1 [60-90 mins]). Participants will receive a PayCard in the mail following the last preparation visit onto which compensation will be loaded for this and future visits. Details of each component are provided below.

RESET Intervention (Video Visit 2-3): A member of the research team will meet with the participant on a secure Zoom Video Visit platform to conduct a total of 4 RESET intervention video visits. Each RESET intervention video visit will occur once or twice per week based on participant preference. The first intervention visit (Video Visit 2 [60 mins]) will include psychoeducation, interoceptive exposure (i.e., G6MW), and interoceptive counseling. At the end of Video Visit 2, participants will complete a series of valid, reliable, and pragmatic 4-item surveys designed to assess the acceptability, appropriateness, and feasibility of the RESET program, as well as the satisfaction of each intervention component and design feedback (e.g., psychoeducation, interoceptive exposure, interoceptive counseling.[13] The other intervention visit (Video Visit 3 [30 mins]) will include interoceptive exposure (i.e., G6MW) and interoceptive counseling. At the end of the last intervention visit (Video Visit 3), participants will complete post-intervention questionnaires and an exit interview. Following the last intervention visit, additional compensation will be loaded onto the participant's PayCard. Details of each RESET intervention component are provided below.

Post-Intervention (Video Visit 3 Continued and/or Phone Call 3): After completing the last RESET intervention visit (Video Visit 3), participants will be asked to complete the post-intervention questionnaires (20 mins), which will take place on the same secure Zoom Video Visit platform as Video Visit 3 or a at a separate date and time based on participant preference. Participants will also be asked to complete the semi-structured exit interview, which will take place via telephone (Phone Call 3 [30 mins]). To accommodate participant preference, participants will be given the option to complete the exit interview phone call immediately following the last RESET intervention visit or at a separate day and time.

After all intervention sessions are complete, the participant will be given the option to keep their devices or receive a pre-paid package to mail back the devices.

3. Compensation

Participants will receive a Bank of America PayCard in the mail after successfully completing the initial/first video visit (60 minutes). Once they confirm receiving the PayCard with study personnel, $50 will be uploaded to the card as compensation for the pre-intervention preparation video visit. Following successful completion of the intervention video visits (2 and 3), post-intervention questionnaires, and audio-recorded exit interview, they will be compensated an additional $100 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 and physical activity tracker (Fitbit Inspire HR) upon completion of the study, which has an estimated value of $100.00 when purchased as new.

4. Risks

There are minimal risks associated with participation in moderate-intensity bouts of physical activity including injury or medical complications. Evidence-based secondary prevention guidelines strongly recommend that post-ACS patients achieve ≥30 minutes of moderate aerobic activity, such as brisk walking, on ≥5 days per week within 2 weeks of hospital discharge.[14] The most common injuries include muscle strains, joint sprains, and bone injuries. During moderate-intensity physical activity, heart rate and blood pressure may increase. In rare cases (risk approximately equal to one event in 60-80,000 hours of supervised patient exercise: ACSM, 2007), this can lead to a serious cardiac event. Only patients deemed medically appropriate for participation will be enrolled in the study. The current RESET intervention will use short bouts (6 mins) of low-to-moderate-intensity physical activity, which is well BELOW the intensity and volume of the evidence-based guidelines. Moreover, patients give biofeedback during treatment to ensure that exercise is occurring at the appropriate intensity. Therefore, the risk of the study intervention is minimal.

Psychological Distress: The questionnaires pose modest risk of psychological discomfort. Patients may experience a range of sensations during exposures (e.g., muscle tightness, increased heart rate, shortness of breath). These symptoms are temporary, and while there is risk for experiencing these sensations, engagement in exposure techniques and physical activity is the treatment for anxiety and exercise is also critical for heart health. Thus, while intervention techniques can initially elicit possible anxiety/physical discomfort, repeated practice and engagement will actually serve to decrease anxiety and increase tolerance for exercise.

Loss of Confidentiality: A potential risk from this study is the violation of the participant's privacy, since patient medical information will be used as a source of data. We have measures in place to protect participant privacy and confidentiality.

A clinical psychology scientist, exercise physiology scientist, and internal medicine physician will be on-call during video visits to provide study personnel with assistance if participants experience any distressing thoughts or feelings during their participation in this pilot study.

5. Benefits

Participants may not receive any benefit from study participation.

Improved psychological symptoms and adherence to the medical regimen: Participants may benefit in terms of decreased symptoms of fear and anxiety related to their ACS. This may help participants be more adherent to their medical treatments including exercise. Participants may also benefit from the attention they receive from study personnel.

Contributions to knowledge: While participants in this study may not directly benefit from their participation, we anticipate results from this study to benefit future research that seeks to reduce fear and improve health behaviors after acute cardiovascular events.

6. Alternatives

The alternative is not to participate in the study. Additionally, the Principal Investigator may withdraw participants from the study after enrollment upon further examination of eligibility criteria and/or at their professional discretion.

7. 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. 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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