Effects of a Walking Program and Inspiratory Muscle Training on Individuals with Chronic Heart Failure

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Protocol Title

Effects of a walking program and inspiratory muscle training on individuals with chronic heart failure - a pilot study

1) Investigator

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2) Objectives

The purpose of this pilot study is to examine the effects of inspiratory muscle training (IMT) plus home-based walking program in individuals with chronic heart failure. The primary outcomes are: respiratory muscle strength as indicated by maximal inspiratory pressure (PImax), cardiovascular endurance (indicated by the six-minute walk test distance), autonomic function (indicated by the heart rate variability) and health-related quality of life. We hypothesize that both groups will have improvements in PImax, cardiovascular endurance, heart rate variability, and quality of life, and that the extent of improvements will be greater for the experimental group (high-intensity IMT) than the sham group (low-intensity IMT). We plan to recruit patients who are discharged within 6 months after acute illness, since these patients may be medically stable and mobility independent, but their overall exercise capacity may not be ready for full function in the community yet.

3) Background

Prevalence of heart failure is approximately 1% [1]. The leading causes of heart failure are coronary artery disease, hypertension and diabetes. Other causes include cardiomyopathy, heart valve disease, arrhythmia and congenital heart disease. Patients often develop symptoms when all compensatory mechanisms fail to provide adequate cardiac output of the heart. General fatigue and dyspnea with exercises often reduce their desire for physical activity. Deconditioning and dyspnea eventually becomes a vicious cycle. Health care cost for patients with heart failure is skyrocketing due to its repetitive, costly, and prolonged hospitalization.[2] With an increasing elderly population, it is estimated that the burden of care would continue to increase for heart failure.

Promoting self-care for individuals with chronic heart failure has been advocated in recent years for reducing hospital readmission and mortality rate.[3, 4]Components of self-care strategies include healthy diets, smoking cessation, regular physical activity, and self-monitoring of weight gain and ankle edema. Among these, physical activity has been shown to reduce body mass index, improve blood pressure control, and reduce all causes of mortality in all populations.[5] More than 50% of individuals with chronic HF lead a sedentary lifestyle with walking for fewer than 5000 steps a day.[6]Daily walking performance has been shown to be an independent predictor in discriminating patients with advanced heart failure.[7] Furthermore, a longitudinal study showed that daily step counts can predict mortality rate.[8] Therefore, the importance of promoting physical activity could not be overemphasized for individuals with chronic heart failure.

Benefits of exercise training in selected individuals with chronic heart failure are well documented, including lower hospital readmission rate, better exercise capacity, and better health-related quality of life.[9, 10] After being discharged from an acute care hospital, individuals with HF may receive a short term phase II cardiac rehab which involves professionally monitored exercise training in out-patient settings. Comparing home-based to hospital-based exercise training programs, it was found that physical activity was maintained in the long term for both groups.[11] For individuals who can not participate in hospital-based exercise program due to issues of transportation, finance, scheduling, or other health-related issues, they may follow up at an out-patient heart failure clinic for routine check-up on symptoms and medications. However, a community-based health promotion program to target their physical activities is not currently available. High quality randomized controlled trials studies and cost-effectiveness evidence is needed for community-based exercise training in selected patients with chronic heart failure.

Respiratory muscle dysfunction is common in individuals with chronic heart failure, which may contribute to their symptoms of exercise intolerance.[12] For them, a systematic review on the effects of inspiratory muscle training showed beneficial effects on respiratory muscle strength, functional capacity, and quality of life.[13] Whether inspiratory muscle training will have additional benefits as compared to aerobic exercise training alone, it is not clear and equivocal due to limited data in the literature.[13] For them, incorporating breathing exercise into self-monitored physical activity may be a viable approach for community-based health promotion programs.

4) Setting of the Human Research

This study will be conducted at the Texas Woman's University (TWU) – Dallas campus and Presbyterian Hospital of Dallas. TWU-Dallas will serve as the primary site for data collection and data management. Presbyterian Hospital of Dallas will serve as a site for subjects' recruitment, specifically the inpatient heart failure unit and the outpatient heart failure clinic. The Institutional Review Board of the TWU-Dallas campus oversees all research projects conducted on the campus from both scientific and ethical perspectives. The THR-IRB will oversee the research in the Presbyterian Hospital of Dallas (PHD). This proposed study has been approved by the TWU-Dallas IRB.

