Title: High-Intensity Interval Training to Improve Symptoms of Deployment-Related Respiratory Disease

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Project Title: High-Intensity Interval Training (HIIT) to Improve Symptoms of Deployment-Related Respiratory Disease – A Pilot Study
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I. Hypotheses and Specific Aims

Specific Aim 1: Generate hypotheses regarding the contribution of cardiac and pulmonary vascular abnormalities to exercise intolerance in patients with deployment-related respiratory disease. Twelve patients with deployment-related respiratory disease will be evaluated. Dyspnea and health-related quality-of-life will be determined by the Short Form (36) Health Survey (SF-36) scale. Functional capacity will be assessed by cardiopulmonary exercise testing (CPET). Cardiac and pulmonary vascular function may be assessed with resting and stress transthoracic echocardiography (TTE). Metabolic changes associated with pathologic right ventricular remodeling will be evaluated using peripheral venous blood metabolomics.(1-3) Hypothesis 1A: Pulmonary vascular remodeling resulting from prior airborne hazards exposures increases exertional pulmonary arterial pressure and right ventricular afterload, resulting in compromised right ventricular exertional performance with abnormal oxygen pulse, ventilatory inefficiency and increased dead space fraction on CPET and increased pulmonary artery systolic pressure during exertion (relative to healthy population norms).(4-6) Hypothesis 1B: Increased right ventricular afterload causes maladaptive right ventricular remodeling which is reflected by increased glycolytic metabolites (compared to a reference healthy population).(2, 3) Hypothesis 1C: Impaired right ventricular performance contributes to reduced maximum oxygen consumption (VO2max) relative to healthy population norms, dyspnea and impaired health-related quality of life.

Specific Aim 2: Demonstrate safety and feasibility of high-intensity interval training (HIIT) in individuals with deployment-related respiratory disease. The same participants described in Aim 1 will complete up to 12 weeks of HIIT. HIIT will include 3 weekly supervised sessions (10 minutes warm-up followed by 4 x 4-minute intervals [4 minutes at 90-95% peak heart rate followed by 3 minutes at 60-75% peak heart rate] followed by 3 minutes cool-down).(7) Participants will also complete three home sessions/week of 40 minutes aerobic exercise at moderate intensity (Borg rate of perceived exertion 12-14. Hypothesis 2A: HIIT is safe and feasible among military personnel suffering from deployment-related respiratory disease, with ≥ 80% participation in prescribed sessions.(8) Hypothesis 2B: Participants will spend approximately 4.5 hours/week engaged in this program and will report that participation was feasible. Hypothesis 2C: Staff will spend approximately 2 hours/participant in exercise supervision and coordination (calculated by [hours spent supervising exercise / number of individuals supervised simultaneously + hours spent scheduling and/or coordinating]. Staff will report that level of supervision and time commitment was appropriate and feasible.

Specific Aim 3: Generate pilot data regarding impact of HIIT on cardiopulmonary performance and its efficacy in improving functional capacity and symptoms in deployment-related respiratory disease. Questionnaire (SF-36), CPET, and peripheral venous metabolomics will be repeated after HIIT intervention. Resting and stress TTE may be performed. Hypothesis 3A: HIIT induces positive right ventricular and pulmonary vascular remodeling, improving right ventricular performance and exertional cardiac output, reflected by decreased glycolytic

metabolites on peripheral venous metabolomics; improved exertional pulmonary artery systolic pressure on TTE (if obtained); and improved oxygen pulse, ventilatory efficiency, and dead space fraction on CPET. Additionally, markers of left ventricular diastolic function on TTE (if obtained) will improve reflecting general positive training adaptations of HIIT.(8) Hypothesis 3B: HIIT improves VO2max among patients with deployment-related respiratory disease. Hypothesis 3C: HIIT improves dyspnea and health-related quality of life (SF-36).

II. **Background and Significance**:

Military personnel with history of airborne hazards exposure during deployment are at an increased risk of exertional dyspnea and exercise intolerance.(9, 10) Nearly three million United States military personnel and 300,000 civilian contractors have deployed to Iraq and Afghanistan between 2001 and 2018.(11) Deployment to those and other areas of Southwest Asia expose individuals to airborne hazards including respirable particulate matter from burn pit combustion products and dust and sandstorms.(11) Approximately 14% of military personnel report new-onset respiratory symptoms after deployment to Southwest Asia,(10) and for up to 75% of those individuals the presenting symptom is exertional dyspnea or decreased exercise tolerance.(12) Identified causes of deployment-related respiratory disease include acquired constrictive bronchiolitis and airway hyperreactivity.(13) However, mechanism(s) accounting for exercise intolerance are undiagnosed in almost half of military personnel suffering from deployment-related respiratory disease.(13) This may relate to underlying disease mechanisms outside the airways. For example, surgical lung biopsies in soldiers previously deployed to Southwest Asia with an undiagnosed cause of exercise intolerance demonstrated pathologic remodeling of pulmonary arteries similar to that seen in pulmonary hypertension due to lung disease,(9) which is known to significantly worsen exercise tolerance.(14)

