PARTNERS HUMAN RESEARCH COMMITTEE
DETAILED PROTOCOL

PROTOCOL TITLE:
Ventilatory Support to Improve Exercise Training in High Level Spinal Cord Injury

10/17/2017

I. BACKGROUND AND SIGNIFICANCE

The cardioprotective effect of regular aerobic exercise in the general population is broadly accepted, but its importance for those with spinal cord injury (SCI) may be even greater.[1] Although regular aerobic exercise with sufficient intensity and duration can improve overall health, daily energy expenditure is low in those with SCI, due to lack of both motor function and options for accessible physical activity. To overcome this, we developed a unique form of exercise for those with SCI that specifically mirrors exercise performed by the able-bodied. Functional Electrical Stimulation Row Training (FESRT) couples volitional arm and electrically controlled leg exercise,[2] increasing the active muscle and resulting in the benefits of large muscle mass exercise. We have found improvements in peak aerobic capacity of up to 50% with FESRT in these patients.[2] However, despite the potential for enhancing aerobic capacity, those with high level lesions (C4 to T4) have the greatest denervation of pulmonary muscle and our preliminary work suggests this limits the aerobic capacity that can be achieved with FESRT. Despite the ability to train the denervated leg skeletal muscle via hybrid FES exercise, the inability to increase ventilation beyond limits set by high level SCI restricts aerobic capacity.

Respiratory restriction in SCI reduces inspiratory capacity in direct relation to lesion level,[3] and those with high level injuries have the greatest compromise. As a result, the increase in ventilatory requirements with FES training results in an imbalance between ventilatory capacity and greater whole body skeletal muscle demand after FESRT. Hence, external ventilatory support could improve the ability to exercise train and hence enhance the adaptations to chronic exercise in high level SCI. In obstructive and restrictive pulmonary disorders, non-invasive ventilation (NIV) during exercise training can enhance exercise tolerance[4, 5] and improve gains in exercise capacity.[6, 7] Therefore, we hypothesize that the use of NIV during FESRT will reduce ventilatory limits to exercise, leading to greater exercise tolerance and increased aerobic capacity in high level SCI.

We have access to a large (N>70) and unique population of individuals with SCI who have been enrolled in FESRT for at least 6 months. Roughly half have high level SCI between C4 and T4.

II. SPECIFIC AIMS

Aim 1: To determine the magnitude of improvement in aerobic capacity after 3 months of FESRT+NIV compared to FESRT+shamNIV in high level spinal cord injury.

Aim 2: To examine the relationship among gains in ventilation and increases in the determinants of aerobic capacity - maximal cardiac output and arterio-venous oxygen difference after 3 months of FESRT+NIV in high level spinal cord injury.

Aim 3: To examine the acute effect of NIV on FES-row VO2max in subjects with both high and low level SCI.

III. SUBJECT SELECTION

FES-Row-Training Group

Thirty individuals with high level SCI who have FES-row trained for at least 6 months will be randomized to (continued) FESRT for 3 months with either NIV or sham NIV. Patients will be medically stable and inclusion criteria are SCI at neurological level ≥T4 with American Spinal Injury Association grade A or B or C, aged ≥ 18 years of age. Before and after training, we will assess maximal aerobic capacity, ventilation, cardiac output, and arterio-venous oxygen difference. Based on our current data, we hypothesize that only those randomized to NIV will experience further increases in aerobic capacity and that these increases will relate to increased cardiac output and arterio-venous oxygen difference. This project will determine the feasibility and effectiveness of this approach to exercise and will lay the groundwork for a larger study of the impact of FESRT+NIV to improve health and function in those with high level SCI.