5) Resources available to conduct the Human Research

a) Co-investigators/research coordinators (Kandice Miller, Marion Wilson) at the Presbyterian Hospital of Dallas will help with subject recruitment from both in-patient heart failure unit and outpatient heart failure clinic. Marion is a research nurse and Kandice Miller is a nurse practitioner in charge of the outpatient heart failure clinic. Both of them have clinical experiences in patients with chronic heart failure, and they are aware of the inclusion/exclusion criteria of the study. Dr. Martin Berk is the Director of Texas Health Resources Dallas - Presbyterian Dallas Heart Failure Program. Based on their clinical experiences, recruiting 30 subjects, who fit the criteria of this study, from the Presbyterian Hospital of

Dallas in one year is feasible.

b) The proposed time to conduct the trial is one year.

c) The Physical Therapy program at TWU-Dallas campus has the equipment and the research space needed for this study. The campus is located in an 8-floor building which was opened in 2011 and housed a few health sciences programs such as nursing, occupational therapy, and physical therapy programs. There are several new equipment and research labs in the building for interdisciplinary research related to qualitative and quantitative studies. There is also a counseling clinic with two experienced clinical psychologists who can provide psychological consultation if needed. There are a few AED (automated external defibrillator) available on certain locations of the campus. In addition, across the street of the campus is the St. Paul Hospital, researchers can send the participant there in case he/she requires medical care as a consequence of the Human Research.

d) The PI will oversee all research activities of the study. There are four DPT graduate students helping with this study involving evaluations, reassessment, data collection, and data analysis. They participate in this project as a requirement of their "Critical Inquiry" courses under the supervision of the PI at the TWU-Dallas campus. They have taken courses related to research methodology and cardiopulmonary physical therapy, and the NIH Human Subjects Protection Training. The PI is an experienced physical therapist whose expertise is in the management of patients with cardiac or/and pulmonary conditions. The research team members are familiar with ECG interpretation and assessment of exercise intolerance. They also had practiced the study protocol a few times to ensure they are skilled in conducting all procedures efficiently and safely. Two of them will conduct the evaluations and the other two research members will conduct the weekly re-assessment. The evaluators will be blinded to the group assignment.

6) Study Design

a) Recruitment Methods

i) Potential subjects will be identified via medical charts by two research coordinators at the PHD.

ii) Potential subjects will be approached via one of the two ways: (1) when discharging from the inpatient heart failure unit, the inpatient research coordinator, Marian Wilson, will talk to potential subjects about the study; or (2) when they return to the outpatient heart failure clinic for follow up, the outpatient research coordinator, Kandice Miller, will talk to them about the study.

iii) It will be emphasized that their participation in the study is completely voluntary, and it will not affect their medical treatments in any ways.

iv) Participants will be paid a total of $50.

v) A total of 30 subjects will be enrolled from the Presbyterian Hospital of Dallas, excluding screening failure.

b) Inclusion and Exclusion Criteria

i) Subjects inclusion criteria:
   (1) adults with chronic heart failure (NYHA Functional Class II-III) who are just discharged from an acute care hospital in the past three months,
   (2) with BMI < 35 kg/m^2,
   (3) greater than 18 years of age,
   (4) walk independently with or without assistive device.
   (note: According to New York Heart Association's Functional Classification, patients who have reasonable compensatory ventricle remodeling and relatively normal cardiac output at rest and with inadequate increase in cardiac output upon exertion belong to Class II and III, whereas those with inadequate cardiac output at rest will be classified as NYHA Class IV.)

ii) The total expected number of subjects needed to complete the study is 50 excluding those screen failure. Thirty subjects will be recruited from the Presbyterian Hospital of Dallas.

c) Study Endpoints

i) The primary study endpoint will be that 30 participants complete all evaluations, reassessment, and 6-week of training program. The secondary study endpoint would be all data management is completed.
ii) The primary safety endpoint would be that participants complete all study protocols without adverse responses. The secondary safety endpoint could be all research data get kept and protected 10 years accordingly.

d) Procedures involved in the Human Research

i) This study will be a double-blind randomized controlled study. Evaluators will not be aware of subject's group assignment. Each subject does not know group assignment either

ii) Timeline of the procedures
   (1) Recruitment: Two research coordinators screen medical charts to identify potential subjects
   (2) initial evaluation
      (a) History taking
      (b) set up ECG electrodes on the holter monitor unit to monitor heart rhythm throughout the session,
      (c) maximal inspiratory muscle strength test (PImax)
      (d) Grip strength test
      (e) 2-min comfortable walking speed test
      (f) single limb stance test at eyes open and eyes closed conditions
      (g) rest for 15 minutes (supine – standing - supine, 5 min each)