Exercise training and in particular high-intensity interval training (HIIT) improves maximal oxygen uptake (VO2max) among healthy individuals and those with pulmonary disease.(7, 15) (16, 17) Fitness gains from HIIT may derive from changes in metabolic and protein expression contributing to muscle adaptation as well as cardiovascular adaptations including increased left ventricular compliance and right ventricular remodeling.(2, 8, 18, 19) For example, in rats the shift to glycolytic metabolism which accompanies pathologic right ventricular remodeling in pulmonary hypertension is attenuated by HIIT,(2, 3) and pulmonary vascular remodeling and right ventricular function improves after HIIT.(2, 20) However, whether HIIT improves symptoms or functional capacity in deployment-related respiratory disease has not been investigated. Moreover, given uncertainties regarding mechanisms of deployment-related respiratory disease, recommendations on management of this syndrome in general are lacking.(21) Therefore, the **primary objectives of this study are: 1) generate hypotheses regarding the role of cardiac and pulmonary vascular abnormalities in contributing to exercise intolerance and 2) generate pilot data regarding the safety, feasibility, and efficacy of HIIT in improving functional capacity and alleviating symptoms in deployment-related respiratory disease.** The results will inform a larger investigation of extrapulmonary mechanisms of symptoms and exercise interventions in deployment-related respiratory disease.

III. Research Methods

A. Outcome Measures:

Primary Outcomes:

- VO2max
- Health-related quality of life (SF-36)

Secondary Outcomes:

- Gas exchange (oxygen consumption [VO2], carbon dioxide production [VCO2] and minute ventilation to generate calculations of oxygen pulse [VO2/HR], ventilatory efficiency [VE/VCO2], and dead space fraction [estimated dead space / tidal volume])
- TTE parameters of cardiac function (right ventricular pulmonary artery systolic pressure, mid-cavity diameter, tricuspid annular plane systolic excursion, right ventricular longitudinal strain, left ventricular ejection fraction, transmitral peak inflow velocity of early rapid diastolic filling / early diastolic mitral annular velocity [E/e'])
- Peripheral venous blood untargeted metabolomics
- Borg rating of perceived exertion (RPE)
- Participation (attendance at supervised exercise sessions and diary of home sessions)
- Adverse events (recorded at supervised exercise sessions or reported from home sessions)
- Time commitment per participant (for participants, calculated as sum of hours exercising; for staff, calculated as [hours spent supervising exercise / number of individuals supervised simultaneously + hours spent scheduling and/or coordinating for that participant])
- Qualitative feasibility collected via narrative survey of participants and staff

B. Description of Population to be Enrolled:

Men and women ages 18-65 with deployment-related respiratory disease and symptoms of exertional dyspnea or exercise intolerance residing in the Veterans Integrated Service Network (VISN) 19 and receiving some or all of their care at VA medical facilities throughout the Eastern Colorado Health Care System (ECHCS) will be recruited. We will enroll up to 12 eligible veterans.

- **Inclusion Criteria:**
    - Deployment of ≥30 days to Iraq, Afghanistan, Kuwait, Saudi Arabia, Bahrain, Qatar, United Arab Emirates, Kyrgyzstan, or Djibouti after September 2001(11)
    - New onset of cough, shortness of breath, chest tightness/wheezing, dyspnea on exertion or exercise intolerance which started during or after deployment(11)
    - Definite or probable distal lung disease (≥1 hyperinflation, emphysema, bronchiolitis, small airways inflammation, peribronchiolar fibrosis, or granulomatous pneumonitis on surgical lung biopsy; or ≥2 centrilobular nodularity, air trapping, mosaicism, or bronchial wall thickening on chest CT),(11) definite or probable deployment-related asthma (≥1 increase in post-bronchodilator forced expiratory volume in 1 second [FEV1] ≥12% and ≥200cc, or methacholine challenge with PC20 FEV1 ≤16 mg/mL)(11) or unexplained dyspnea on exertion or exercise intolerance despite noninvasive testing including pulmonary function testing, methacholine challenge, transthoracic echocardiography, and/or chest computed tomography(9, 13)
    - Current symptoms of dyspnea on exertion or exercise intolerance
    - Residence <90 miles from RMR VA and ability / willingness to attend in-person HIIT sessions and research visits
- **Exclusion criteria**:
    - Active / uncontrolled cardiovascular or pulmonary disease (e.g. hypertension with blood pressure >160/100 despite antihypertensive therapy, known hypertensive response to exercise [systolic blood pressure >220 mmHg in men / >190 mmHg in women], coronary artery disease, left ventricular ejection fraction ≤45% or heart failure with preserved ejection fraction with ongoing symptoms despite diuretic therapy, uncontrolled arrhythmia, moderate or severe valvular abnormality, diabetes with HbA1c >8.5% documented within the prior year, chronic obstructive

