Building strength through rehabilitation for heart failure patients- BISTRO STUDY

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Section 1: Background and Significance

Heart Failure (HF) has become one of the most discussed chronic conditions due to its high incidence, increasing prevalence, and treatment costs. Benjamin, et al. estimated 6.5 million people in the U.S. have HF and 915,000 new cases are diagnosed each year.[11] This number is projected to rise to 8 million by 2030 with direct and indirect costs rising from $39.2 billion to $70 billion.[12,13] With the increasing prevalence and rising costs of HF, consideration of ways we can decrease the negative effects become essential. One approach to improving outcomes is by assisting patients with HF to exercise.

Of those admitted to the hospital for heart failure, lower extremity weakness was common with 40% of them unable to rise from a chair without using the arm rests, and profound weakness with 6 minute walk distance of 178 meters the day before being discharged home.[14] Due to the profound weakness, interventions that improve strength without causing further fatigue is critical to improving outcomes for this population. Skeletal muscle function has been found to deteriorate in HF patients, when compounded in muscle wasting that is common in any patient admitted to the hospital, additional interventions are needed for this very fragile group.

Exercise has many personal benefits for patients with HF, such as improvement in exercise capacity, skeletal muscle strength and endurance, endothelial function, skeletal muscle chemistry and decreased sympathetic activity.[15,16] Other probable benefits include: increased cardiac output, improved left ventricular characteristics and skeletal muscle histology, decreased plasma neurohormones, and an anti-inflammatory effect.[15,16] All of these benefits should decrease the need for hospitalizations and extra clinic visits along with improving patient's quality and satisfaction of their care in addition to improving their quality of life.[15]

Patients have difficulties adhering to the exercise portion of most study protocols.[4-6] Further compounding the problem of getting patients to exercise is the fact that many patients with HF are not willing to begin exercising or they discontinue the exercise regimen once they start.[17] Pain, shortness of breath and poor activity tolerance are common in those with HF and may help to explain the resistance to exercise by patients with HF.[2,18] Considering the extra attention patients of exercise trials receive to encourage them to stay in study protocols, the finding that the majority are still unable to meet the exercise requirements indicates that more research needs to be done to improve adherence.

One way to improve patients with HF poor activity tolerance and thus adherence is by using electrical stimulation to increase muscle strength and endurance. Neuromuscular electrical stimulation (NMES) has been shown to increase muscle strength and endurance in many patient populations including those with HF.[10] In a systematic review examining the effect of NMES on patients with chronic diseases, those with HF found improvements in peak workload, oxygen uptake, muscle strength, health status, exercise duration, and fatigue.[10] The benefits of NMES can also be found in the capillary beds after only two days of use with gradual increases in the number of capillaries with a plateau at four weeks of therapy.[19] Improved venous and lymph return decreases edema and the stimulation reduces vasoconstriction by increasing nitric oxide production. With these improvements, muscles show less fatigue and better

physical performance due to the increase in blood in the muscle area and thus improved removal of metabolic wastes.[19]

Fortunately exercise and NMES can improve local blood flow, exercise capacity and muscle mass.[7] Banerjee found an average improvement of 0.24L in peak VO_2 when using NMES to increase strength in healthy sedentary adults.[8] Maillefert found an increase in exercise capacity and muscle volume when low frequency NMES was used in those with HF.[9] While this was a small sample, peak VO_2 increased 2.4 ml/kg/min, 6-minute walk test (6MWT) saw an improvement of 40 meters. Maillefert found low frequency NMES was safe, well tolerated and effective.[9] In the systematic review by Sillen, in the nine HF studies using NMES as an intervention, researchers reported NMES was safe, but the protocol's varied widely and some of the patients dropped out due to discomfort.[10]

The hypothesis is that by using NMES, patients with HF will, in part, reverse the muscle wasting that occurs with HF and actually increase muscle mass and strength.[20,21] With this increase in muscle, it is expected that patients will become more active, thus reversing the downward spiral that has been observed with doing less leading to less ability. One of the key factors in choosing this modality is that patients only need to apply the electrodes to their thighs and then sit back and let the machine do the work. Patients will be instructed to also add active quadriceps muscle contraction during the passive NMES contraction to decrease any discomfort and also to aid the building of muscle.[22] Thus, NMES is used as the first step in an exercise program that is tailored for this very difficult population in order to improve exercise initiation, adherence, and sustained practice. Bruckenthal suggests in order to improve attitudes and adherence towards exercise by those with HF we need to increase the entertainment value or likeability of the options.[23] Being able to begin an exercise program without getting short of breath or having to invest a lot of energy in a population that is highly fatigued and short of breath, should improve the likeability and practicality of the option. With the increase in strength the patient may begin to feel some success which may then lead to increases in other activities leading to an overall improvement in exercise tolerance, improved functional ability, quality of life, and participation formal exercise programs.

Innovation

NMES uses a lightweight, battery powered electrical stimulation unit (which is attached to the patient via self-adhesive electrodes) to produce a controlled contraction of the underlying muscle. It can be self-administered at home while the participant is passively sitting or lying down thus decreasing the demands of exercise while still allowing the participant many of the same benefits.[24] Previous studies using NMES and those with HF have shown benefit, but, the protocols have varied widely, the outcome variables of interest have also varied widely, in addition there was no further formal exercise program encouraged upon completion of the study. The innovation of this study is that all the previous knowledge gained has been merged into a protocol that is double blinded, patient centered protocol to improve compliance, tolerability, and ease of use. Also, this proposal focuses on NMES being used as the stepping stone to enable those with HF to participate in structured exercise program.

Section 2: Rationale and Specific Aims Research Design and Methods

The purpose of this double blinded, randomized, controlled, longitudinal study is to determine if NMES will increase muscle mass and strength, decrease sedentary time, and improve HF symptoms and exercise capacity, thus improving quality of life in patients with HF. It is hypothesized that with this increase in muscle mass, patients will improve overall exercise tolerance and capacity. In addition, after the intervention patients will be better able to tolerate an exercise program thus improving adherence to exercise recommendations. After 6 weeks of intervention, patients will be encouraged to participate in a formalized exercise program.

Specific Aim 1: Test the effect of NMES on muscle mass and strength in patients with HF. We will use DXA and dynamometer to evaluate this aim. We hypothesize that NMES will increase lean muscle mass and decrease fat mass of the thighs. Also that strength and force of the thighs will improve.

Specific Aim 2: Evaluate the effect of NMES on exercise capacity and activity in patients with HF. We will use 6-minute walk test to evaluate exercise capacity and ActivePal accelerometer to evaluate activity levels. We hypothesize that exercise capacity and the amount of daily activity will increase while sitting/lying time will decrease from pre intervention to post intervention time points.

Specific Aim 3: Assess the effect of NMES on HF symptoms and health-related quality of life (HRQOL). We will use the Memorial Symptom Assessment Scale-HF and Minnesota Living with Heart Failure Questionnaire (MLHFQ) to evaluate this aim. We hypothesize that HRQOL will increase while HF symptoms decrease.

Specific Aim 4: Evaluate the effect of NMES on enrollment and utilization of a formalized exercise program. We hypothesize that patients in the NMES group will be more likely to participate in a formalize exercise plan following the intervention than the sham group.

We will use a double blinded, randomized controlled longitudinal study design to determine if NMES will increase muscle mass and strength, decrease sitting and lying time, and improve HF symptoms and exercise capacity thus improving likelihood of engagement with a structured exercise program. Patients will be randomized to either intervention that includes NMES or to a sham/wait list control group.

Importance of the Knowledge to be gained

Research has shown that patients with HF see significant improvement in their HF symptoms, decrease hospitalizations, and find improvement in their overall health when they follow a prescribed exercise regimen. Many patients are not willing or able to begin exercising or discontinue the exercise regimen once they do start one due to high levels of fatigue and shortness of breath due to muscle wasting that occurs with HF. Having a lower starting point (starting with passive NMES) for exercise and building muscles up before enrolling in a cardiac rehabilitation program to meet the current exercise recommendations will likely improve the success for patients in being able to exercise. It is expected that all patients will benefit from a formalized exercise program regardless of NMES or Sham randomized group.

