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Unlocking the Barriers to Improved Functional Capacity in the Elderly: Rationale and Design for the “*Fit for Life Trial*”

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Abstract

Advancing age is associated with an increase in physical impairment, functional limitations, disability, and loss of independence. Regular physical activity conveys health benefits, but the yield on physical function in the elderly, is less clear. Current exercise guidelines are focused predominantly on aerobic programs despite evidence that age-associated declines are mediated by peripheral tissue changes. The *Fit for Life* trial proposes a new paradigm of exercise training for the elderly that uses a low-mass high-repetition training regimen specifically focused on peripheral tissue beds or body regions (Regional Specific Training Stimulus-RSTS). RSTS is designed to deliver a localized stimulus to the peripheral vasculature, bone and muscle, without imposing a significant central cardiorespiratory strain.

The purpose of this study is three-fold; 1) derive effect sizes from the RSTS intervention by which to power a subsequent larger, confirmatory trial; 2) assess fidelity of the RSTS intervention; 3) to assess the interrelationship of the primary endpoints of physical impairment/fitness (VO₂peak, 1 repetition maximal contraction) and function (Senior Fitness Test scores) following two versions of a 4 + 8 week protocol

Men and women over 70 years, at risk for losing independence will be randomized to either 4 weeks of RSTS or “aerobic” exercise, followed by an identical 8 weeks of progressive whole-body training (aerobic plus resistance). The guiding hypothesis is that the magnitude of adaptation after 12 weeks will be greatest in those initially randomized to RSTS. Possible mediators of the

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DISCLOSURES

None of the authors have any conflicts of interest.

LIST OF APPENDICES

Appendix 1: The Telephone Screening Questionnaire

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intervention effect - physical impairment/fitness and function relationship, including vascular function, muscle mass, strength, and physiology will also be assessed.

Keywords

Aging; Functional Capacity; Exercise Independence; Peripheral Adaptations; Vascular

1. Introduction and Background

The number of individuals over the age of 65 years in the U.S. is expected to increase from 35 million in 2000, to 73 million by 2030(1). The ability to maintain functional independence in this population results in an increased life expectancy without a corresponding increase in health care costs(2). Thus, there is a need to identify interventions that can attenuate the age-related decline in function and prevent the early onset of physical disability and loss of independence.

Regular participation in physical activity by older adults contributes to health benefits including reductions in the incidence or severity of hypertension, coronary heart disease, cancer, type II diabetes etc.(3). However, the effects of exercise training on function are not as clear. A recent review on strength training in older adults showed that despite gains in strength, the effects on function were limited and the training did not lead to benefits in measures of disability(4). In addition, a meta-analysis on aerobic training, including 41 trials and 2,102 subjects >60 years old, a 3.78 ± 0.28 ml/kg/min increase in peak $\dot{V}O_{2\text{peak}}$ was observed due to the training. This improvement is less than the average decline per decade in this population (-5.4 and -6.3 ml/kg/min for 60-69 and 70-79 years respectively). (5)

The American College of Sports Medicine exercise guidelines for older individuals recommend a well-rounded, whole-body training program applied in the context of the participant's needs, goals, and baseline functional abilities, with a gradual progression in the duration and intensity of effort for cardio-respiratory, muscular strength and endurance, and flexibility components (6). This prescription unfortunately provides little insight into how to effectively incorporate the principles of specificity, overload and progression into the regimen in order to achieve maximal functional benefits. Implementation typically starts with low to moderate intensity aerobic training (AT), with a gradual increase in time and intensity as tolerated and resistance training (RT) added later in the program.

Many of the age-related declines in function are correlated with peripheral mechanisms, including (a) reduced vascular function and blood flow delivery, (b) reduced skeletal muscle mass, and (c) impaired muscle oxygen utilization(7). It is important to determine whether more innovative strategies are needed to prevent or postpone functional decline in older adults. This issue is directly in line with concerns communicated by the 2008 Physical Activity Guidelines Advisory Committee report (3).

In order to address this challenge, the *Fit for Life* study, a dual-center randomized controlled trial, was developed to determine if a Regional Specific Training Stimulus (RSTS) could serve as a primer to remove peripheral barriers that limit physical fitness and function in the elderly. RSTS consists of muscular contractions starting at approximately 50% of the 1 repetition maximal contraction (1RM) at a cadence of 1 every 4 seconds for a period of 3-5 minutes (Table 2). Pilot results have consistently demonstrated that this strategy is associated with rapid improvements in localized vasodilation and strength gains in young, (8) old, (9) and diseased populations (10). RSTS is hypothesized to deliver a localized training stimulus to the vasculature, muscle and bone, without imposing a significant cardiorespiratory strain (Figure 1).