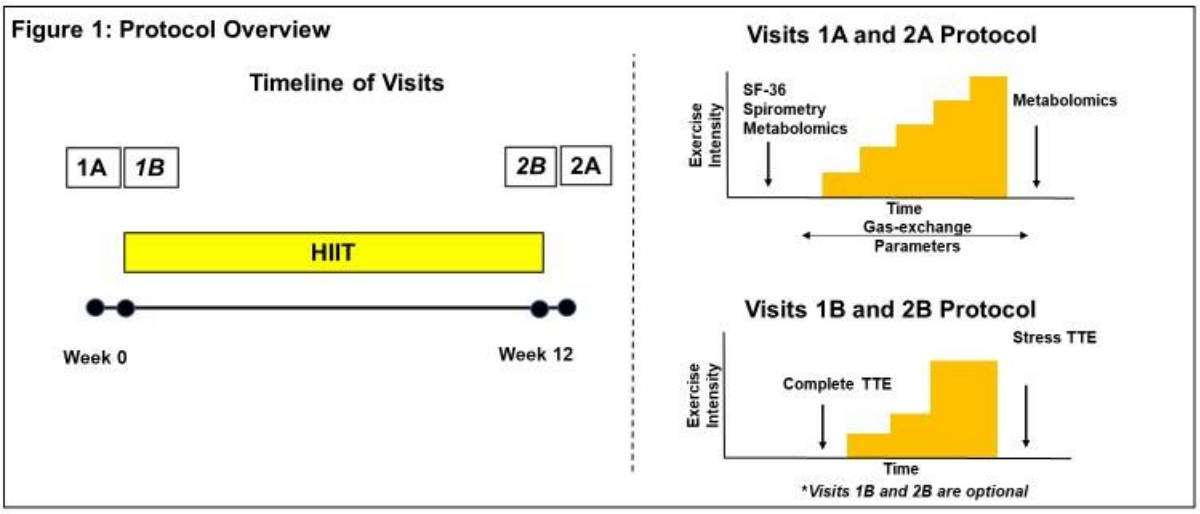
pulmonary disease or asthma exacerbation requiring steroids within 4 weeks of enrollment, , interstitial lung disease, untreated severe obstructive sleep apnea)

- Pre-deployment history of cardiovascular or pulmonary disease including coronary artery disease, left ventricular ejection fraction ≤45% or heart failure with preserved ejection fraction requiring diuretic therapy, arrhythmia, valvular abnormality, chronic obstructive pulmonary disease, asthma (excluding childhood asthma that did not persist into adulthood), interstitial lung disease, or pulmonary hypertension
- Body mass index <18.5 or >45 kg/m^2
- Anemia with hemoglobin <10 g/dl
- Disorders that adversely influence exercise ability or ability to complete CPET and HIIT intervention using an upright stationary bicycle (e.g. arthritis or peripheral vascular disease)
- Current fitness program (e.g. >30 minutes at METs >6 3 times/week or more or >90 minutes spent at METs >6/week)(8)
- Pregnancy or possible anticipated pregnancy during study duration
- Breastfeeding status
- Respiratory symptoms determined to be due to alternative cause, including long COVID

Potential participants evaluated at the recruitment sites typically undergo significant evaluation for respiratory symptoms to exclude causes unrelated to deployment-related respiratory disease, increasing the feasibility of applying the exclusion criteria. Additionally, participants may be excluded at the discretion of Principal Investigators (PIs Drs. Forbes, Krefft and Cornwell) if any conditions are discovered during screening that may increase risk of study participation.

C. Study Design and Research Methods

The proposed study is a single-arm clinical trial to generate pilot data regarding the safety, feasibility and efficacy of an exercise intervention. Participants will complete a baseline assessment (Visits 1A +/- 1B) at 0 weeks followed by up to 12 weeks of HIIT intervention followed by a repeat assessment (Visits 2A +/- 2B). An overview of the study protocol is provided in Figure 1.



Visits 1A/1B and 2A/2B: Visits 1A and 2A will be performed in the inpatient unit of the Clinical and Translational Research Center at the University of Colorado. Each visit will include administration of SF-36 questionnaire, spirometry, and a cardiopulmonary exercise test. Peripheral IV will be placed for the purpose of venous blood draws for complete blood count, ferritin and untargeted metabolomics analysis.(1) Radial arterial line will be placed for continuous blood pressure monitoring and measurement of arterial blood gas and lactate. Participants will be oriented to VO2max testing protocol. Baseline fitness will be assessed by questioning to determine step protocol. Once arterial line is in place, participants will complete a symptom-limited CPET on an upright stationary bicycle. Workload will begin at 0 Watts and increase every minute by 10-30 W (based upon pre-testing questioning) to achieve volitional exhaustion with maximum workload at 8-12 minutes.(22) Heart rate and rhythm, blood pressure, oxygen saturation, and gas exchange parameters (VO2, VCO2, and minute ventilation) will be continuously measured. Borg RPE, arterial blood gas and lactic acid will be measured at rest, every 4 minutes during exercise, and at peak exertion. Attainment of a high-quality VO2max will be determined based upon achieving one or more of the following: a plateau in VO2; attainment of predicted VO2max, work rate, or heart rate; respiratory exchange ratio >1.15, and Borg Scale rating 9-10 on a 0-10 scale.(6) Peripheral venous blood draw for untargeted metabolomics analysis will be repeated at peak exercise.