(h) 6-minute walk test on a hallway- first trial: assess subject's physiologic responses closely
(i) resting for 15-20 minutes in sitting and completing two surveys
(j) 6-minute walk test – 2nd trial : monitor subject's physiologic responses closely
(k) give a pedometer, an accelerometer, a breathing device, a heart rate monitor

(3) exercise training program at home
(a) for participants :
(i) daily walking routine: record daily step counts, duration of breathing exercise, and training target of PImax in the log
(ii) weekly follow-up for re-assessment of PImax at heart failure clinic or at the research participant's home
(b) for researchers:
(i) ask subjects for any concerns/difficulties during walking program and breathing exercise at weekly follow up: determine whether to continue the study or discontinue

(4) final evaluations : repeat the same tests as those done during the first visit

iii) Procedures:
The initial evaluation session will last approximately two hours which will include the interview to gather basic demographic and medical data such as names, telephone number, complete address, email address, dates of treatments and birth date, medications, height, weight, age, and past medical history. After the interview, we will measure the maximal inspiratory pressure (PImax) that the subject can generate by a pressure threshold spirometer (Micro Direct, Inc. ME 04240), which is directly related to respiratory muscle strength. Then, the individual will be connected with a holter monitor to monitor their heart rate activity.

Since most individuals with heart failure are older than 50 years of age, so we include 3 outcomes specific to older people. (1) Grip strength: A dynamometer for grip strength will be used for 3 trials. (2) Single limb stance test at both eyes open and eyes closed conditions. The time to maintain single limb stance will be recorded for 3 trials at both conditions. (3) Comfortable speed: the participant will be asked to walk at their comfortable speed back and forth over a 44-foot segment of hallway for two minutes. The times for completing the 44-foot distance will be measured. Heart rate variability will be recorded during the above 3 outcome measures. After these measures, the participant will rest for 15 minutes in the following positions: supine (5 min), standing (5 min), then in supine again (5 min). The holter monitor will continue to monitor their heart rate activity when resting in these 3 positions.

After rest, we will set up telemetry ECG system and administer the six-minute walk test. The participant will be instructed to walk for 6 minutes and to cover as much distance as they can. The distance walked, symptoms and signs of exercise intolerance will be monitored and recorded. After the first trial, the participant will be

allowed to rest for about 15 minutes to allow heart rate returns to initial baseline (+/- 5 beats). During this rest period, we will have the participant fill out the 2 questionnaires (Minnesota Living with Heart Failure Questionnaire and SF36 Questionnaire). Then, we will repeat the six-minute walk test to account for learning effect. The SF-36 questionnaire asks a question regarding sexual difficulties. Subjects can refuse to answer if they find it uncomfortable.

All the initial outcome evaluations will be repeated after 6 weeks. There will be two research team members doing the evaluations and another two research team members conduct the weekly re-assessment.

Each participant will be unknowingly assigned to one of the two groups: (1) a walking program with a sham (low-intensity) Inspiratory Muscle Training (IMT) protocol, and (2) a walking program with a real (high intensity) IMT at 60% of maximal inspiratory pressure (PImax). Research team members who conduct evaluations will be blinded to the group assigned. Only the primary investigator and those research members who conduct the weekly re-assessment of PImax know the group assignment.

Each participant will be given an accelerometer to track their 7-day physical activity for the first and the last week of training. The home-based walking program will consist of walking at an intensity of "somewhat hard" to "hard" on the Rating of Perceived Exertion (RPE) scale. Participants will be educated on the 10-point RPE scale to judge their fatigue level. For example, at rest, they would rate their exertion level as "nothing at all" which is equivalent to "zero" on the RPE scale. If they were very tired and shortness of breath after any exhausted activities such as climbing two to three flights of stairs, they probably rate their exertion level as "very, very, very hard." The scale has been shown to be highly related to a person's heart rate. They will be advised to slow down if they feel their exertion level is toward the "very hard" level. Participants will begin walking at least 15 minutes twice a day, or as tolerated, for 7 days a week and eventually progress to 45-50 minutes a day by six weeks. They will also be instructed to wear a simple pedometer each day to record step counts. During their weekly re-assessment visit, a research team member will calculate the "mean" and "standard deviation" of their previous 7-day step counts. They are encouraged to reach the mean step counts for the following week; however, if they are tired on a specific day, they are encouraged to at least reach the lower target (e.g., the mean minus one standard deviation of previous week's step counts). We found this approach to be effective based on a case study.