2. Hypothesis and Specific Aims

The *Fit for Life* trial proposes a new paradigm of exercise training for elderly by initially focusing on peripheral tissue beds using RSTS. It is anticipated RSTS at multiple selected, peripheral sites will serve as a physiological primer capable of removing peripheral barriers known to limit physical fitness and functional ability. Given the novelty of the intervention, it is relatively difficult to accurately estimate the subject numbers needed to achieve statistical or clinical significance. Essentially this trial is designed to allow us to derive effect sizes of the RSTS intervention, assess the fidelity of the RSTS intervention, and to assess the between group differences in the primary endpoints of physical impairment/fitness ($\text{VO}_{2\text{peak}}$, 1 repetition maximal contraction) and function (Senior Fitness Test scores) following two versions of a 4 + 8 week protocol in 100 subjects.

The working hypothesis of this trial is that the magnitude of adaptation to training after 12 weeks will be greatest in those randomized to RSTS for the first 4 weeks. Subjects will be randomized to either 4 weeks of either RSTS training or standard “aerobic” exercise training (AE) [Phase 1], followed by 8 weeks of progressive whole-body training regimen [Phase 2].

We will attempt to determine effect sizes and differences between the groups at the end Phase 1 and Phase 2. Additional outcome measures for this study include measures of vascular function, skeletal muscle physiology, body composition, and quality of life (see Section 5).

3. Methods

3.1 Study Design

Fit for Life is a randomized, two-arm, prospective design outlined in figure 2, with measurement points at baseline, 4 and 12 weeks. To maximize internal validity, study personnel, time of the day, equipment and order of testing will be consistent for each of the assessment time points.

3.2 Eligibility

We aim to recruit and randomize 108 sedentary (exercising 1 day per week), men and women over 70 years of age equally distributed between two sites, Duke University Medical Center (Durham, NC) and Pennington Biomedical Research Center (PBRC; Baton Rouge, LA), which should result in 100 analyzable subjects, allowing for 10% attrition (25/group at each site). Efforts will be made to obtain a study population of both men and women as well as a significant portion of minorities.

In the design considerations of this trial, we structured the eligibility criteria in order to include those most at risk for losing their independence and for whom this intervention could putatively provide the greatest impact. Screening criteria for this study stems from the work of Cress and Meyer who examined the relationship between peak VO_2 and physical function in older adults (11). The authors identified a threshold score believed to accurately predict the risk for losing independence. The threshold score on the physical function test was associated with a peak VO_2 between 17.33 and 22.92 ml/kg/min. Those above this range lived independently. Those below the range showed a steep drop in the probability to remain “functionally independent” (11), with the majority of individuals below 10ml/kg/min having less than a 10% probability of independence. It is the aim of this study to recruit subjects whose peak VO_2 is within the range of 10 to 20 ml/kg/min, or considered on the “steep” slope of functional decline. Given the expense and time required to perform treadmill maximal cardiopulmonary exercise testing on each subject for screening, we will utilize data (unpublished) from the Louisiana Healthy Aging Study (n=286) using the 6

minute walk distance from a similar subject population to set our cut-offs. Accordingly, those individuals with a maximum walking distance on the 6-minute walk test between 200 to 450 meters (i.e. 10 to 20 ml/kg/min) are considered on the “steep” slope. Thus, we will use these 6-minute walk distances as cut-offs for subject inclusion into the study. Subjects will be unaware of this target range and instructed to cover as much distance as possible within 6 minutes without running. They must be able to walk for 6 minutes without the use of assistive devices.

Subjects will be excluded if they have had recent changes to medications (within 3 months), are current smokers, oxygen dependent, have fixed rate pacemakers or an Automatic Implantable Cardioverter Defibrillator threshold within or below the required heart rate training range, uncontrolled hypertension (resting SBP>140 or DBP>90) or diabetes (fasting blood glucose > 200), have positive ECG changes or angina during the maximal cardiopulmonary exercise test (CPET), or are unable to complete a maximal CPET to volitional fatigue. Subjects with a history of unstable angina, AHA Class D, or NYHA Class III or IV heart failure will also be excluded.

3.3 Recruitment Strategies and Baseline Testing

We anticipate that this study will have continuous rolling enrollment until recruitment goals are met. Subjects will be recruited in three main ways: 1) newspaper and age-related publication advertisements; 2) selected talks and flyer postings at regional retirement communities and recreational centers; and 3) patient databanks containing a list of subjects who previously gave consent to either the Duke University Aging Center or PBRC to be contacted regarding future research studies for which they may be eligible. Subjects will be screened over the phone to assess eligibility prior to inviting them to an informed consent session on site (Appendix 1: Telephone Screening Questionnaire).