Visits 1B and 2B are optional. If completed, they will be performed in the outpatient unit of the Clinical and Translational Research Center at the University of Colorado. Visit 1B will occur within 2 weeks of Visit 1A and will coincide with the first exercise training session (see “HIIT exercise intervention”). Visit 2B will occur ideally with 1 and at most within 2 weeks of Visit 2A and will coincide with the last exercise training session (see “HIIT exercise intervention”). Visits 1B and 2B will include a baseline resting TTE. A modified exercise protocol on an upright stationary bicycle including 5 minutes of warm-up and a 4-minute interval with a target of 90-95% peak heart rate (from baseline CPET) in the final minute of exercise will be performed. Immediately following peak exercise, participant will transition to a supine position. Stress TTE images will be obtained with a goal acquisition time of <1 minute to facilitate image interpretation at peak heart rate.

HIIT exercise intervention: HIIT sessions will be administered at the outpatient University of Colorado Clinical and Translational Research Center through the Investigations in Metabolism, Aging, Gender and Exercise (IMAGE) Research Group exercise lab. HIIT intervention will include 3 weekly supervised sessions (10 minutes warm-up followed by 4 x 4-minute intervals [4 minutes at 90-95% peak heart rate followed by 3 minutes at 60-75% peak heart rate]).(7) HIIT sessions will be performed on an upright stationary bicycle. Additionally, participants will be requested to complete 3 40-minute sessions of moderate aerobic exercise each week (Borg rate of perceived exertion 12-14). Aerobic exercise may be performed using any exercise modality. During the first three weeks of the exercise program, the exercise prescription will be modified to facilitate orientation to the training program and physiologic adaptation. Specifically, the first session will be performed with one-on-one supervision from a research coordinator. The coordinator will assist with identifying appropriate an exercise workload based upon the baseline CPET. Subsequent sessions will be performed with ready availability of coordinators to ensure heart rate targets are achieved. The first week of the program HIIT sessions will be modified to include 1 x 4 minute intervals (with a 10-minute warm-up and 3-minute cool-down for a total of ~20 minutes exercise). The second week HIIT sessions will include 2 x 4 minute intervals (with a 10-minute warm-up and 6-minute cool-down for a total of ~30 minutes exercise). The third week HIIT sessions will include 3 x 4 minute intervals (with a 10-minute warm-up and 4-minute cool-down for a total of ~35 minutes exercise). During the first week participants will complete home sessions of 20 minutes aerobic exercise. During the second week participants will complete home sessions of 30 minutes aerobic exercise. During the third week participants will complete home sessions of 35 minutes aerobic exercise. Participation and adverse events will be recorded at supervised sessions and through a diary of home aerobic sessions including time, activity, heart rate at approximately half-way point of exercise, symptoms and adverse events. The exercise diary will be recorded via REDCap MyCap (mobile device application to capture participant reported outcomes) or on paper according to participant preference.

D. Description, Risks and Justification of Procedures and Data Collection Tools:

Recruitment methods: Individuals evaluated in the Airborne Hazards and Open Burn Pit Registry Evaluation Clinic, Post-Deployment Cardiopulmonary Evaluation Network Clinic, Chest Exposure Clinic, or Chest Clinic at ECHCS will be recruited for participation in-person at clinic appointments or by informational flyers provided via mailing. After study information has been shared in-person or via mailings, the study team may follow-up with the potential participant via telephone call. The study will also be registered on the UCD Clinical Trials website.

Screening and consent: Individuals who contact the PI regarding participating in the study or who express interest during a follow-up phone call will be pre-screened over the phone or in RMR VA clinics as described above. This conversation will be conducted by the PI and will include a pre-screening consent followed by questioning regarding inclusion and exclusion criteria. This questioning is anticipated to take 5-10 minutes. If a potential participant appears likely to qualify for the study based on their answers, verbal consent will be obtained to access the electronic medical record (CPRS) to verify relevant health conditions. If eligibility is confirmed, then the potential participant will be scheduled for a visit within the following 4 weeks. At that visit, the PI will go through the written informed consent form in detail with the potential participant and all questions will be answered. This is anticipated to take up to 30 minutes. Information collected in the screening process will be stored only if a potential participant decides to enroll in the study.