FES-Row-Exercise Testing Only Group (Cross-Sectional)

Fifteen individuals with SCI who have FES-row trained for >6 months will perform FES-VO2max row tests on separate days with and without the use of NIV to determine maximal aerobic capacity and ventilation. Patients will be medically stable and inclusion criteria are SCI at neurological level C5-T12 with American Spinal Injury Association grade A or B or C, aged ≥ 18 years of age. In our first four subjects, we have observed an increase in maximal aerobic capacity at baseline with NIV assisted increases in ventilation. This was unexpected; we hypothesized that we would increase ventilation during the test at baseline, but that aerobic capacity would not be higher because it would be proportional to the voluntary (unassisted) maximal ventilation. However, this indicates that maximal aerobic capacity in these individuals exceeds maximal voluntary ventilation. It will be important to determine the consistency of this response and at what level of injury it is not observed. We have a large population of potential subjects who have completed six months of FES-row exercise training across a range of SCI level (C5-T12). Hence, we can determine the consistency of the effect and the dependence of the effect on SCI level. (E.g., We could obtain data from those with high level SCI who do not want to enroll in 3 months of training with NIV or sham NIV.)

Exclusion criteria for all subjects are blood pressure>140/90 mmHg, significant arrhythmias, coronary disease, chronic respiratory disease, diabetes, renal disease, cancer, epilepsy, current grade 2 or greater pressure ulcers at relevant contact sites, other neurological disease, peripheral nerve compressions or rotator cuff tears that limit the ability to row, and history of bleeding disorder.

Note: Any changes in cardioactive medications during the exercise testing or training protocols will be evaluated by the Principal Investigator and could lead to removal from the study.

IV. SUBJECT ENROLLMENT

Research study staff will obtain volunteer consent in accordance with guidelines established by the Institutional Review Board during the first visit to the Laboratory. Participants will be sent the consent form at least 48 hours in advance so they have ample time to read and ask questions. Participants are encouraged to ask questions and are reminded that participation is strictly voluntary and will not affect their current or future care at Spaulding Rehabilitation Hospital or any of its affiliates.

V. STUDY PROCEDURES

Once recruited for the study the volunteer will visit the laboratory for a health screening session to further determine eligibility. This one-hour session will include obtaining informed consent, detailed health history, height and weight measurements, resting blood pressure, resting heart rate and NIV-device familiarization trial.

Subjects may also be asked to provide additional medical records or may need further testing to determine their eligibility and the safety of their participation in this program which includes regular vigorous exercise. These additional tests may or may not be covered by insurance. The subjects will be responsible for obtaining any additional testing and providing the program with medical records or results.

FES-Row-Training Groups and Training Protocols

NIV support. Participants randomized to NIV will perform row training while receiving bi-level positive airway pressure ventilation applied through a full-face mask (Phillips Respironics, Murrysville, USA). The ventilator will be set in a spontaneous mode with a ramp to reach a minimal pressure of 12 cmH2O during inspiration and 4 cmH2O during expiration. A minimal duration for inspiration time may also be imposed if the patient desynchronizes with ventilator support. Parameters will then be adapted according to participant's comfort and ventilatory requirement during exercise.

Sham-NIV. In the sham group, similar conditions will be used but the ventilator will be applied with maximal pressure support of 5 cmH2O of inspiratory pressure and 2-4 cmH2O of positive end-expiratory pressure to overcome the resistance of the breathing circuit.

Subjects in the NIV support group and Sham-NIV group will be blinded to which group they are in and how much NIV support they are receiving.

FES-Row Training. The FES row system will optimize the contribution of the pre-trained muscle components of quadriceps and hamstrings. To maintain the proper training stimulus at the same relative intensity, a maximum FES-rowing test will be performed at baseline for intensity to be determined. The goal is for each volunteer to achieve an exercise intensity of 75-85% maintained for at least 30 minutes performed three times each week. Measurements of force produced at the foot and handle during FES-row training sessions will also be used to monitor training and possibly improve rowing technique. Subjects exercise programs will be tailored specifically to their fitness level but should progress quickly to the prescribed intensity as all subjects

There is no limit or specific requirement for training sessions that must be attended to continue participating in this protocol. Subjects will be encouraged by study staff to attend three training sessions per week. Un-reported missed training session will be followed up with a phone call to document why the training session was missed and to encourage prompt return to training sessions as soon as possible.