Small groups of interested subjects who are eligible following the screening questionnaire will attend an orientation visit (Figure 2). The study details and informed consent process will be presented to the group and then in one-on-one sessions participants will be given the opportunity to ask questions and discuss any outstanding concerns. At this point subjects can choose to decline study involvement or sign the informed consent. A review of their medical history and medications will be performed at this time by an exercise physiologist and a physician assistant who have a good deal of experience with clinical populations and exercise testing. Subjects will then perform a 6-minute walk test to determine if they meet study inclusion criteria. There are minimal safety concerns with the 6-minute walk –given the inclusion and exclusion criteria the subjects should be at risk for losing independence but not a huge concern for acute events. We will have medical staff available for any emergency situation that may occur.

If the subject qualifies, they will undergo a physical examination and repeat medical history and medications review by qualified medical staff. Participants will then be scheduled for baseline assessment visits including measures of physical fitness and function, which will form the primary outcomes for the study (CPET with 12 –lead EKG and peakVO₂ assessment, one repetition max strength, and Senior Fitness Test measurements). Subjects will be instructed to take their medications as prescribed prior all exercise testing. Whole body and regional peripheral markers of vascular function, body composition (DXA-PBRC only) and muscle biopsies (DUKE only) will be taken to provide information on the potential mechanism or mediators of change in function. The Godin, Self-efficacy and LL-FDI questionnaires will also be administered at all 3 assessment visits. An outline of tests performed at each assessment visit is shown in table 1 and methodological details of each of the assessment visits are outlined in section 5.

3.4 Randomization

Following initial screening and baseline testing, subjects will be randomized through standard computer based procedures (random number generator) using a randomized block design. There will be separate computer generated blocks for white women, white men, minority women and minority men for each of the two study sites (DUKE and PBRC). Subjects will be randomized during Phase I to either a) an initial four weeks of AE or b) an initial 4 weeks of RSTS followed by Phase II, an identical 8 weeks of a “traditional” combined program consisting of both “aerobic” and resistance exercises (see Section 4).

4. Exercise Interventions

4.1 Overall Program and Attendance Requirements

All subjects will attend supervised exercise training sessions three times per week for a total of 12 weeks at the Duke Center for Living or the PBRC Fitness Center. Each session is structured to last approximately 45-60 minutes, including warm-up, training and cool down. Subjects will be supervised by a trained exercise physiologist and heart rates continually monitored by Polar heart rate monitors (Polar; Kampele, Finland) programmed with individualized heart rate ranges (determined from peak HR measured at the baseline CPET). The heart rate data will be downloaded following each session and the data analyzed for time spent in the prescribed training range and average heart rate achieved during each session will be calculated. Additionally, heart rate and exercise intensity will be documented on paper every five minutes and adjusted if needed. Body weight will be assessed weekly.

In order to meet minimum exercise session attendance requirements, participants will need to complete at least 10 exercise sessions during the first four weeks of AE or RSTS [Phase I] and at least 20 sessions during the following eight weeks of aerobic and resistance exercises [Phase II]. Counseling will be provided to subjects not meeting this attendance requirement in an attempt to retain them in the study. If a subject drops out or is removed from the study their data for the major testing visit (baseline or 4 weeks) prior to that point will be included in the final analysis. Drop out rates from both groups will be reported.

For the duration of the trial we will instruct all participants to maintain their normal activity levels and will administer the Godin Leisure-Time Exercise Questionnaire (GLTEQ) (12), at each of the three testing visits (baseline, 4weeks and 12 weeks) (see section 5.4).

A problem ubiquitous to exercise training trials is blinding of the study staff to the intervention allocation when the interventions are obviously different. In order to address this issue, we will maintain 2 teams of exercise physiologists/trainers who are naïve to the overall aims and are dedicated to working in a specific phase of the trial (first 4 or second 8 weeks). This will hopefully reduce any possible trainer treatment bias to either of the intervention arms. Additionally, we will have the testing for a particular variable (for example all vascular measures) done by the same person for every subject who is blinded to the intervention group and not involved in the subject training. Additionally, to ensure that each assignment group will give equal effort, we have set strict heart rate zones targets during exercise.

4.2 Exercise Intervention

A. Phase I – Aerobic Exercise Regimen (AE)—Subjects assigned to AE during the initial 4 weeks of training will perform whole-body aerobic exercise at >50% of heart rate reserve (HRR) for 45 minutes, three days per week. Subjects will exercise on an Airdyne cycle using both arms and legs for 20 minutes (including a five minute warm up) and then walk on a treadmill for 25 minutes (including a five minute cool down). In the event that a

subject is unable to exercise using one or both of these modalities, they will be given the option to use a recumbent bicycle. Subjects will exercise until the prescribed duration is achieved on each modality or until fatigue at which point they will either reduce the intensity or stop until they recover and are able to resume training. The protocol allows for subjects to take breaks as needed, however we impose that they take a full 30 seconds minimum break (and or multiples of 30 seconds). It is a delicate balance between ensuring they are pushed to work sufficiently hard and not pushed beyond what they can do. All training intensities will be based around Heart Rate reserve so it is individualized. Subjects that are unable to meet the training requirements initially will be slowly progressed over subsequent sessions.