Subject compensation: Participants are anticipated to complete up to four study visits (Visit 1A is anticipated to last 1.5 hours, Visit 1B is anticipated to last 1.5 hours, Visit 2A is anticipated to last 1 hour, and Visit 2B is anticipated to last 1.5 hours) as well as a total of up to 27 hours of supervised exercise and 27 hours of home-based exercise. Each participant will be compensated $50 for each of Visits 1A, 1B, 2A and 2C and $400 for the exercise program study visits as a token of appreciation for their time and effort, as well as to offset costs associated with their participation including transportation, exercise gear, etc. Thus, each participant will be eligible to receive a total of $600 for study participation. Participants will be paid at the completion of the study. If a

participant withdraws from the study early (either by the participant's choice or due to medical safety concerns on the part of the study team), the participant will be paid a prorated sum for all completed study visits (including exercise program study visits).

Questionnaires / surveys: Visits 1A and 2A will include administration of and health-related quality of life (SF-36) questionnaire. Additionally, at conclusion of study participants will be asked to complete a short survey regarding their experience. Questionnaires will be administered via paper format or CCTSI REDCap MyCap mobile application on the participant's mobile device in a de-identified format. Risks are anticipated to be minimal but may include mild psychological distress.

Cardiopulmonary exercise testing: All exercise tests will be performed on an upright stationary bicycle according to the protocol described above. Anticipated risks include fatigue, leg discomfort, and shortness of breath. Additionally, participants may experience minor discomfort or claustrophobia related to face mask used for continuous gas exchange monitoring. There is a minimal risk (~1/10,000) of adverse cardiovascular events during exercise testing in all-comers.(23) Participants will be continuously monitored and test will be terminated for any concerning vital sign abnormalities or unexpected symptoms.

Spirometry: Prior to exercise test, participants will perform baseline spirometry including measurement of forced vital capacity and forced expiratory volume in 1 second. During exercise test, participants will perform inspiratory capacity maneuvers every 4 minutes. Participants may experience cough, mild discomfort from taking deep breaths or lightheadedness from blowing out forcefully. All of those symptoms resolve quickly with cessation of spirometry maneuvers. Spirometry will be terminated for significant/bothersome symptoms.

Controlled breathing: Prior to exercise test, participants will undergo blood pressure monitoring while breathing normally for 5 minutes and then practicing controlled breathing for 5 minutes. This will enable later analysis of autonomic function. There is a small risk of discomfort with controlled breathing.

Arterial line insertion: During Visits 1A and 2A, an arterial line will be inserted in the radial artery to monitor blood pressure and blood gas and lactate levels during the CPET. Risks include pain/bleeding at the site of catheter insertion and infection. Pain will be minimized through use of topical lidocaine cream and subcutaneous lidocaine injection. Risks of bleeding and infection will be minimized through use of ultrasound guidance during placement and sterile technique. The risks are felt to be justified due to the improved sensitivity and specificity conveyed by arterial line placement.

Arterial blood sample collection: Arterial blood gas and lactate samples will be collected at rest, every 4 minutes during exercise, and at maximal exercise. Arterial blood samples of ~2 cc each will be collected via the radial arterial line, minimizing additional risks. Each sample will be ~2 cc (with an anticipated total of 4-5 samples for 8-10 cc blood). Blood sample collection has a risk of discomfort.

Peripheral intravenous catheter: A peripheral intravenous catheter (IV) will be placed for the purpose of peripheral blood draw and/or intravenous access during Visits 1A and 2A. Peripheral IV insertion has a risk of pain, bleeding, infection and thrombophlebitis.

Peripheral venous blood sample collection: Peripheral venous blood samples will be collected during Visits 1A and 2A. Samples will be collected from the peripheral IV. Five samples of 3-5 cc each will be collected at rest and two samples of 3-5 cc each will be collected after maximal exercise (a total of 7 samples = 21-35 cc blood). One sample from rest will be used to obtain a complete blood count and ferritin. One sample from each timepoint will be saved for storage in a -80° C freezer accessible to the study investigators in University of Colorado Research Complex Building 2 for future analyses. The other two samples will be processed via 2000 g centrifuge for 10

minutes at 4° C. Plasma and red blood cells will be isolated into separate tubes prior to storage in the same -80° C freezer. The plasma and RBC samples will be transported later to the University of Colorado School of Medicine Metabolomics Core lab. Metabolomic assessment will be performed using Vanquish ultra-high-performance liquid chromatography coupled to Q Exactive mass spectrometry (UHPLC-MS; Thermo Fisher Scientific, San Jose, CA, United States). Additionally, two samples will be used for isolation of monocytes/macrophages (one will be placed in an EDTA tube for separation into red blood cells, monocytes/macrophages, and plasma and one in an untreated tube for plasma; both will be separated via a Ficoll gradient technique and resuspended in RPMI media). Risks of peripheral venous blood sample collection include pain and bleeding.