Strength Training during FES-RT

As subjects will already have been participating in FES-row training they will also be given the opportunity to continue or start the FES-leg strength training at home concurrently on non FES-rowing days (~3 days/week, 30-60 minutes/session). This will be possible after the subjects have demonstrated the knowledge and ability of proper use of the stimulation unit for home use. This will be

closely monitored, as they will also be FES-rowing three times per week at Spaulding Cambridge.

Study Assessments

FES-Row Training Group
All Assessments will be performed at baseline and after three months of FES-row training. There will be 2 separate FES-VO2max row tests, 2 separate Cardiac Output row tests and 1 Pulmonary Function test done at each time point (done at least 48-hours apart). Both NIV Support and Sham-NIV groups will perform tests with and without use of the NIV-machine.

FES-Row Exercise Testing Only Group
Subjects will perform FES-VO2max row tests on separate days with and without the use of NIV to determine maximal aerobic capacity and ventilation. Both FES-VO2max Row tests will be performed at least 48-hours apart

Measurements and Testing Protocols:

FES-Row-VO2maxTesting
Individuals will refrain from eating for 2 hours prior, from caffeine and alcohol for 24 hours prior, and from vigorous physical activity for 48 hours prior to testing. Aerobic power will be determined from online computer-assisted open circuit spirometry and expired gas analysis will be performed continuously throughout the test with the Innocor rebreathing system (Innovision, Odense, Denmark, see details below). A heart rate monitor (Suunto, Valimotie 7 FI-01510, Vantaa, Finland) will be used throughout the tests. The baseline graded FES row test protocol will be based on each individual's initial FES row response, and 1- to 2-minute workloads well be selected to achieve test protocols of 8 to 12 minutes of incremental exercise. The same protocol will be used for the 3-month posttest unless the initial workload has become too low to allow proper FES rowing technique. In this case, the initial workload will be the second workload from the pretest. To ensure attainment of peak exercise capacity, at least 3 of the following criteria must be met: 85% of age predicted maximal heart rate (220 - age), respiratory exchange ratio >1.1 at end exercise, plateau in oxygen consumption despite increasing workload, blood lactate level (Lactate Plus, Nova Biomedical, Waltham MA) of 8 mM or above, rating of perceived exertion of at least 17 on the Borg scale of 6 to 20, and precipitous decline in power >20W during maximal leg stimulation. Peak oxygen consumption will be defined as the highest value achieved over 30 seconds.

Immediately after FES-rowing has stopped at the end of the VO2max test, subjects will have a finger tip pricked with a safety lancet in order to get a drop of blood that will be used to measure peak lactate levels in whole blood. Peak lactate levels will be used to evaluate exercise intensity as well as to monitor training status.

Cardiac Output Row Testing
Individuals will refrain from eating for 2 hours prior, from caffeine and alcohol for 24 hours prior, and from vigorous physical activity for 48 hours prior to testing. Cardiac output will be measured at rest and during a three to six minute FES-row steady state exercise bout at an intensity of 80% of peak heart rate. Cardiac Output is measured using the inert gas re-breathing method (Innocor, Innovision, Odense, Denmark), a previously validated non-invasive method for rest and exercise measures. Notably, inert gas re-breathing measurements of cardiac output do not require steady state conditions and hence can be

obtained during graded tests. An oxygen-enriched mixture of an inert soluble gas (0.5% nitrous oxide) and an inert insoluble gas (0.1% sulphur-hexafluoride) are used to indirectly assess pulmonary blood flow and lung volume, respectively. In the absence of pulmonary shunt, cardiac output = pulmonary blood flow. Arteriovenous oxygen difference will be derived by applying the Fick principle: arteriovenous oxygen difference = oxygen consumption / cardiac output. Subjects will do 2 re-breathing maneuvers at rest and 2 re-breathing maneuvers once they have achieved target heart rate.