As the trial progresses, subjects will be encouraged to increase workout intensity without exceeding 85% of HRR. Training volume per session will be documented in kilocalories per exercise session according to revolutions per minute (RPM) during Airdyne cycling and according to speed and percent grade for treadmill walking.

B. Phase I – Regional Specific Training Stimulus (RSTS)—The RSTS protocol is designed to focus on specific peripheral muscle groups without imposing a significant cardiorespiratory strain (see Figure 1). Eight specific exercises (in no specific order) will be performed to target all major muscle groups and enable the routine to be completed within 60 minutes including warm-up, rest periods and stretching between exercises, and cool down exercises (see Table 2). Each exercise involves contractions with moderate load but with an extended duration of up to six minutes. Subjects will be asked to maintain a cadence of one contraction every four seconds. The last of the four seconds consists of a conscious effort to make sure the muscle group is unloaded. This was designed to maximize the contraction induced hyperemic response (as blood flow through a contracted muscle is significantly decreased due to vascular compression the preceding 3 seconds).

During each exercise subjects will be allowed to take rest breaks as needed but we have pre-specified that each break must be for a minimum of 30 seconds. Subject progression will initially occur by decreasing the number of required rest periods during each exercise. When the subject can complete the whole duration of the exercise without rest the load will be increased by 10 percent. The volume for each exercise will be calculated by multiplying the weight lifted by the number of repetitions completed and calculated as volume per exercise and total volume lifted per exercise session (sum of all exercises).

C. Phase II – Combined Aerobic and Resistance Training—Following the first four weeks of training all subjects will be progressed in a well-rounded whole body exercise training regimen using established ACSM guidelines (13). This eight-week training regimen includes a 5-minute warm-up, 30 minutes of “aerobic” activities, 20 minutes of traditional resistance exercises, and 5 minutes cool-down (see Figure 3).

Subjects will initially exercise on an Airdyne cycle using both arms and legs for 20 minutes (including a five minute warm up) and then walk on a treadmill for 20 minutes (including a five minute cool down). In order to ensure intensity progression during Phase II, subjects will be encouraged to work at an exercise intensity which elicits a heart rate response consistent with an intensity of 60 and 85% of heart rate reserve (based on the baseline CPET test data) during training weeks 5-8 and between 65 and 85% of heart rate reserve during training weeks 9-12. Depending on individual responses the assigned exercise physiologists will be instructed to encourage the subjects to work closer the higher target heart rate range when possible. If the subject feels fatigued they will be allowed to reduce the work intensity or stop exercising until they have recovered sufficiently and can resume. Work volume completed will be recorded as described in section 4.2A.

Following the aerobic component of this session, participants will then complete the resistance-training component. This will consist of one-set of 10 to 15 repetitions for 8 exercises designed to employ different major muscle groups (see Table 3). Subjects will begin with a load at which they were able to perform 10 repetitions using the correct technique. The load will be increased by 10% when the subject is able to complete 15 repetitions. Stretches targeting the involved muscle group were performed after each exercise. The volume of work performed for each exercise will be calculated by multiplying the weight lifted by the number of repetitions. Work volume completed will be recorded as described in section 4.2B.

In order to maximize inter-site consistency for exercise training and testing, appropriate supervisory staff will visit the corresponding site for joint practical education sessions which included they types of encouragement and feedback to give to subjects. We have also produced a protocol manual with instructions on exercise training techniques to ensure accurate prescription. Additionally, Dr. Allen trained for his Ph.D. under the supervision of Dr. Welsch so each of the site principal investigators are intimately aware of the implementation of the testing protocols.

5. Outcome Variables

The primary endpoints of the study are measures of fitness (VO_{2peak} , maximal 1RM) and function (Senior Fitness Test scores). In order to provide some mechanistic insight into possible mediators of any changes in functional capacity/ability markers of a) vascular function (via ultrasonography, pulse wave velocity and reflection, and nitric oxide bioavailability); b) Skeletal muscle mass (via Dual X-Ray absorptiometry (DXA), PBRC only), and physiology (via biopsy tissue, DUKE only); and c) physical activity levels, self-efficacy, perceived limitations, and health-related quality of life will also be assessed (via questionnaires). Table 1 shows the data collection time points for each of these outcome measures, and methodological details are outlined below.