Echocardiography: Transthoracic echocardiography may be utilized in Visits 1B and 2B to collect information on right and left ventricular function at rest and immediately after peak exercise. It is possible that participants may feel slight discomfort from a probe sitting over the skin.

COVID-19 rapid antigen testing: According to outpatient CTRC facility guidelines, immediately prior to Visits 1B and 2B participants may be asked to perform a COVID-19 rapid antigen test. If positive, the visit will be terminated and rescheduled. Participants will self-administer COVID-19 test by gently inserting a cotton swab into both nares. Risks include discomfort or inconvenience at identifying asymptomatic COVID-19 infection.

HIIT intervention: Participants will perform 3 x ~40-minute sessions/week (10 minutes warm-up followed by 4 x 4-minute intervals [4 minutes at 90-95% peak heart rate followed by 3 minutes at 60-75% peak heart rate]) for up to 12 weeks with a three-week “phase-in” period as described in the protocol above.(7) Sessions will be supervised by a Basic Life Support-trained research assistant experienced in monitoring safety during exercise. Supervision will occur at a ratio of no more than 1 research assistant per 5 exercisers. Heart rate will be monitored throughout HIIT sessions using a Polar chest strap heart rate monitor (Polar Electro; Kempele, Finland). Heart rate data will be displayed and recorded during exercise via the Polar Flow application on the participant’s cell phone. Each participant will be assigned an anonymized account on the Polar Flow application to which the participant and the study team will have access information. Anticipated risks of HIIT training include fatigue, shortness of breath and leg discomfort, and participants will be counseled of these risks. Additionally, study team will closely monitor for adverse events through observation as well as participant report. Adverse events will include the following: minor – hypotension (BP < 90/60), lightheadedness, hypoxemia (SpO2 <80% for >60 seconds),(24) chest pain, arrhythmia, or need to terminate exercise for another reason; major – major adverse cardiac event (stroke, myocardial infarction or cardiovascular death) or hospitalization. Exercise session will be terminated for any minor adverse event and PI and study safety monitor will be notified. Patient will be referred to Emergency Room if any member of the study team or the participant feel referral is indicated. Additionally, participant will be evaluated by PI prior to engaging in any future sessions. If further participation is felt to be of risk to the patient by either PI or the study’s safety monitor, then participation in study will be terminated. Major adverse events are not anticipated, but if any should occur patient will be transported immediately to the Emergency Room. HIIT has been studied in various populations including those with good health but sedentary lifestyle,(8) moderate to severe asthma,(17) and coronary artery disease,(25) and similar or identical HIIT regimens to that described in this protocol studies have demonstrated >80% compliance without attributable adverse events.(8, 25) Additionally, the study design includes an initial baseline assessment with symptom-limited CPET. If the initial CPET identifies safety concerns with completing the study exercise protocol, those concerns will be addressed prior to participant completing any further intervention. If unable to be addressed then the participant will be removed from the study. Therefore, the proposed protocol is anticipated to be safe for participants.

Home exercise: In addition to HIIT sessions described above, participants will perform three sessions / week of 40 minutes aerobic exercise at moderate intensity (Borg rate of perceived exertion 12-14). Home exercise will be prescribed to minimize the risk of confounding from

paradoxical decrease in non-HIIT day physical activity (an effect described in the literature of exercise training interventions).(26) The home exercise program will include a three-week "phase-in" period as described in the protocol above. Participants will keep a diary of home exercise as described above in "Study Design and Research Methods" that includes a field for symptoms and adverse events. Study personnel will collect the diary at 4-week intervals and at that time will also question participant regarding any adverse events not reported through other means. Home exercise has been studied in populations including those with chronic lung disease and pulmonary arterial hypertension without significant attributable adverse effects.(27, 28) Additionally, as described above all participants will undergo baseline CPET and if risks to engaging in an exercise regimen are identified they will be addressed prior to any further intervention.

Risks to a pregnant woman, embryo or fetus: Due to physiologic changes of pregnancy which are anticipated to impact response to exercise training, pregnant women will be excluded from this study. Women of child-bearing age will complete a urine pregnancy test prior to testing during Visit 1. If the test is positive, the participant will be informed and removed from the study. Additionally, participants will be counseled to avoid pregnancy during the study and will be removed from the study should pregnancy occur.

Loss of confidentiality: Data to be collected include demographics, health conditions, and study information including results of testing and exercise monitoring (including heart rate during HIIT sessions and exercise diaries). Study data will be stored in a deidentified fashion. Only the PI's will have access to the deidentification code. Data collected via internet applications or mobile devices, such as questionnaires (REDCap, MyCap) and heart rate data (Polar Flow application), will be de-identified/anonymized. While every effort will be made to keep participant information confidential, there is a potential risk of loss of confidentiality any time information is collected. Additionally, loss of confidentiality may occur through participants' participation in a gym exercise setting. However, the only personal information which will be used in that setting will be participant name, and heart rate monitoring will be done in a deidentified format. All research personnel involved in the study are trained in protecting privacy and confidentiality. Participants will be counseled regarding the nature of the information stored, the risk of loss of confidentiality, and the measures in place to maintain confidentiality.