For the IMT, the training threshold will be set at 60% of PImax (maximal inspiratory pressure) for the experimental group. The participant will perform the breathing exercise one session daily with a nose clip used, so the participant breathes completely through the mouth. The 6 Interval Levels: (6 inspiratory efforts in each level): (1) 60s rest interval; (2) 45s rest interval; (3) 30s rest interval; (4) 15s rest interval; (5)10s rest interval; (6) 5s rest interval, trained to exhaustion. The sham IMT group will be trained at fixed 15% PImax which is lower than the training threshold

(i.e., 30% PImax) reported in the literature. The time commitment for their IMT exercise is about 15-20 minutes per day for both groups. Each participant will have weekly follow up visit which can be done either at our facility or a research team member will do a home visit for about 15 to 20 minutes to reassess their new PImax and reset the new IMT intensity for the following week. In addition, the research team will record their ambulatory activity of the previous week.

Study will be conducted in the research suite (8^{th} floor) at the T. Boone Pickens Institute of Health Sciences – Dallas of TWU. There will be no other personnel in the area except the research team members. The weekly sessions for reassessment of respiratory muscle strength will be conducted in the research suite on TWU-Dallas campus, at the outpatient heart failure clinic of the PHD, or at the patient's home whichever is convenient for the participant.

e) Data management

i) The PI, research coordinators, and research graduate assistants will be responsible for data collection and transmission of data.

ii) No specimens will be collected.

iii) Data will be transferred from the hard copies of data collection forms to the password protected computer for further data management with Excel program and SPSS statistical software.

iv) Only subjects' initials and other study related findings will be record in the data forms. During data management, only codes will be used. For example, each participant will be coded as "group number + subject number" (e.g., C-1 (control group, subject 1); E-1 (experimental group-subject 1)). An excel file containing the master list of subjects' initials and codes will be kept in a password protected computer. The data will be stored in a locked cabinet at Room 5610, School of Physical Therapy of the TWU- Dallas campus. Only the research team members have access to the data. All data will be coded. The data will be stored for 10 years after completion of the study and it will be destroyed after 8/31/2023.

v) Data Analysis: Two-way (group x time) repeated measure ANOVA (or multivariate ANOVA) will be used to compare the primary and secondary outcome measures between the 2 groups (sham IMT vs. real IMT) and across the 2 time points (pre- vs. post-training). The PI will consult a statistical consultant for final data analysis in the future.

vi) Most of previous similar studies had sample sizes ranging from 20 to 50 each group. So, we plan to screen enough subjects and enroll 30 subjects from the PHD site in one year, excluding screening failure. Other site of the study is the TWU-Dallas campus. Eligible patients can refer themselves to our campus via words by mouth and flyers.

vii) Justification of sample size:

Based on the systematic review on the effects of inspiratory muscle training (IMT) in patients with chronic heart failure by the PI (Lin S. et al 2012), it showed that patients with CHF demonstrated significant improvements in several outcome measures when compared to control groups after IMT training. The improvements include: (1) functional capacity (1.5422 standardized mean difference (SMD), 95% C.I. with a range of 0.8416 to 3.6553, $p<0.0001$); (2) PImax (1.3605 SMD, 95% C.I. with a range of 1.0510 to 1.6700, $p<0.0001$); (3) V02 Peak (1.7835 SMD , 95% C.I. with a range of 1.3625 to 2.2046, $p<0.0001$);(4) Dyspnea (-0.5973 SMD, 95% C.I. with a range of -1.0000 to -0.1946, $p<0.0037$) . The high standardized mean difference (SMD) in all four outcome variables indicates large effect sizes. The low p-values in the four outcome variables indicate the large effect sizes are unlikely due to chance. Based on the large effect size and the power of 80%, a sample size of 15 in each group is determined. Considering potential drop out, we plan to enroll about 25 participants in each group for the whole project.

f) Provisions to monitor the data for the safety of subjects

N/A - this study only involves minimal risks to subjects.

g) Withdrawal of subjects

Subjects may withdraw at any time without consequences of any kind or loss of benefits to which subjects are otherwise given. If a subject's medical condition got worsen for any reasons and would not benefit from the study, the PI or research staff can stop his/her participation. When a subject drops out from the study, data management will depend on the extent of data has been collected. The PI will consult statistician on this issue at a later stage of the study.