Pulmonary Function Tests

Spirometry will be used to measure lung function, specifically the measurement of the amount (volume) and/or speed (flow) of air that can be inhaled and exhaled. Specifically, Forced Volume Vital Capacity (FVC) and Maximum Voluntary Ventilation (MVV) tests will be administered.

Regional Cerebral Blood Flow

A Near-Infrared Spectroscopy (NIRS; PortaLite, Artinis Medical Systems) probe placed on the forehead contralateral to the dominant hand will be used to measure blood oxygenation during maximal exercise testing. NIRS-derived blood oxygenation levels will be used as a measure of cerebral blood flow at the prefrontal cortex.

VI. BIOSTATISTICAL ANALYSIS

This pilot project will employ a simple and straightforward statistical approach to compare changes within and between groups. Statistical significance will be set at 0.05, and power at 80%. Normality and equality of variance will be assessed using tests of skewness and kurtosis. Within and between group (FESRT+NIV vs. FESRT+shamNIV) comparison of changes will be made using a general linear model accounting for potential baseline differences and the intervention effect. Correlations between ventilation, aerobic capacity, and hemodynamics variables (cardiac output and arteriovenous oxygen difference) will be assessed by Pearson's or Spearman's coefficient depending on the normality of the variables. If significant relations are found, appropriate regression analyses will be employed.

VII. RISKS AND DISCOMFORTS

Moderate risks are associated with exercise testing and exercise training. Some discomfort and feeling of fatigue will be experienced during these tests. There are other risks associated with these tests including abnormal blood pressure responses, fainting, irregular, fast or slow heart rhythm, and in rare instances, heart attack, stroke, or death. Wearing the face-mask during the VO2max testing and FES-row training may cause feelings of claustrophobia. Exercise training may induce some muscle or joint discomfort when beginning an exercise program and could result in tendonitis and/or musculoskeletal overuse injuries over time. Subjects may feel lightheaded or short of breath during use of the NIV machine and during the cardiac output measurement. The electrical stimulation unit can cause tingling, pins and needles sensations on the skin, skin irritation, increased muscle spasticity and autonomic dysreflexia (signs include: headache, nausea, rise in blood pressure, sweating, and goosebumps). There is some discomfort with the lancet used on the finger for lactate measurement and there is a small possibility of swelling and bruising at the site(s), there is also a slight chance that individuals become dizzy and even faint. Subjects may feel lightheaded or short of breath during the pulmonary function tests, there is also a slight chance that individuals become dizzy and even faint.

VIII. POTENTIAL BENEFITS

Volunteers will have the opportunity to participate in a supervised exercise program, which may

improve their overall cardiovascular fitness and endurance during activities of daily living as well as decrease risk of chronic disease.

IX. MONITORING AND QUALITY ASSURANCE

The research coordinator will be responsible for monitoring the completeness of all data and source documents. The Principal Investigator will monitor the informed consent procedures in accordance with the Informed Consent Compliance Checklist of Partners HealthCare Systems HRQIP. The subject's data/protocol adherence will be monitored by the research coordinator at each step in the study including. Checklists and note pages are used to note any deviations or omissions from the protocols. The Cardiovascular Research Laboratory Medical Emergency Safety Plan will be followed in the case of an adverse medical event. Any clinical/health related issues would be immediately presented to the subject (i.e. abnormal EKG, etc) to determine appropriate notification (ie. current physician or appropriate specialist)

At each visit, study staff will prompt the participant to report any occurrences of health changes or problems. Any serious or non-serious adverse event will be recorded in the participant's study folder and adverse event log and reviewed by the PI. Serious and non-serious adverse events will also be reported to the Human Research Committee in accordance with Human Research Committee reporting guidelines, following the timeframes specified by the Partners Investigator's Guidelines. In case of a serious adverse event appropriate diagnostic and therapeutic measures will be taken, as determined by the investigator.

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