5.1 Measures of Physical Function

a. Peak Oxygen Consumption (VO_{2peak})—Peak oxygen consumption will be measured by a cardiopulmonary exercise test (CPET) with a 12-lead electrocardiogram and expired gas analysis using a Modified Naughton treadmill protocol. Heart rate, blood pressure and rate of perceived exertion will be obtained at the end of each minute throughout the test and expired gas from the last 30 seconds of the test will be averaged to determine peak VO_2 . The criteria for determining if peak VO_{2peak} is achieved will include 3 of the following; a plateau in VO_2 with increasing workload, an RER of greater than 1.1, peak HR within 20 beats of age predicted maximum and an RPE of 16 or greater.

We used ACSM guidelines to determine when we should terminate the CPET test (these include, the subject requested it, 2mm S-T segment depression, SBP>250mmHg, etc. (14)

b. Skeletal Muscle Strength—Skeletal muscle strength will be assessed using a 1RM measurement obtained for the seated row, chest press, leg press and handgrip. In order to accurately achieve 1RM each subject will be allowed 5 lifts at different weights, guided by a qualified exercise physiologist, to reach their 1R. For the Leg Press, Seated Row and Chest Press participants will be allowed a dynamic warm-up using a light weight (6 repetitions), followed by 4-6 trials to reach their maximum weight. These trials will start with a low weight for which they will provide a rate of perceived exertion and followed by two to three minutes rest. Each subsequent attempt will be with a heavier weight until maximum is achieved. “Maximal strength is defined as the maximum weight that could be lifted through a full range of motion with proper form” (15).

For the handgrip testing subjects will start with their hands by their sides, squeeze the gripper as hard as they can without bending the elbow and move their arm in an upwards swing extended from their body as they squeeze. Three trials will be allowed with the maximal value recorded.

c. The Senior Fitness Test—The Senior Fitness Test is a previously validated battery of 6 physical tasks of daily living used to assess strength, flexibility and endurance in order to detect and predict future limitations in functional capacity(16, 17). The test is designed to evaluate physical fitness domains including upper-body strength (Arm Curl), lower-body strength (Chair Sit-Stand), upper and lower body flexibility (Back Scratch and Chair Sit and Reach), balance and coordination (8 foot Up and Go), and endurance (Six Minute Walk). This test is easy, time-effective and safe and has been validated through tests of over 7,000 men and women between the ages of 60 and 94 (16).

5.2 Measures of Vascular Function

Prior to imaging, subjects will be instructed to withhold medications, fast and refrain from exercise for 12 hours and alcohol for 48 hours. All vascular testing will be performed between 8am and 11am in a temperature-controlled room following 15 minutes of quite relaxation.

a. Endothelial Function (Brachial Artery Reactivity)—All imaging will be performed on the left arm and with the subject in a supine position with the forearm extended and slightly supinated. Brachial artery assessments are obtained using high-resolution ultrasound and a 12.5MHz linear array transducer with a technique as previously described(18, 19). Brachial artery images will be obtained at baseline (following 15 minutes of supine rest), during five minutes of forearm occlusion, and continuously on r-wave trigger for two minutes following cuff release (hyperemia). Absolute and relative changes in brachial artery diameter will be calculated as follows:

$$((\text{peak posthyperemia diastolic diameter} - \text{baseline diastolic diameter}) / \text{baseline diastolic diameter}) * 100$$

b. Vascular Stiffness—Central blood pressures are those at which many of the internal organs are perfused and have been shown to more strongly related to outcomes than upper arm blood pressure (20). Therefore, analyses of radial artery pulse wave patterns collected via applanation tonometry will be used to derive central blood pressures and stiffness parameters. Radial waveforms are processed using dedicated software with a validated generalized transfer function to derive a corresponding central aortic pressure waveform (SphygmoCor version 8.0, AtCor Medical). Aortic waveforms are then further processed to identify diastolic and systolic blood pressure, mean arterial pressure and pressure product along with the pressure augmentation (P) (due to wave reflection) and the Pressure Augmentation index AIx (AIx=(DP/PP)100).

To capture pulse wave velocity, sequential measurements of arterial pressure waves at the carotid and femoral arteries are made using an applanation tonometer (SphygmoCor). The surface distances from the suprasternal notch to the carotid and femoral sites are measured. Pressure wave transit times to each site are measured using the foot-of-the-wave method:

$$PWV = \frac{\text{Distance (ss notch to femoral} - \text{ss notch to carotid)}}{\text{Time (ekg to femoral} - \text{ekg to carotid)}}$$