The data collected in this study will be used to prepare a NIH RO1 application, which will launch my independent program of research. Using NMES to improve exercise use in patients with HF is of specific interest to the NIH due to all the potential improvements previously discussed. There is a great potential for extramural funding for development of non-pharmacologic interventions that maintain/improve independence, increase quality of life, decrease hospitalizations, and improve patient outcomes. This study will add to the science by determining if NMES can be used as a stepping stone for enrollment into formalized exercise rehabilitation program, or as an approach for those who are unable to exercise.

Section 3: Inclusion and Exclusion Criteria

Inclusion criteria

Adult patients with a recent hospitalization or clinic visit for heart failure, (ICD-9 428; ICD-10 I50) and one of the following: BNP >400 OR NT-proBNP>900 (If renal dysfunction >1200) OR Echo showing myocardial remodeling, dilation, hypertrophy, or dysfunction will be included in this study. In addition patients must live at home, and not regularly exercise (10 minutes or more a day of exercise most days of the week for the past week).[25] Sedentary patients are the focus of this intervention because they would most likely see significant improvement with the intervention.

Exclusion criteria

Patients, who have undertaken cardiac rehab within the 12 months prior to enrollment, have a cognitive or other impairment which prevents accurate application of intervention or inability to provide informed consent, End Stage Renal Disease or receiving mechanical ventilation, receiving non-approved FDA-investigational agents or devices, has received a heart transplant, a destination Ventricular Assist Device (LVAD), pacemaker, or implantable cardiac device, previously used NMES (Neuromuscular electrical stimulation) or TENS (Transcutaneous electrical nerve stimulation) or Uncontrolled arrhythmia's or 3 degree AV heart block, are unable to correctly apply and operate the device even after instruction (as determined by the Research Assistant), those with wounds over area of proper placement of electrodes, or those who are unable to speak and write English. Women who are pregnant or planning to become pregnant.

Children will not be included in this study. Although HF can occur in all ages, it is primarily a disorder of the elderly. In addition the causes of HF in children is very different than adults.

Section 4: Enrollment and Randomization

Patients who meet eligibility criteria will be referred to the investigator or the research assistant by cardiology, heart failure, or emergency room providers during their routine evaluation of patients eligible for participation in other heart failure research studies through the medical record system. In addition, a clinical research systems

request has been made to allow for notification to the PI the identification all heart failure patients admitted to the hospital so the PI or RA can screen for eligibility. In addition, Dr. Susan Pressler will release names and contact information for previous participants in her HF study to the PI if the participant has previously indicated they would like to be contacted for future research studies for screening to determine eligibility to participate in this study. The patient will then be contacted by a BISTRO team member for a full explanation of the study and determine interest in participating. If they are interested and are also willing to participate in the FIT Core study (IRB #170755085), an appointment for follow up discussion and possible consenting for both studies) will then be set up for the following week or two. At which time they will come to the school of nursing for final consideration, potential consenting, begin data collection.

In order to ensure that the two groups are comparable between treatment and sham interventions, the participants will be randomized according to gender. Randomization via minimization will be used in order to avoid an unbalanced number of women in the two comparison groups due to chance.[26] A file of the computer-generated random assignments will be kept by the research assistant so the PI/data collector remains blinded in a protected Box Health account.

Section 5: Study Procedures
Intervention and Sham/Wait List Control Conditions

The PI will collect all baseline data before the participant is randomized to the intervention or sham/wait list control group. In order to ensure rigor, patients and PI are blinded to study assignment. The intervention/sham will be set-up by the RA and will be collected after the PI leaves the department so those collecting data will not know which group the participant has been/will be participating in. The RA who is trained in both NMES and Sham intervention will then look at the randomization schedule, and set up and train the participants on equipment use after the data has been collected.[27] Once trained, participants will be contacted via phone weekly by the RA who initially trained them (in order to maintain blinding) to determine if participants are following protocol and placement as taught, if the participant is tolerating the intervention, skin condition under the electrodes, and if there are any questions or problems with the machine. The RA applying the intervention will not have any part in the data collection of the rest of the measurements (other than adherence, tolerance and problems with equipment).

The Empi Continuum electrotherapy system made by Empi, Inc. (Clear Lake South Dakota) is chosen for NMES in this study because it is already available to the PI, it has both the intervention and sham settings, and is able to track adherence (total number of sessions, total session time, average session time, average intensity). Each machine will be calibrated before use for each participant and also checked with each return visit. The output of the stimulator will be checked with an oscilloscope to ensure consistency between the current reading on the stimulator and the actual current output every time the participant returns. NMES will be set up with the machine on simultaneous large muscle atrophy setting with 500 ohm with peak of 50 volts, the “self-adhesive electrodes positioned on the thighs approximately 5 cm below the inguinal fold and 3 cm above the upper patella border” as described by Gobbo.[28] When applying the stimulation, the intensity will be gradually increased from an intermittent tingling until a

gentle pumping sensation is felt. Participants will direct the amount of stimulation acceptable on both thighs to improve acceptance of the modality.[10,24,29-31] To assist better tolerance large electrodes (2x4) will be used and participants will also be instructed to be in a seated position with chair close to the wall so that their leg is 90-degree angle and then push against the wall to decrease any uncomfortable feeling during the contraction. For the Sham group, electrodes will follow the same landmarks, but the stimulation will only increase to an intermittent tingling sensation with the machine setting on TENS instead of NMES which is not enough to make noticeable changes in muscle mass or circulation.[32] Participants in both groups will be given written instructions and contact information of the person (RA) to contact should there be any problems or concerns with the intervention. All participants will do a return demonstration to assure proper knowledge has been gained. Adherence to the study protocol will be determined by the amount of time the EMPI machine records that it was used, the intensities utilized along with verbal verification during the weekly phone calls.

NMES Protocol Summary

- 5 sessions per week for 6 weeks done independently at home, with 15 minutes per session (15 stimulations per day/session, 15 seconds stimulation on, 15 seconds recovery time) to both legs.
- Intervention group only: We expect the participant to develop tolerance to the treatment and thus increase the intensity of the NMES over time.
- At the end of the trial, the participants will return to have all measures repeated. Sham group will then be offered the active treatment. In previous HF studies (non-NMES) done by the mentor of this grant, no participants have accepted the offer of the intervention after completion of the sham/control so this number is expected to be very small.
- Participants will be encouraged to begin a formalized exercise plan such as Silver Sneakers, a home based cardiac rehabilitation or institutional cardiac rehabilitation program.
- Finally, 3 months after the intervention/sham was completed participants will return one final time to have all measures repeated to allow for evaluation of activity levels following completion of the intervention.

Retention

Participants will be told prior to enrolling in the study that they could be randomized to the sham treatment group, and if so, they will be given the opportunity to participate in the NMES protocol after completing the sham intervention. Individualized calendars will be provided to participants to assist in reminding them when which assessment is scheduled. Participants in both groups will be provided the same compensation of $50 for each visit where physical data are collected, $10 for each weekly phone call ($60) with RA to assess adherence/problems. Total money paid to participants completing all components of participation will be $210.

- Payment 1: $50 for baseline measures (paid upon return of ActivPal, paid via voucher checks sent in the mail)
- Payment 2-6: $10 for phone call/verification (paid weekly following the phone call via voucher checks sent in the mail)

- Payment 5: $50 for post intervention measures (paid upon return of ActivPal, after the second physical testing visit-mailed to participant)
- Payment 6: $50 for Final post intervention measures (paid upon return of ActivPal after the third physical testing visit-mailed to participant)

If participants fail to return the equipment they will not receive the payment scheduled for that visit.