Additional safety measures:

- Participants may withdraw from study at any time for any reason. All participants will be counseled regarding this component during informed consent process.
- A study safety monitor with dual University of Colorado and VA appointments will be appointed. The study monitor will review the study after six participants have completed the study protocol and again after all participants have completed the study protocol. Additionally, any adverse events will be reported immediately to safety monitor and any that are determined to be unexpected, related to the research intervention, or serious will be reported to the IRB.

E. Potential Scientific Problems:

Recruitment of participants: This pilot study seeks to study 12 individuals in a one-year timeframe. Dr. Silpa Krefft, a PI and an expert in deployment-related respiratory disease,(11, 29-31) is the director of the Rocky Mountain Regional Post Deployment Cardiopulmonary Evaluation Network. Her presence lends feasibility to this proposal's participant recruitment. With >200 patients enrolled in research initiatives through the RMR PDCEN and Chest Exposure Clinic and based on the research team's experience recruiting for similar exercise assessment protocols (COMIRB #16-1635, 17-1042, 19-1141, 21-4354),(8, 32, 33) a sample size of 12 is feasible to recruit and study in one year.

Heterogeneity of study population: Deployment-related respiratory disease is by nature a heterogeneous condition. While narrowing the study population to a particular pathophysiologic subgroup might strengthen the study's conclusions, for the purpose of collecting pilot data in the specified one-year timeframe this study will include individuals with multiple phenotypes (i.e. distal lung disease, asthma and unexplained dyspnea; see "Inclusion Criteria"). However, to minimize additional heterogeneity participants will be carefully screened and excluded for comorbid conditions (see "Exclusion Criteria"). Additionally, a heterogenous BMI range is included again for the purpose of collecting pilot data in the specified one-year timeframe. BMI will be tested as a covariate in the statistical analysis, and based upon these analyses future studies may be designed with a more narrow BMI inclusion range.

Lack of control group: The lack of a control group will limit conclusions regarding efficacy of HIIT intervention. However, for the purpose of collecting pilot data in the proposed timeframe this is felt to be appropriate. This study will instead inform future larger randomized controlled trials of exercise interventions in this population.

Feasibility of exercise training program: A three-week familiarization / physiologic adaptation period has been built into the HIIT program to maximize the likelihood of participants being able to successfully perform the exercise training program. However, there is still the possibility of individuals being unable to complete the full intended training program due to injury or other reasons. Successful completion of HIIT sessions (including meeting target heart rate) will be assessed by the study team at least every 4 weeks. If an individual demonstrates >3 sessions over a 4-week period in which they fail to meet the exercise prescription, a study team member will discuss with the participant barriers to meeting the exercise prescription and help identify ways to address those barriers as appropriate. If an individual develops an injury which prevents them from completing the prescribed exercise program, they will be transitioned to a continuous exercise training regimen if possible (i.e. substituting "light exercise" training sessions for HIIT sessions) until able to resume HIIT, at which time they will begin HIIT with a repeat three-week familiarization / physiologic adaptation period. If they are unable to complete continuous exercise training, they will discontinue exercise training until able to resume. Completion rates of HIIT and continuous exercise training will be assessed as part of the analysis of the study (Aim 2).

E. Data Analysis Plan:

Specific Aim 1:

Hypothesis 1A: Pulmonary vascular remodeling resulting from prior airborne hazards exposures increases exertional pulmonary arterial pressure and right ventricular afterload, resulting in compromised right ventricular exertional performance with abnormal oxygen pulse, ventilatory inefficiency and increased dead space fraction on CPET and increased pulmonary artery systolic pressure during exertion (relative to healthy population norms).(4) Oxygen pulse, ventilatory efficiency, and dead space fraction will be analyzed using descriptive statistics. Results will be presented in reference to healthy population norms (ATS/ACCP guidelines).(6) Pulmonary artery systolic pressure will be analyzed using descriptive statistics. Results will be presented in reference to healthy population norms (American Society of Echocardiography guidelines).(5)

Hypothesis 1B: Increased right ventricular afterload causes maladaptive right ventricular remodeling which is reflected by increased glycolytic metabolites (compared to a reference healthy population).(2, 3) Metabolomics partial least squares discriminant analysis and t-test or ANOVA will be performed. Exercise metabolomics data collected in a healthy population (COMIRB 21-4354) will be used as a reference.