c. Nitric Oxide Bioavailability during CPET testing (plasma nitrite changes)—

Prior to initiation of the CPET, a 20gauge I.V. catheter will be placed in an antecubital vein. Approximately, five ml of blood will be taken prior to the CPET (Pre), immediately post exercise (Peak) and at 10 minutes following exercise termination (Post). Samples are then separated into 1ml eppendorf tubes containing 5uL heparin (1 to 1000U/ml) and centrifuged at 5000g for one minute. Plasma samples are then removed into separate tubes, snap-frozen in liquid nitrogen and stored at -70°C until analysis. All NO metabolite concentrations are measured (within 30 minutes of defrosting) by chemiluminescence using Ionics/Sievers nitric oxide analyzer (NOA 280), as per manufacturer's instructions (Sievers Instruments, Boulder, CO). The reductant used for nitrite analysis is potassium iodide in acetic acid, which has the reduction potential to convert nitrite to NO but is insufficient to reduce any higher oxides of nitrogen such as nitrate and thus is relatively specific for nitrite. To obtain concentrations of total plasma nitrogen oxides (NOx), we used the same apparatus with a stronger reductant, vanadium chloride in HCl at 94°C. This stronger reductant reduces the sum of all nitrogen oxides with an oxidation state of +2 or higher, which is predominantly nitrate [μM] but also includes both nitrite [nM] and nitrosothiols [nM].

5.3 Skeletal Muscle Mass, and Physiology

a. Body Composition (PBRC Only)—Body composition will be measured using DXA scans (DXA; QDR 4500A, Hologic Inc., Bedford, MA). Scans will be analyzed for whole-body and regional lean mass, fat mass, and bone mineral density.

b Skeletal Muscle Biopsies—Prior to muscle biopsies, subjects suspended anticoagulant therapies for 3 days. Biopsy samples are obtained from the vastus lateralis muscle using a modified Bergstrom needle technique (21). Biopsy sites will be anesthetized with a 2% lidocaine solution and a 0.5 cm incision was made through the skin and *fascia lata*. All samples are prepared immediately by weighing and then dividing the samples for later analysis. A portion is mounted in cross-section in optimal cutting temperature (OCT) compound immediately prior to being frozen in isopentane, cooled by liquid nitrogen for fiber type determination and other histological studies. The remaining samples are snap frozen in liquid nitrogen and stored at -80°C until future analysis. Capillary density (mm^2) and capillary to fiber ratio will be evaluated. Endothelial cells (CD31 antibody) will be identified in histological sections using immunofluorescence techniques with an established endothelial cell-specific monoclonal antibody in methods described (22). Fiber type will be determined by staining serial sections for myosin ATPase (23) after preincubation at pH of 4.37, 4.6 and 10.4, to identify for types I, IIa and IIb muscle fibers.

5.4 Physical Activity and Psychosocial Factors

Physical activity levels will be assessed using the Godin Leisure-Time Exercise Questionnaire (GLTEQ) (12), a three-item measure that assesses the frequency of strenuous (e.g., jogging), moderate (e.g., strength training), and mild (e.g., light strength training or easy walking) exercise over the previous 7 days. In addition to activity participation, we will also assess physical and psychosocial factors that previous literature has shown to be associated with physical activity in older adults. Self-efficacy has emerged as the single most consistent determinant of physical activity initiation and maintenance in older adults (24) and as such, we will assess self-efficacy for exercise in this study sample. Because functional limitations predict both disability and physical activity participation, we will also assess perceived limitations using the abbreviated version (25) of the Late-Life Function and Disability Instrument (LL-FDI) (26, 27). This measure assesses basic lower extremity function, advanced lower extremity function, and upper extremity function.

Health-Related Quality of Life will be assessed with the 12-item version (SF-12) (28) of the Medical Outcomes Study 36-item Short Form Health Survey (SF-36) (29). Scores on the Physical and Mental Health scales, as well as the physical functioning, role physical, bodily pain, and general health subscales will be examined.

6. Power Calculations and Statistical Analysis Plan

Given the novel RSTS intervention, it is difficult to anticipate the overall changes within group as well as the group differences in fitness ($\text{VO}_{2\text{peak}}$, 1RM) and functional (Senior Fitness Test) outcomes. One of the major aims from this trial is to allow us to accurately derive accurate effect sizes for the RSTS intervention.

As described the primary endpoints of the study are measures of fitness ($\text{VO}_{2\text{peak}}$, 1RM) and function (Senior Fitness Test scores). These endpoints will be assessed at baseline (pre-randomization), after four weeks (the end of Phase I training-RSTS v AE), and after 12 weeks (the end of Phase II training). To address the main hypothesis of this study the two change scores from baseline to 12 weeks for the primary endpoints will be analyzed. The changes for each period will also be calculated. We will use a per protocol criteria - only data from subjects who complete the entire 12 week testing period will be included in the final analysis. We will employ a repeated measures mixed model, controlling for the baseline value for each change score for the outcome of interest at the beginning of testing period 1. The analysis will assess a group and group by time interaction, with statistical significance declared at an alpha of 0.05 (two-tailed). Since this work is exploratory, we will not control for the overall Type-I error rate inherent in testing multiple outcomes by, for example, methods like Bonferroni or Hochberg corrections.