Instruments and Measures

1. Dual-energy x-ray absorptiometry (DXA) will be used to determine if there is a measurable change in fat mass and skeletal muscle mass as a result of NMES intervention (**specific aim 1**). Other studies have found an increase in muscle strength but muscle mass was not measured with DXA. DXA is chosen because it is quick (10-15 minutes), relatively cheap (compared to CT), analysis is straight forward and patients are more accepting of DXA procedures than CT.[33] Hologic Discovery-W densitometer is the DXA machine we will be using with Apex software version 2.3. Calibration will be conducted every day a participant is scheduled to come in and weekly scanning of manufacturer supplied supine phantom will also be ran to determine that no instrumentation drift has occurred. Coefficients of variance were reported to be between 1-3% thus showing this machine to have an excellent precision.[33] DXA is the gold standard in the measurement of body composition.[34] Total and segmental (bilateral upper leg) body composition will be assessed according to the differential degree of photon attenuation at two levels of energy as described by Steiner.[35]

2. Strength Assessment will be done using a Biodex isokinetic dynamometer (Biodex Medical Systems, Shirley, NY) (**specific aim 1**). The load cell will be calibrated prior to testing daily using manufactures guidelines. The patient will be seated with padded straps placed across their chest and thigh to reduce movement of the trunk and thigh during testing (see image to right). The knee will be flexed to 90° following the protocol described by Toonstra.[36] An inelastic strap attached to the testing arm of the instrument will be placed around the leg just above the ankle. Participants will be asked to tighten their thigh and straighten their knee as hard as they can. The arm of instrument will allow the knee to be straightened at 60 degree per second, with the instrument's load cell measuring force. Participants will be given 5 minutes to familiarize themselves with the device and perform practice trials prior to testing. When instructed, subjects will kick (tighten their thigh muscle and try to straighten their knee as hard as they can against the testing machine). This will be performed 5 times on the dominate leg with a 120 second rest period between each set of 3 attempts. The second part of the test includes kicking 50 times in a row. Following the 50 kicks participants will be given 30 seconds to rest, then asked to repeat 3 kicks for a series of 5 times. The leg strength test will take approximately 40 minutes to complete. These testing procedures have yielded excellent reliability in healthy population with ICC = .92 and minimal detectable change with 95% confidence of .42 Nm.[36]

3. The 6-min walk test (6MWT) estimates the person's ability to perform everyday activities by measuring the distance walked in a set time period.[37] It will be used to measure exercise capacity, **specific aim 2**.[38] Participants will be allowed use of an assistive device and will be instructed to move as quickly as they feel safe and comfortable over the 100-meter course for 6 minutes. As per the protocol, participants will be allowed to stop and rest if necessary. This test is recommended by the American Thoracic Society for patients with moderate to severe heart or lung disease.[39] A clinically significant difference due to treatment effect has been established as the increase in distance walked must be at least 5% higher than baseline.[40] A high degree of concordance (80%) for positive or neutral response to exercise interventions for HF treatment accurately reflect clinical effects induced by the intervention.[40-42]

4. ActivPal4 is an accelerometer that also has an inclinometer built in to differentiate between lying/sitting, standing and walking. It will be used to measure physical activity levels (**specific aim 2).** Analysis of data is straight forward as data are recorded in minutes and seconds of time spent sitting/lying, standing, moving, and actual number of steps taken. Patients will be instructed to wear the ActivPal for 7 days continuously during each time point. It is worn on the thigh and placed under a waterproof "bandage" after having the skin protected with skin prep. This allows the patient to put it on and forget about it even in the shower (not swimming or prolonged underwater activity) to also assist in complete data being recorded. Reliability was found to be 0.99 when compared with direct (camera recorded) observation for sitting and transitioning from sitting to standing.[43] The correlation between the ActivPal and direct observation of position and number of step taken was = 0.94.[44] Lastly, the ActivPal was tested in sedentary older adults with impaired function and found to agree 100% of the time with direct observation with sitting and standing time.[45]

5. Use the Memorial Symptom Assessment Scale-Heart Failure (MSAS-HF) is a measure of HF symptoms, that will be used (**specific aim 3)**. MSAS-HF is a measure of 32 heart failure symptoms (27 physical and 5 psychological), which rates each symptom on the basis of presence or absence, and if present, the frequency, severity and level of distress the symptom causes over the past 7 days.[46] Administration takes approximately 5-15 minutes after going through instructions, depending on the number and severity of the symptoms, and can be interviewer or self-administered. There is an average score for each symptom, and subscales in HF, physical, and psychological symptoms.[46] Reliability of burden scores in each subscale was examined using Cronbach's α, which were 0.80–0.87 for the physical symptom subscale; 0.83–0.91 for the psychological symptom subscale; and 0.73–0.85 for the HF symptom subscale.[47,48]

6. Minnesota Living with Heart Failure Questionnaire (MLHFQ) is a measure of HF quality of life and reflects the effect of HF and treatments for HF on an individual's ability to live as they want. It will be used to measure quality of life (**specific aim 3)**. Administration takes approximately 5 minutes after going through instructions, and can be interviewer or self-administered. Test-retest Reliability: total scale score r=0.93, physical r=0.89, emotional r=0.88. Internal Consistency: Total scale alpha 0.94, physical

0.94, emotional 0.90. Construct validity correlates with several other measures depending on extent of conceptual overlap.[49]

7. Demographic, and comorbidity status will be collected using a standard questionnaire, the Charlson comorbidity index and chart review. Demographics collected via patient report, will be used to characterize the participant sample and obtain potential confounding variables such as age, sex, race/ethnicity, marital status, education completed, employment status, NYHA classification, and income. The clinic record will also be used to evaluate additional hospital stays (**specific aim 4**), and medications. The Charlson Comorbidity Index is a method of evaluating the effects of comorbidities in patients based on the International Classification of Diseases diagnosis codes found in billing data. The comorbidity has an associated weight, based on the adjusted risk of mortality or resource use, and the sum of all the weights results in a single comorbidity score for a patient. The higher the score, the more likely the predicted outcome will result in mortality or higher resource use.[50]

8.The PROMIS Fatigue Scale assess a range of self-reported symptoms, from mild feelings of tiredness to an overwhelming, debilitating, and sustained sense of exhaustion. Fatigue is measured by frequency, duration, and intensity as well as the impact of fatigue on physical, mental, and social activities.[51] The fatigue short form-8 is universal rather than disease-specific and assess fatigue over the past seven days. Each question usually has five response options ranging in value from one to five. With 1= not at all, to 5=very much). To find the total raw score for a short form with all questions answered, sum the values of the response to each question. For example, the lowest possible raw score is 8; the highest possible raw score is 40. A higher PROMIS T-score represents more of the concept being measured. For negatively-worded concepts like fatigue, a T-score of 60 is one SD worse than average. By comparison, a fatigue T-score of 40 is one SD better than average Patient-Reported Outcomes Measurement Information System (PROMIS) 7-day recall Fatigue Item Bank (www.assessmentcenter.net/). Validity was determined by multidisciplinary panel made of nurses, physicians, pharmacists and psychologists. [51-54] Reliability was found to be 0.95 correlation with the FACIT-Fatigue scale.[53] Support for using PROMIS fatigue in heart failure patients was found in one study, although the reliability scores were not printed.[55]

9. Self-Efficacy for Exercise Scale is used to evaluate how strongly patients feel they can exercise in the face of common barriers. There are 9 items with 10 choices ranging from 0 meaning no confidence to 10 meaning very confident they could/would exercise despite the barrier. Reliability was demonstrated with a alpha coefficient of 0.93 and validity, by factor loadings of all 9 items greater than 0.50 and path coefficients greater than 0.70.[56,57] This scale has been validated in a group healthy minority older adults and in a group of older adults ~85+ living in a retirement community (Caucasian, female and unmarried).[56,57]

10. Outcome Expectations for Exercise Scale-2 is used to measure positive and negative expectations for engaging in exercise. There are 13 items with 5 choices on a scale range from 1 strongly agree, 2 agree, 3 neither agree or disagree, 4 disagree, 5 strongly disagree. There are 2 subscales, one for the positive (9 items) or benefits

expected by engaging in exercise and the other on possible negative (4 items) outcomes from exercise. The each sub scale is then summed and divided by the number of items giving you an average score for positive and negative expectations score.[58] Validity was demonstrated by factor and Rasch anylasis with a caveat of the negative subscales loaded on 2+ concepts suggesting some overlap.[58] Internal consistency of both subscales was 0.93 for positive and 0.80 for the negative.[58] Reliability score was 0.98 and 0.91, respectively.[58]