Hypothesis 1C: Impaired right ventricular performance contributes to reduced maximum oxygen consumption (VO2max) relative to healthy population norms, dyspnea and impaired health-related quality of life. VO2max will be analyzed using descriptive statistics and presented in reference to healthy population norms (ATS/ACCP guidelines).(6) Dyspnea and health-related quality of life will be assessed by SF-36 with scores analyzed by descriptive statistics. Scores will be presented in

reference to disease population references.(34, 35) Linear mixed models will be used to assess the relationship between impaired right ventricular performance as measured by pulmonary artery systolic pressure and VO2max. Covariates including BMI, gender, age and type of deployment-related respiratory disease will be included.

Specific Aim 2:

Hypothesis 2A: HIIT is safe and feasible among military personnel suffering from deployment-related respiratory disease, with ≥ 80% participation in prescribed sessions.(8) Attendance will be calculated as (number of supervised sessions attended + unsupervised sessions reported by exercise diary) / total number of supervised + unsupervised sessions. Feasibility will be based upon attendance of >80% of prescribed exercise sessions, with separate analyses for HIIT sessions, "light exercise" sessions, and combined sessions. Safety/acceptability will be based upon an absence of major adverse events attributable to the exercise training program and <5% minor adverse events (calculated as the number of adverse events divided by the total number of exercise sessions throughout the program) attributable to the exercise training program.

Hypothesis 2B: Participants will spend approximately 4.5 hours/week engaged in this program and will report that participation was feasible. Total hours spent in exercise program will be calculated based upon number of supervised sessions and reported unsupervised sessions. Qualitative assessment of feasibility will be collected via narrative report.

Hypothesis 2C: Staff will spend approximately 2 hours/participant in exercise supervision and coordination. Staff will report that level of supervision and time commitment was appropriate and feasible. Staff time spent in exercise supervision will be calculated by [hours spent supervising exercise / number of individuals supervised simultaneously + hours spent scheduling and/or coordinating]. Staff's qualitative assessment of feasibility will be collected via narrative report.

Specific Aim 3:
Hypothesis 3A: HIIT induces positive right ventricular and pulmonary vascular remodeling, improving right ventricular performance and exertional cardiac output, reflected by decreased glycolytic metabolites on peripheral venous metabolomics; improved exertional pulmonary artery systolic pressure on TTE; and improved oxygen pulse, ventilatory efficiency, and dead space fraction on CPET. Additionally, markers of left ventricular diastolic function on TTE will improve reflecting general positive training adaptations of HIIT.(8) Metabolomics heat maps, partial least squares discriminant analysis, and t-test or ANOVA will be performed to compare pre- vs post-exercise training glycolytic metabolites. Pulmonary artery systolic pressure on TTE and oxygen pulse, ventilatory efficiency, and dead space fraction on CPET will be analyzed using descriptive statistics and compared pre- and post-exercise program by t-test. Resting left ventricular diastolic function (E/e') will be analyzed using descriptive statistics and compared pre- and post-exercise training by t-test.

Hypothesis 3B: HIIT improves VO2max among patients with deployment-related respiratory disease. VO2max will be analyzed using descriptive statistics and compared pre- and post-exercise training by t-test.

Hypothesis 3C: HIIT improves dyspnea and health-related quality of life (SF-36). SF-36 pre- and post-exercise training will be analyzed using descriptive statistics and compared pre- and post-exercise training by t-test.

Results will be analyzed according to an intention-to-treat protocol. A p-value of <0.05 will be used to establish statistical significance. Statistical analysis will be performed using SAS v 9.4 (SAS Institute Inc., Cary, NC, USA). For metabolomics data, the MetaboAnalyst 4.0 package will be used for analysis and XY graphs will be created using GraphPad Prism 8 (GraphPad Software Inc., La Jolla, CA, United States).

Sample Size: Based on published data in patients with asthma,(17) who represent the most similar disease phenotype undergoing HIIT interventions reported in the current literature, a sample size of 10 is anticipated to provide 90% power to detect a difference in VO2max of 2 ml/kg/min after HIIT, assuming a standard deviation of 1.8 ml/kg/min at an alpha = 0.05 and up to a 10% dropout rate. For the purpose of this pilot study, a sample size of 12 is anticipated to yield sufficient preliminary data regarding cardiac and pulmonary vascular abnormalities and safety, feasibility and efficacy of HIIT in the described patient population with the intent of future analysis in a larger study.

F. Summarize Knowledge to be Gained:

This study will generate hypotheses of pulmonary vascular and cardiovascular contributions to exercise intolerance after airborne hazards exposure, particularly among patients who currently remain undiagnosed with traditional evaluation. Additionally, it will demonstrate safety and feasibility of HIIT in this population and generate preliminary data regarding its efficacy in improving cardiopulmonary performance and symptoms of exercise intolerance. **The results will 1) inform larger investigations of extrapulmonary mechanisms of post-deployment dyspnea, particularly pulmonary vascular and cardiovascular abnormalities and 2) provide justification for a randomized controlled trial of different exercise modalities' efficacy in improving exertional dyspnea after airborne hazards exposure.**

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