In a set of follow-up sensitivity tests, we will examine (1) the association between the change in the volume of training (volume at the end of week 12 compared to the volume at the end of week four) as it mediates the group and group by time effects in the outcomes, and (2) the relationship of change between domains (e.g. is the change in $\text{VO}_{2\text{peak}}$ related to the change in brachial artery flow mediated dilation). Finally, several subgroup analyses will be performed to examine potential moderator effects on the primary endpoints.

8. Discussion

Aging is accompanied by a reduction in aerobic capacity ($\approx 1\%$ per year)(30, 31) and a loss in muscle mass(32, 33) and associated force production(34, 35). Furthermore this decline is accelerated with advancing age(7). Data from the Baltimore Longitudinal Study of Aging suggests, rather than central factors,(36) these deficits may be related to reductions in peripheral tissue oxygen extraction due to reduced ability to deliver blood flow to exercising muscle(37, 38) and intrinsic changes to the muscle itself that impair oxygen utilization(39). These deficiencies persist even in relatively small muscle mass exercise, which minimizes any central pump deficiencies (e.g., one-legged knee extension)(40). Additionally, endothelial function(41) and compliance(42, 43) in conduit arteries are reduced with aging. Apart from lower peak VO_2 , a reduction in tissue blood supply and oxygen extraction lowers the threshold at which “anaerobic” metabolism dominates energy production and contributes to a greater perception of effort and earlier onset of fatigue. In addition to the reductions in peripheral tissue oxygen extraction, adequate muscle strength and endurance are also major determinants of the ability to perform activities of daily living and in-turn, quality of life and maintenance of functional independence.

Combined, there is a relatively compelling rationale for an intervention primarily focused on peripheral tissue beds. Recent evidence points toward the importance of muscle contraction-induced hyperemia known to increase local vessel shear stress and trigger regional vascular

modifications (44). Arguably, in frail individuals, low-to-moderate intensity whole-body aerobic exercise does not produce a sufficient peripheral stimulus to increase local vascular shear stress and initiate vascular modifications (45). In addition, current guidelines for resistance training (1 or 2 sets of 10 to 15 repetitions), although adequate to improve muscular strength and physical function, do not provide a sufficient frequency of contraction/relaxation to adequately modulate vessel shear stress and initiate vascular adaptation.

The current knowledge regarding exercise training in the elderly is lacking an optimal strategy to progress individuals through training, and to maximize the effect on functional outcomes. In addition, there is a distinct gap in the literature regarding the underlying biological effects of exercise training in the elderly and their association with functional outcomes. The challenge, is to implement a sufficiently high intensity training program that provides an optimal stimulus to remove peripheral factors known to limit functional capacity, and can be well tolerated in the elderly.

Preliminary findings from our laboratory suggest RSTS results in rapid improvements in both localized vasodilation and strength gains in young(46), old(47) and disease populations(48). The underlying trigger for these rapid improvements is thought to be muscle contraction induced hyperemia and increased local vessel shear stress(44). Use of RSTS at multiple, strategically selected peripheral sites at the onset of a training program, may allow for a higher frequency, intensity and duration of training in these muscle tissues than could otherwise be tolerated (see Figure 1). Additionally there should be relatively little central (cardiac) strain. Thus, it is predicted that early vascular and muscular improvements in the periphery with RSTS versus traditional training will allow for a greater potential for improvement in fitness and function once the individual is progressed into a well-rounded training program that includes central (cardiac) stimulation.

8.1 - Study Limitations

In order to effectively screen subjects for this study, six-minute walk criterion was established by estimating previously reported peak VO_2 parameters associated with disability and functional independence (11, 45). Although necessary for screening purposes, the six-minute walk scores selected as a cut-off for inclusion into this trial may not directly correlate with the peak VO_2 guidelines as anticipated. This will be taken into account during data analysis.

Although the main thrust of the trial is to derive effect sizes and assess the fidelity of the RSTS intervention, we will only be examining the responses to training in the elderly in a supervised setting, little will be learned regarding how these individuals will respond outside of the clinical domain. Certainly, individuals in general are less compliant with exercise when training on their own. The RSTS regimen in particular may be difficult for individuals to perform without assistance while practicing proper technique. In addition, it is unknown if the benefits obtained during the course of the three month training period can be maintained long term. The results of this study may, however, provide the information to adequately power a larger trial and initial results may be of interest to the growing number of well-educated and experienced exercise professionals who offer high quality programs in a number of settings (e.g., retirement housing complexes, community centers, etc.).