11. Repeated Sit to Stand Test is an objective physical test in which the person is asked to rise from a seated position 5 times as quickly as possible. This measures leg strength as well as balance and mobility.[59,60] A systematic review was completed and found this test is good to high test-retest reliability using interclass correlations of 0.76-0.99 across studies, in most populations and settings.[59,61,62] Excellent interrater reliability was demonstrated with interclass correlation of 0.99 across multiple clinicians in multiple health care settings.[60-62] Poor performance on this test is associated with disability.[63]

12. Timed up and Go Test (TUG) is an objective measure of physical functional status is a simple technique for evaluating competence in basic activities. The test measures in seconds how long it takes for someone to, stand up from a chair, walk forward 10 feet, turn around, walk back to the chair, and sit down.[64] Reliability was been demonstrated by test-retest interclass correlations of 0.978-0.99 across studies done within 7 days.[65] Construct validity is acceptable with the measure demonstrating a specificity ranging from 87-97% and sensitivity from 83-87% for predicting older adults likely to fall.[66,67] With 12.3 seconds as the cut off score for predicting falls in the ensuring 6 month time frame with no ceiling effect demonstrated.[66] TUG scores changed following a quadriceps and hamstrings strengthening program for patients with rheumatoid arthritis compared with subjects who received no strengthening. A reduction in time greater than or equal to 1.4 seconds is a major change and 0.2 is an unimportant change.[68]

13. The Brief Pain Inventory Short Form (BPI-SF) is used to assess pain intensity and interference along with currently used pain management therapies. The BPI-SF assesses: intensity of pain through four items rated from 0 (no pain) to 10 (worst pain imaginable) that are averaged into one intensity score, current treatments being used (one item, open ended question), perceived pain relief (one item rated on a 0 to 100% scale), and extent that pain interferes with daily living through seven items rated from 0 (no interference) to 10 (completely interferes) that are averaged into one interference score.[69,70] The interference questions assess two types of interference with daily activities: affective social functioning (e.g., interaction with others) and physical functioning (i.e., ability to carry out daily activities).[69,70]

The 15-item BPI-SF was developed for cancer pain patients, but has shown consistent validity and reliability for many conditions.[71] Reliability in arthritis and low back pain patients is .82 for severity scale and .95 for the interference scale.[72] Reliability in osteoarthritis patients for both severity and interference scales is 0.80 or greater.[69] The BPI-SF is recommended for chronic pain clinical trials by IMMPACT.[73]

14. The Patient Health Questionnaire (PHQ-8) was used to measure depression. The PHQ-9 is based on the Diagnostic and Statistical Manual of Mental Disorders for clinical

depression diagnostic criteria.[74] Participants were asked to rate each of the 8 items by how often they had been bothered by the item over the past two weeks. The items are on a scale of 0= not at all, 1=several days, 2=more than half the days, 3=nearly every day. Time for participants to self-administer the instrument is less than 5 minutes (Kroenke, 2001).[74] A total score of ≥10 has been shown to have a sensitivity and specificity of 88% in diagnosis of major depression and we used this cut off in this analysis.[74] Due to the false positive reports on the last question of the PhQ-9, the PHQ-8 has been recommended as the validity and reliability remain the same as the PhQ-9 with correlation of 0.997, sensitivity of 50%, and specificity of 90%.[75]

Table of variables and when they are obtained

Variable	**When Collected**
Demographics, clinical data, Charlson	Once Pre
DXA (muscle mass)	Pre, post, 6 months
Dynamometer-Strength and torque (muscle)	Pre, post, 6 months
6-MWT (exercise capacity)	Pre, post, 6 months
ActivPal (time spent active)	Pre, post, 6 months
MSAS-HF (HF symptoms)	Pre, post, 6 months
MLHFQ (HF quality of life)	Pre, post, 6 months
Telephone interviews	Weekly during intervention phase
Promis Fatigue	Pre, post, 6 months
Self-Efficacy for Exercise Scale	Pre, post, 6 months
Outcome expectations for Exercise Scale	Pre, post, 6 months
Repeated Sit to Stand	Pre, post, 6 months
Timed up and go	Pre, post, 6 months
Self-Care of Heart Failure Index	Pre, post, 6 months
Brief Pain Inventory	Pre, post, 6 months
PHQ-8	Pre, post, 6 months
Compliance Data from EMPI machine	Once post

Section 6: Reporting of Adverse Events or Unanticipated Problems involving Risk to participants or others

The following standard definitions will be used for this study:

Adverse Event (AE)

Any untoward or unfavorable medical occurrence in a human study participant, including any abnormal sign (e.g. abnormal physical exam or laboratory finding), symptom, or disease, temporally associated with the participants' involvement in the research, whether or not considered related to participation in the research.

Serious Adverse Event (SAE)

Any AE where the participant is at immediate risk of death from the event as it occurred, or results in inpatient hospitalization, prolongation of existing hospitalization, persistent or significant disability/incapacity, or death.

Unanticipated Problem

As Defined by DHHS 45 CFR part 46, any incident, experience, or outcome that meets all of the following criteria:

- 1) is unexpected, in terms of nature, severity, or frequency, given (a) the research procedures that are described in the protocol-related documents, such as the IRB-approved research protocol and informed consent document; and (b) the characteristics of the study population;
- 2) is related or possibly related to participation in the research (in this guidance document, possibly related means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research); and
- 3) suggests that the research places participants or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.

AEs will be graded according to the following scale:

- *Mild*: An experience that is transient, and requires no special treatment or intervention. The experience does not generally interfere with usual daily activities. This includes transient laboratory test alterations.
- *Moderate*: An experience that is alleviated with simple therapeutic treatments. The experience impacts usual daily activities. Includes laboratory test alterations indicating injury, but without long-term risk.
- *Severe*: An experience that requires therapeutic intervention. The experience interrupts usual daily activities. If hospitalization (or prolongation of hospitalization) is required for treatment it becomes an SAE.

Attribution of AEs will be categorized as:

- *Not related*: The AE is clearly not related to the study procedures (i.e., another cause of the event is most plausible and/or a clinically plausible temporal sequence is inconsistent with the onset of the event).
- *Possibly related*: An event that follows a reasonable temporal sequence from the initiation of study procedures, but that could readily have been produced by a number of other factors.
- *Likely Related*: The AE is clearly related to the study procedures.

Reporting of AEs, and unanticipated problems will follow the guidelines of the IU Standard Operating Procedure for Reporting Unanticipated Problems and

Noncompliance. Specifically, the following events will be reported promptly (i.e., within five business days) to the IRB:

- *AEs* that are assessed by the PI or coinvestigators as (1) unexpected, (2) related or possibly related to participation, AND (3) suggests that the research places subject(s) or others at greater risk of harm than was previously known;
- *Major protocol deviations* that may, in the opinion of the PI, (1) impact subject safety, (2) affect the integrity of the data, OR (3) affect study participant' willingness to participate in the study;
- *Noncompliance*, which includes any action or activity associated with the conduct or oversight of the research that fails to comply with federal or state regulations, institutional policies governing human study participant research, or the requirements or determinations of the IRB.

Unanticipated problems that do not meet the criteria for prompt reporting will be reported at time of protocol renewal to ensure the IRB has a full understanding of the conduct of the research.

Data Safety Monitoring (DSM) Plan

Although the intervention is low risk, we will evaluate all expected and unexpected events to ensure the safety of participants and integrity of the study protocols and data. Research team members (RA, PI) will meet weekly and review all aspects of the study, including preparation of materials and equipment, recruitment, accrual, drop out, data collection, data entry, and protocol adherence for the first 3 months then at least monthly after that. Questions and concerns will be addressed at that time.

The PI, Dr. Haedtke, will be responsible for overall monitoring of the study. The PI and Co-investigators will attend monthly meetings. Dr. Haedtke will be responsible for submitting necessary reports to the members.