7) Risks to subjects

a) Possible risks include fatigue, overexertion, or loss of confidentiality. The fatigue or overexertion could occur during their daily walking program or breathing exercise which will last only a few minutes. Subjects will be advised to judge their tolerance with these exercise, then progress the intensity and duration gradually according to their own tolerance.

b) Risks such as embarrassment from filling out sensitive questionnaires could happen. If a subject finds any questions in the survey or questionnaire discomforting, he/she does not have to answer that question.

8) Potential benefits to subjects

Subjects will benefit from free access to the breathing exercise training program and individually tailored walking program. They may improve their exercise tolerance and breathing strength through the study. A free pedometer, a heart rate monitor, and a breathing device will be provided to them for free. Each subject will also receive $25 at the initial evaluation and another $25 at the final visit after 6 weeks of home-

based training.

9) Provisions to protect the privacy interests of subjects

The evaluations and weekly follow-up will be conducted in a private room or space where only the participant and research team members are present, except when they are performing the walking tests on a hallway. No other personnel will be allowed in the interview area.

10) Provisions to maintain the confidentiality of data

a) The data will be coded. For example, each participant will be coded as "group number + subject number" (e.g., C-1 refers to control group-subject 1); E-1 refers to experimental group-subject 1). An excel file with the master list linking subjects' initials and codes will be stored in a password protected computer. Only research team members have access to the computer. During most of the data management processes, only the codes will be used.

b) The data will be stored in a locked cabinet in Room 5610 at the School of Physical Therapy of the TWU- Dallas campus. Only the research team members have access to the data. The data will be stored for 10 years after completion of the study and it will be deleted from the computer and hard copies will be shredded after 8/31/2023.

11) Medical care and compensation for injury

N/A - this study only involves minimal risks to research participants

12) Cost to subjects

This walking program and breathing exercise will be free to research participants in the study.

13) Consent process

a) Subjects will be asked to sign a study consent form after receiving a complete explanation of the study.

b) The consent process will be initiated with the subject wherever they are when the subject decides they are interested in the study. This will be in one of two locations within the Presbyterian Hospital of Dallas: inpatient unit of heart failure patients - location A, or outpatient heart failure clinic - location B, if the subject is identified while receiving medical services. Prior to initiation of the study, an IRB approved copy of the written informed consent form will be obtained. Study procedures, guidelines, restrictions and process will be explained to the subject by the research coordinator and/or investigator. The subject will then be allowed time to read the informed consent and ask any questions. After all questions have been answered, the most current approved informed consent will be signed by the research subject and witnessed (if required). This must all be done prior to any study related procedure being performed. A signed copy of the informed consent will be maintained in the hospital chart if the subject is an inpatient. A signed

copy will be given to the subject. The original informed consent will be maintained in the subject's research chart. Once research participants are identified by the research coordinators at THR Dallas, these potential research participants can call our research lab to schedule the initial evaluation at our facility, School of Physical Therapy, TWU Institute of Health Sciences- Dallas They can withdraw from the study any time if they decide not to continue.

c) If during the study an amendment to the protocol should occur and the current informed consent no longer covers the change caused by the amendment, then the IRB will be notified and approval obtained for an amended informed consent. When there is an amendment to the informed consent, each subject will be informed of the study changes and a copy of the amended informed consent shall be obtained from all research subjects if indicated. All informed consents signed by a subject will be kept with study records throughout the duration of the study. Once the study is completed these consents will be maintained in storage until released for destruction by the sponsor.
d) For research participants, their primary language is not English, an interpreter will be used.

14) Process to document consent in writing

Research participants will sign an informed consent if they are interested in participating in this study.

15) Vulnerable populations: N/A

16) Drugs or Devices: N/A

17) Multi-site Human Research

Results of the study will be shared among research members on the TWU-Dallas campus and the Presbyterian Hospital of Dallas. Any modifications of the study protocol will be communicated within the research team via face to face contacts, phone call, text messages, or emails, whichever is the most accessible at the time for immediate subject's protection.

18) Sharing of results with subjects

If the subject would like to know the result of his/her training program, the research team will send the participant a hard copy. It is anticipated that the findings of the study will be presented in a state or a national conference in the future, and the research team will send a copy of the abstract to the participant if he/she is interested.

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