Lastly, the hypothesis of this study was based upon the ability of RSTS training to initiate significant changes in the periphery and therefore lead to greater subsequent functional improvements during well-rounded training. This implies that elderly individuals are often intolerant to train at an intensity sufficient to facilitate these peripheral adaptations. Although many vascular and muscular variables will be measured in addition to peak VO_2 ,

no direct information related to central hemodynamic or structural cardiovascular changes with training will be collected. These changes will be inferred from the peripheral and peak oxygen capacity information collected throughout the course of the study. These variables may be incorporated in a larger subsequent trial.

8.2 - Potential Impact

The Fit for Life study is a pilot study to investigate a new paradigm for exercise training in elderly subjects where RSTS serves as a physiologic primer capable of removing physiologic barriers to improving function. The RSTS regimen was designed to promote a localized training stimulus at the onset of an exercise-training program without eliciting significant cardiorespiratory strain. It is anticipated that early improvements in the periphery resulting from this regimen will allow for greater potential functional gains once the individual is progressed into a well-rounded training program that includes central (cardiac) stimulation. If the RSTS intervention proves to be a particularly effective method for improving functional capacity in the elderly, we may be able to accept or reject the overarching hypothesis with the current subject enrollment – in a subset of variables. Either way, data from this trial will potentially allow us to understand the feasibility of using a peripheral training approach in the elderly and other populations with significant peripheral limitations, including those with type II diabetes, peripheral vascular disease, sarcopenia and metabolic syndrome.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1.
The Hypothetical Model for RSTS

Figure 2.
Study Design

Figure 3.
Phase 2 Combination Exercise Training Sessions Components
Legend: HRR-Heart Rate Reserve

Table 1**Study Assessments**

	0 (Baseline)	Weeks 4 Weeks	12 Weeks
Physical Exam	BV1		
Fasting Blood Glucose	BV3		
Physical Function Test	BV1	4WT3	12WT3
Cardiopulmonary Exercise Test	BV2	4WT2	12WT2
1 Repetition Maximal Strength Test	BV5	4WT1	12WT1
Muscle Biopsy (DUMC)	BV4	4WT4	12WT4
Dual X-ray Absorptiometry (PBRC)	BV4	4WT4	12WT4
Questionnaires (Godin, Self-Efficacy, & LL-FDI, HR-QOL)	BV2	4WT2	12WT2
Vascular Function Testing (Nitric Oxide, BAR, PWV)	BV3	4WT3	12WT3

Legend: DUMC-Duke University Medical Center; PBRC-Pennington Biomedical Research Center; Godin-Godin Leisure-Time Exercise Questionnaire (GLTEQ); LL-FDI -Late-Life Function and Disability Instrument; HR-QOL-Health-Related Quality of Life; BAR-Brachial Artery Reactivity; PWV-Pulse Wave Velocity, BV-Baseline Visit Day#; 4WT-4 Week Testing Visit Day#; 12WT-12 Week Testing Visit Day#.

Table 2**Regional Specific Training Stimulus (RSTS) Exercise Protocol**

Exercise	Days/week	Duration (min)	Starting Intensity	Progression	Ideal Cadence	Comments
Calf Raises	3	5	Body Weight	8-10% of Body Weight	¼ second	Both Legs
Handgrip	3	5	50% MVC	8-10% of previous load	¼ second	Alternating Hands
Leg Press	3	6	40-50% MVC	8-10% of previous load	¼ second	Both Legs
Seated Row	3	5	40-50% MVC	8-10% of previous load	¼ second	Both Arms
Chest Press	3	5	40-50% MVC	8-10% of previous load	¼ second	Both Arms
Modified Squats	3	5	Body Weight	8-10% of body weight	¼ second	Use of Chair or Exercise Ball
Low Back	3	3	As tolerated	8-10% of previous load	¼ second	Crossed Arms
Abdominal	3	3	As tolerated	8-10% of previous load	¼ second	Pads on movement arm on chest

Legend: MVC-Maximal Voluntary Contraction

Table 3**Resistance Training (RT) Exercise Protocol**

Exercise	Days/week	Sets	Reps	Starting Intensity	Progression	Comments
Calf Raises	3	1	10-15	Body Weight	8-10% of Body Weight	Both Legs
Handgrip	3	1	10-15	60% MVC	8-10% of previous load	Alternating Hands
Leg Press	3	1	10-15	50% MVC	8-10% of previous load	Both Legs
Seated Row	3	1	10-15	50% MVC	8-10% of previous load	Both Arms
Chest Press	3	1	10-15	50% MVC	8-10% of previous load	Both Arms
Modified Squats	3	1	10-15	Body Weight	8-10% of body weight	Use of Chair or Exercise Ball
Low Back	3	1	10-15	As tolerated	8-10% of previous load	Crossed Arms
Abdominal	3	1	10-15	As tolerated	8-10% of previous load	Pads on movement arm on chest

Legend: MVC-Maximal Voluntary Contraction