- Susan J. Pressler, PhD, RN, FAAN, FAHA, Co-investigator, Professor and Sally Reahard Chair Director, Center for Enhancing Quality of Life in Chronic Illness (CEQL), Indiana University School of Nursing; participate in meetings and be particularly involved with advising on recruitment, accrual, retention, reports of expected and unexpected adverse events, and data quality.
- 2) Peter Pang, MD, MS, FACEP, FACC, Co-investigator, Director of Clinical Research, Chief Science Office, CORE, Indianapolis EMS, Indian University School of Medicine; participate in meetings and be particularly involved with recruitment, accrual, retention, and reports of expected and unexpected adverse events.
- 3) Janet Carpenter, PhD, RN, FAAN, Independent reviewer, School of Nursing Associate Dean for Research, Distinguished Professor, will perform an independent review of the expected/unexpected adverse event data to assure non-bias by the PI on a monthly basis.

Minimizing research-associated risk.

- Protocols for teaching patients how to safely apply the electrodes and monitor their skin will be verbalized with the patient. Following the teaching the patient will teach back what was learned. If not complete or correct, additional information will be given with the patient again verbalizing all key points. If the patient is unable to complete this task, they will be excluded from the study. We will provide written handouts with directions and pictures of proper placement of electrodes. The RA will call the patients weekly while they are using the EMPI machine to determine safety and potential skin irritation or muscle soreness.
- For patients who have scores on the PHQ-8 suggestive of high depressive symptoms (scores > 10) Dr. Haedtke will follow-up with patients' individual physicians after alerting the patient.
- Adherence to the safety protocols will be reviewed at weekly team meetings and at monthly Co-Investigator meetings. In addition, Dr. Haedtke will provide continuous, close monitoring of protocol adherence and referral of patients if needed.

Dr. Haedtke will be responsible for reporting unexpected adverse events and unanticipated problems as required by the IU IRB. The IU IRB will be notified in writing of adverse events within 5 business days of identification of events. During each visit, the PI or RA will question the patient about adverse events using an open question, taking care not to influence the patient's answers, e.g. "Have you had any unusual symptoms or medical problems since the last visit?" It is expected that many HF patients will have events that are commonplace due to their HF and associated comorbidities.

Determining if an Adverse Event needs to be reported to the IRB

1. Is the occurrence **unexpected** during the course of the study?
    a. We expect skin irritation and minor muscle soreness, complications that occur as a result of protocol-mandated use of the EMPI machine, these events will not be reported.
2. Is the occurrence <u>related</u> (or possibly related) to the study?
    a. Not including the expected events, if yes and unexpected, then the event will be reported to the IRB.
3. Does the event put participants at greater risk of harm?
    a. Is there something we could change in the protocol to decrease the likelihood of another event, if yes, then modification will be submitted.
    b. Was this participant specific and unlikely to happen to other participants? If yes, no changes will be made.

Each reported adverse event will be described by its duration (i.e., start and end dates), and suspected relationship to study protocol. These relationships are categorized as likely, possible, and not related. To ensure consistency, PI will apply the following general guideline:

- Yes - There is a plausible relationship between the onset of the adverse event and administration of the study protocol.
    - The adverse event cannot be readily explained by the subject's clinical state, inter-current illness, or concomitant therapies; event abates or resolves upon discontinuation of use of the EMPI machine.
    - No - Evidence exists that the adverse event has an etiology other than the study protocol (e.g., preexisting medical condition, underlying disease, inter-current illness, or concomitant medication); and/or the adverse event has no plausible relationship to the study.

The RA will notify the PI of any event if found when PI was not present and give all information collected so far. The PI will review the medical chart to assist in determining potential causes if necessary. Next, the PI will contact members of the clinical care team to clarify uncertainty related to inadequate documentation, if necessary. Third, if the PI is unable to decide for certain if an adverse event is study related, he or she will have the option of sending a personal health identifier-stripped, written narrative of the event to the other co-PIs who will assist as to whether the event constituted an adverse event. All adverse events will be followed through resolution, stabilization, or until the subject is lost-to-follow-up.

Dr. Haedtke will conduct a literature search and review scientific reports monthly to determine if new studies/protocols/warnings have been published about NMES/TENS interventions in HF or other conditions. If new publications are found, they will be reviewed by the PI and if deemed important, Co-Investigators for impact on the safety of participants or ethics of the study.

Section 7: Study Withdrawal/Discontinuation

A participant may withdrawal from the study at any time verbally or by providing this request in writing as described in the informed consent document. As outlined in the consent document, if the participant/patient wishes to withdraw consent, the PI will not take back any research/analyses already completed.

Section 8: Statistical considerations

Data Management and Analysis

Data collection will occur at the CTSI in IU Health main campus. All data are entered online using the REDcap system. REDcap is a secure web based application for building and managing databases, sponsored by a consortium of 118 research institutions. It offers a streamlined process for building a database, interface for data collection and validation, and automated export procedures for downloading to statistical packages. All REDcap data are stored on a secure web server located behind a firewall on the CCTS network. The ActivPal data will be downloaded from the device directly to a Box Health account with Study ID used as the identifier.

The risk of breach of confidentiality of patient data will be minimized by ensuring all involved personnel have a full understanding of the Health Insurance Portability and

Accountability Act (HIPAA) rules and the protection of privacy guidelines for conducting medical record reviews through the completion of all IRB-mandated HIPAA training and education. Data gathering instruments and procedures are carefully designed to limit the access of personal information. Password protected laptop dedicated for this study only will be used to enter data. Each participant will be assigned a unique identification number and all of their records marked only with this number. All hard copies of data (consents) will be kept in a locked file in the PI's office separate from the files containing the identification key. All digital data reside on computers with encryption software that are password protected and that are kept in locked offices in a locked office suite available only to members of the research team.

Missing Data

The research associate will review all data collected for completeness and readability, correcting any errors prior to data analysis. We will collect "reason for drop out" if a participant stops the study. We will continue to try to schedule subsequent data collection interviews even if the participant is not able to complete a previous one. During each data collection session, team members will work with participants to encourage response to all items and will review data to ensure all data points are completed unless the participant prefers not to answer. Nonetheless, missing data will occur and this will be acknowledged in the analysis.[76] We will conduct initial analyses using the maximum likelihood approach, as it emphasizes the use of all available data. The use of random effects modeling techniques, in particular repeated measures mixed modeling, allows for missing data by adjusting the estimation process to account for bias resulting from data missing at random. Baseline data from those with and without missing data will be compared to determine whether there are systematic differences, using demographic and personal variables. If the data are not amenable to the maximum likelihood method random effects analysis, multiple imputation will be used as an alternative procedure for handling missing data. Multiple imputation produces results similar to maximum likelihood when used under identical conditions. We will use multiple imputation in the sensitivity analyses; this will allow for the comparison of study results under a variety of assumptions to assess the robustness of the findings.

Statistical Analysis

Data analysis will be done using SPSS, v. 22; an alpha level of .05 will be used for all tests except where noted. Study measures will be examined using univariate statistics, including means, standard deviations and frequency distributions, and graphical techniques, such as box plots and histograms. Distributions for continuous outcome measures will also be examined for violations of normality using normal probability plots. If there is evidence of lack of normality for a particular outcome, transformations (e.g., logarithmic) will be used so that the distribution of the transformed variable more closely approximates normality. The analysis strategy to be used to test all aims is repeated measures analysis of variance (ANOVA). Each ANOVA model will include the main effects of Time (baseline, 6 weeks, 6 months' post intervention period) and Group (intervention and sham intervention), as well as the Time by Group

interaction. Post-hoc pairwise comparisons of means will be done using Fisher least significant difference procedure. The repeated measures models will be estimated using the MIXED procedure in SAS. This analysis will: **test the effect of NMES on muscle mass and strength in those with HF (Aim 1); evaluate the effect of NMES on exercise capacity and activity (Aim 2);** and **assess the effect of NMES on HF symptoms and quality of life (QOL)**; and finally, e**valuate the effect of NMES on enrollment and utilization of a formalized exercise program (aim 4).** There will be a separate model for each outcome variable, and the significance of the main and interaction effects will indicate the effect of the intervention over time.

Power Considerations

With at least 27 subjects per group (treatment and sham) completing the study and an alpha level of .05, the ANOVA F test will have approximately 97% power to detect a significant main or interaction effect, assuming a large effect size, and a modest degree of correlation among observations from the same individual. A large effect size in this context is one such that the ratio of the standard deviation of the means to the standard deviation of the observations within the populations is at least 0.4.[77] In addition, the ANOVA F tests will have at least 69% power to detect main effects and 95% power to detect an interaction effect, with alpha set at .05 and at least a medium effect size (i.e., ratio of standard deviation of means to standard deviation of observations within populations is at least 0.25). Given that we expect a large effect between the groups for many outcomes, in addition to the estimated power of at least 95% for the detection of a Group by Time effect in the presence of a medium to large effect, the sample size chosen for this exploratory study will provide sufficient power to detect this significant group differences over time with a high probability; in addition, this study will allow us to more precisely measure expected power in order to plan future studies.

Section 9: Privacy and Confidentiality Issues

Patients' confidentiality will be preserved by coding each data sheet with a unique subject number, and storing the code number key in a locked file cabinet in a locked research office located in the School of Nursing. Protection against breach of confidentiality is provided by training all individuals involved in the research process about the necessity for complete confidentiality, housing all data collected in locked file cabinets in an access-restricted area, and by use of password protected computers and secure servers. Most data are collected using the REDcap system, and any additional files with be stored in Box Health on IU Servers. Although there can be no absolute guarantee of confidentiality, every practical precaution will be taken.

Section 10: Follow-up and Record Retention

Study recruitment will be ongoing. The duration of the entire study is expected to be 18 months, while each participants expected duration is 6 months. The de-identified data will be retained on computer files indefinitely. Hard copy study documents will be kept in a locked, file cabinet in a locked room. Electronic study information will be stored

on a specified, password-protected network that is backed up daily (BOX Health). Only the study team and the relevant personnel will have access.

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Section 12 Appendix

Section 12A SOP for ActivPal

Standard Operating Procedure for Programming ActivPal

Step 1: Open the ActiPal spreadsheet and find the corresponding serial number

Step 2: Open Pal app, make sure the docking station is plugged into the USB port on the computer, and place the monitor in the end spot that says “PC interface”.

Step 3: put in Study ID BISTROxx, for 14 days

Step 4: Click on Set up Recording, this takes a few minutes

Standard Operating Procedure for Downloading data from ActivPal

Step 1: participant returns ActivPal either in person (baseline visit) or receive unit in mailer, remove any tape or waterproofing that may still be applied.

Step 2: Wipe down the outside of the monitor with cleanings wipes and allow to dry.

Step 3: open PALstudio app, make sure the docking station is plugged into the USB port, and place the monitor in the end spot that says “PC interface”.

Step 4: click on “transfer”, the computer then looks to find the ActivPal. It will show you the serial number of the ActiPal data that is getting downloaded. Double check to make sure the one you mean to be downloading is in fact the one getting downloaded. This takes a few minutes so work on something else while you wait. Once the files are then downloaded and then “verified” by the program.

Step 5: Open BOX Health, verify the file is there and open file to be sure data is in the file.

Step 6: Click on Analyze in the PAL studio app, click on all 4 boxes to get all data.

Step 7: Click on Reports and chose the “ASOD”- The standard algorithm with inverted wear correction” option then click Generate reports.

Step 8: Look in BOX Health and verify the file is there and open all files to be sure there is data in the file.

Instructions for Participants

BISTRO Patient: ActivPAL Instructions

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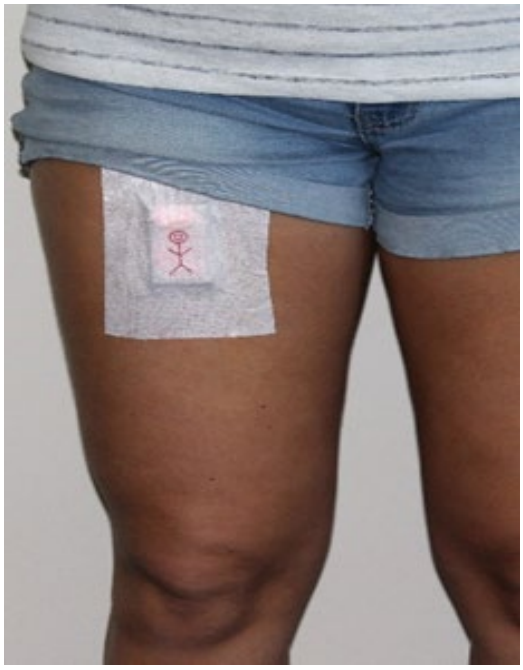
The ActivPAL is designed to monitor activity levels and identify periods of sitting/lying, standing, and walking. We have incorporated the ActivPAL into our study to determine if the intervention will affect your activity level and exercising habits. We ask that you wear it 3 times during the study for one week each time. First when you begin the study, second after participating in the intervention, and third at the 3-month mark following completion of cardiac rehabilitation.

During each use, we request that you wear the ActivPAL on your thigh, 24 hours a day for 7 days. We will supply a waterproof covering for the ActivPAL, which will cover the ActivPAL at all times, even when you shower. If needed, extra materials to reapply the ActivPAL will be supplied at no cost to you.

Once the ActivPal is programed for your use, the bottom light on the ActivPAL will flash green. If the light stops flashing at any time during the week you have it, please contact the research assistant listed in the study paperwork given to you when you joined the study. Also, if skin irritation occurs at any time while you are wearing it, please contact the research assistant.

How to Apply the ActivPAL:

1. Carefully wash and dry the area of skin where the ActivPAL will applied.
2. Obtain the ActivPAL. Orient it so that the body on the ActivPAL is standing up. (See picture above.) You will notice the rounded side is up, and the square side is down. Lights face away from your skin.
3. Cover the ActivPAL with the waterproof covering and roll the end to the side away from you.
4. Sit down on a chair when attaching the monitor so that it will be easier to find the best place for attachment. You want to place it on the top 1/3rd of the length between your groin and your knee in the midline width of your thigh as shown in the picture below.



5. Apply the Skin-PREP wipe to the area of skin where the ActivPAL will be. This will protect your skin from the adhesives in the tape and allow the tape to perform better.
6. Place the covered ActivPAL in the correct orientation on the upper thigh. See picture above. The ActivPAL should be worn on your non-dominant side.
7. Use a large piece of Tegaderm tape to completely cover the ActivPAL. Ensure that this adheres directly to the skin.

Removing the ActivPAL:

1. Carefully peel the Tegaderm away from the skin by lifting up a single corner of the material and gently pulling away from your skin, but level to the bandage.
2. Remove the ActivPAL, encased in its waterproof covering, from the skin.
3. Carefully wash and dry the skin where the ActivPAL was applied with mild soap. If skin irritation has occurred, please contact research assistant.
4. Place the ActivPAL in the bubble mailer we gave to you and place it in any US mail box for return to us.
5. ActivPAL needs to be received by us before we can issue your study participation check.

If you have any questions about the ActivPAL or the study at any time please call the research assistant.

Thank you for participating in our study!

Section 12B SOP for EMPI

EMPI Standard Operating Procedure for setting up TENS

Machine Set up: do this before you see the participant. Please note, you may not need to make adjustments to the machine due to previous programming, so if the correct option is chosen move on to the next item.

1. Turn on machine
2. Press “Home” button
3. Press the TENS button (bottom Left)
4. Press the lower left bottom button until “Custom”, then press OK
5. Change “Time” to 15 MIN, Use the right buttons to raise or lower to 15 MIN, then press bottom left button to progress to “Rate”.
6. Leave “Rate” at 100Hz , then press the bottom left button to progress “Cycle”
7. Set “Cycle” to 15S, then press the bottom left button to progress to “Span”
8. Set “Span” to 50%, then press the bottom left button to progress to “Mode”
9. Set “Mode” at MOD, then Press OK
10. Now the machine is set up for participant to test the comfort level.

Once the Data collector has told you the participant is ready for the intervention explain the machine to them by giving them the EMPI handout and going through each step with the participant following the directions and you clarifying when necessary. Make sure a garbage can and table with a bowl for warm water and wash cloth and towel is within reach, (show them how to use the trimmer if necessary), give them the EMPI handout, go through each step of the process with them. Once the patches are placed and the participant is ready to turn on the machine, show them the picture on page 3 and explain the need to use the on/off button and the increase/decrease intensity buttons. Have them start increasing the intensity on either channel slowly at first and closely monitor their reactions to it. For this intervention we are just looking for a general “feeling it”. They should not increase the intensity to the point where a muscle contraction happens!

Once you are confident the participant settings are comfortable for the patient and only intensity needs to be adjusted, LOCK the device so the participant cannot change the settings themselves.

1. Press the Home button, config (right lower), locks (right lower)
2. Notice the NMES L. Muscles and press the right top button, which locks that option
3. Press the left lower button to bring up S. Muscles and press the right top button twice to get a circle with a line through it. Now that option will no longer show for participants. Repeat for TENS and Edema then press home and note only L. Muscles is an option besides config.

EMPI Standard Operating Procedure for setting up NMES

Machine Set up: do this before you see the participant. Please note, you may not need to make adjustments to the machine due to previous programming, so if the correct option is chosen move on to the next item.

1. Turn on machine
2. Press “Home” button
3. Press the NMES button (top left)
4. Large muscle (top left)
5. Press the Custom button (bottom right)
6. Change time to 15 minutes, then press bottom left button to progress to “off time”
7. Change Off time to 15 Seconds, then press bottom left button to progress to “rate
8. Increase “Rate” to 50Hz, then press the bottom left button to progress to “Width”
9. Leave “Width” at 300 to start. Press bottom left button to progress “waveform”.
10. Leave “waveform” at SYM/ASY
11. Change Cycling “LAG” for both legs at the same time.
12. Leave “Lag” at 0S
13. Leave “CH1 Ramp +” at 2S
14. Increase “ON TIME 1” to 11S
15. Leave “CH1 RAMP –“at 2S
16. Leave “CH2 Ramp +” at 2S
17. Increase “ON TIME 2” to 11S
18. Leave “CH1 RAMP –“at 2S, then press OK
19. Now the machine is set up for participant to test the comfort level.

Once the Data collector has told you the participant is ready for the intervention explain the machine to them by giving them the EMPI handout and going through each step with the participant following the directions and you clarifying when necessary. Make sure a garbage can and table with a bowl for warm water and wash cloth and towel is within reach, (show them how to use the trimmer if necessary), give them the EMPI handout, go through each step of the process with them. Once the patches are placed and the participant is ready to turn on the machine, show them the picture on page 3 and explain the need to use the on/off button and the increase/decrease intensity buttons. Have them start increasing the intensity on either channel slowly at first and closely monitor their reactions to it. The intensity needs to be strong enough to cause the muscle to contract. Demonstrate how actively using the muscle during the contraction lessens any discomfort.

20. If the participant reports the feeling is uncomfortable or “bity” adjust the “Rate” to make the sensation more “smooth”. Decrease the Rate by 5 to 45 then have the participant try again. (Can adjust in increments of ±1 to get the “best” feel for participants. Be sure to record the final setting you programed into the machine in both Redcap and the participant call sheet.) To make adjustments to Rate, (you not the

participant!) press the home button, NMES, Custom, the press the left lower button until you see “Rate”, then use the right lower button to make the adjustment, then press OK and have the participant try again.

21. If the participant reports the feeling is still uncomfortable or “bity” lower the WIDTH by 8 and see if that makes it better. (Can adjust in increments of ±4 to get the “best” feel for participants. Be sure to record the final setting you programed into the machine in Redcap and on your participant call sheet.) To make adjustments to Width, You (not the participant!) need to press the home button, NMES, Custom, the press the left lower button until you see “Width”, then use the right lower button to make the adjustment, then press OK and have the participant try again.

Once you are confident the participant settings are comfortable for the patient and only intensity needs to be adjusted, LOCK the devise so the participant cannot change the settings themselves.

1. Press the Home button, config (right lower), locks (right lower)
2. Notice the NMES L. Muscles and press the right top button, which locks that option
3. Press the left lower button to bring up S. Muscles and press the right top button twice to get a circle with a line through it. Now that option will no longer show for participants. Repeat for TENS and Edema then press home and note only L. Muscles is an option besides config.

Standard operating procedure when EMPI units are returned

Expect participants to bring the unit in the study canvas bag along with any unused sealed supplies.

Step 1: log into RedCap, bring up the data entry for the EMPI machine, enter the study ID.
Step 2: once you have the Canvas bag with EMPI unit, use the wipes designated for cleaning the machine to wipe down the outside of the machine and the lead wires and allow them to air dry.
Step 3: turn on the machine, identify if NMES or TENS showing on the main menu and enter that data into RedCAp
Step 4: press the home button, config button (right lower), data button (left upper).
Step 5: enter the number of sessions into RedCap, press the left down button
Step 6: enter the Total hours into RedCap, press the left down button
Step 7: enter the average time into RedCap, press the left down button
Step 8: enter the CH 1 intensity into RedCap, press the left down button
Step 9: enter the CH 2 intensity into RedCap, press the home button. Double check you have entered all data into RedCap.
Step 10: press the home button, config, clear (right lower), data, and then home. The data has been erased from the machine and is ready for the next participants set up.

BISTRO Patient Instructions: Empi Unit

We have provided the following with your Empi unit for your use during the study: a canvas bag, patches, wires, skin preparation pads, notebook with pen, trimmer (optional for those with hairy thighs), and extra AA batteries. If you need additional supplies at any time, call the research assistant.

Before beginning the treatment, you must protect your skin.

Skin Preparation:

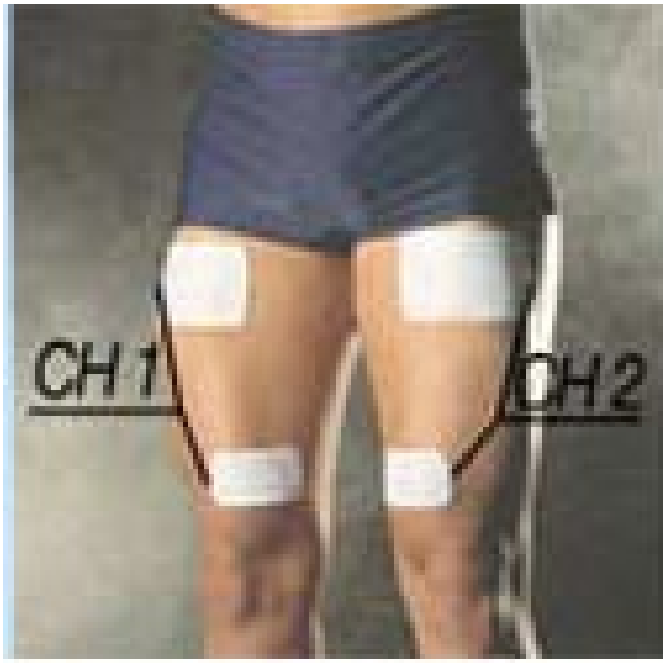
1. Always check the skin carefully prior to beginning stimulation. The skin should not have any cuts, open sores, rashes, or inflammation.

What to do if a skin problem occurs: Carefully wash and dry the area with mild soap (unscented), rinse, and use a soft towel to dry the area. Call the research assistant and inform them of your skin problem. You will need to pause treatment until your skin heals.

2. If your skin is healthy, wash the skin where the patches will be placed (see picture below). Do not apply any lotions, gels, or perfumes to the skin. Gently dry the skin with a soft towel.

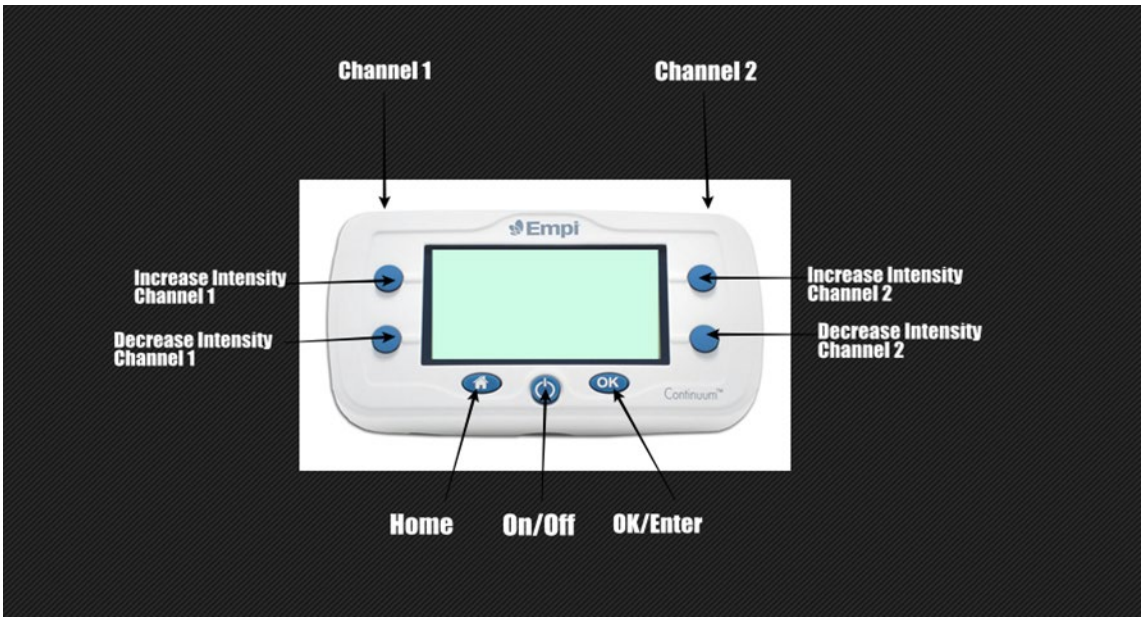
3. If there is any hair in the area where the patches will be placed, remove the hair with a trimmer. **Do Not** use a razor as this will lead to skin irritation and minor cuts.

4. After washing, drying, and the removal of hair, open the skin preparation pads (SKIN-PREP) found in the canvas bag and thoroughly wipe the area where the patches will be placed. Wait 30 seconds for the SKIN-PREP to dry, then place the patches.



Using Your Empi Unit

1. Make sure that the skin where the patches will be placed has been washed, dried, and SKIN-PREP applied.
2. Make sure that the unit is turned off.
3. Open the sealed bag with the patches found in the canvas bag. Gently peal the patches off the plastic sheet and save the sheet to return the patches when your session is complete. The patches are reusable and should be changed every week. If the patches don't want to stick they maybe dry. You can add 1 or 2 drops of water to the patch, if it still doesn't stick, use a new set.
4. Plug the wire connector from the patch to the wire on the machine. Note: The wire connectors may connect to either the red or black connectors. The black wire connected to the patch at the top of the thigh and the red connector the patch near the knee. If there is wire damage call research assistant for a new set.
5. Place the patches in the correct locations as indicated in the diagram on page 2. Stick the center of the patch on the desired area of the skin, and then flatten the sides of the patches onto the skin.



6. Remove the unit from the canvas bag and turn the unit on using the ON/OFF button in the middle of the bottom row on the unit, just below the screen. When you turn on the unit, the screen will present the Empi logo (See picture above).
7. Next, the screen should display an “In-Progress” message indicating that the unit is ready for use.
    a. If the screen goes to a menu that displays options for you to select (i.e., NMES, TENS, EDMEA, CONFIG), call the research assistant as additional directions will be needed for you to safely use the machine.
8. Once the “In-Progress” screen appears, you need to increase the level of intensity for treatment. Adjust the intensity to the level specified by the research assistant.
    a. To increase the intensity for Channel 1, press the top button on the left-hand side of the screen. To decrease the intensity for Channel 1, press the bottom button on the left-hand side of the screen.
    b. To increase the intensity for Channel 2, press the top button on the right-hand side of the screen. To decrease the intensity for Channel 2, press the bottom button on the right-hand side of the screen.

c. Note: Once the intensity is set and left alone for 20 seconds, the unit will lock the buttons to prevent an unwanted change. In order to change the intensity after the unit is locked, press the decrease intensity button on the desired channel to unlock the unit so you can change the intensity.

d. Unit will stop running after 15 minutes. You can now turn off the machine by pressing of on/off button for 2 sections and remove the patches.

9. Removing the patches

   a. Turn off the unit before removing the patches.

   b. Carefully pull the patch off the skin starting at a corner. The wire connectors should **not** be used to help pull the patches off! Pressing on the skin with your other hand close to where you are removing the patch makes removal easier.

   c. Reapply the patches to the liner. Making sure the patch is flat on the liner.

   d. Separate the wire from the connector of each patch by gently unscrewing and lightly tugging where they join. Seal the bag with the patches to keep them from drying out. Return the machine and patches to the canvas bag for storage until your next use.

10. Carefully wash and dry the skin where the patches were applied with mild soap, rinse, and wipe with a soft towel. Some redness is expected after immediate removal of patches. If the redness remains after an hour or is bothersome in any way, write down what you are seeing and feeling in the notebook included in the canvas bag and call the research assistant. (For details see Skin Prep section on page 2)

Caring for the Empi Unit:

Maintenance:

- The unit is designed to function without regular maintenance. Call the research assistant if you have concerns.

Cleaning:

- If the unit becomes dirty, use a nonabrasive, damp cloth to wipe off the unit. Refrain from use any chemicals or cleaning solutions to clean the unit. Do not place the unit in any liquids.

Storage:

- Although the unit will be used regularly, avoid leaving the unit out following use. The wires are easily tangled, targets for pets, or a potential tripping hazard. Use the canvas bag provided to store the unit at room temperature.

Having problems with the Empi Unit?

If the unit displays the low battery symbol or message or the unit will not turn on replace the batteries.

How to replace the batteries:

1. Turn off the device.
2. Turn the unit over so the backside towards you. Remove the battery cover by placing your thumb on the notch and the bottom backside of the unit and pushing up while pulling out.
3. Remove the old batteries.
4. Place new batteries in the unit by matching the + and – ends of the battery with those on the unit. Only use the AA batteries provided by the study to replace the batteries in the unit. If you do not have any AA batteries left, call the research assistant.
5. Replace the battery cover by inserting the small lip at the base of the cover. Then, insert the top of the cover and press until it clicks securely in place. Check the batteries in the unit and make sure that the + and – ends on the batteries match the + and – symbols on the unit. Check to ensure that there is nothing hindering the batteries from touching the respective + and – ends of the unit.

If the unit powers on but the buttons are not functioning properly, check the following:

a. Disconnect the wires from Channel 1 and Channel 2.
b. Remove the batteries from the unit. And leave the batteries out for 10 seconds.
c. Replace the batteries in the unit and try running the treatment again.

If the unit powers on and the screen appears correct but you do not feel any stimulation, check the following:

a. Check to make sure that the intensity is to the minimum level specified by study personnel.
b. Check the lead wires and make sure that they are properly connected to both the patches and the unit in the proper locations (i.e., Channel 1 and Channel 2).
c. Check the wires for any damage or disconnections to either the unit or the patches. If the wires are damaged on the machine call the research assistant for a new pair. If the connection on the patches is damaged, use a new pair.

If the unit powers on and the screen displays an “OPEN” error message check the following:

a. Turn off the machine and check to make sure that the patches and wires are connected correctly to one another and the unit. If they are, remove the patches from your skin check “stickiness” of the patches and add 1-2 drops of water if needed. Then, reapply the patches to the skin. If there still isn’t a good response from the machine, or the patches were very “sticky” replace the patches with a new set.
b. If the error message still appears when you turn on the machine, then call the research assistant and report the problem.

If the unit powers on but the intensity cannot be changed, try unlocking the device (page 5 section #8).
If the unit is damaged or if it is not working correctly call the research assistant. Do not attempt to repair or use the unit.