Date: ___01/30/2013_____
Principal Investigator: ___Dr. Amy Bastian___
Application Number: ____NA_00068967____

JHM IRB - eForm A

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1. Abstract

We recently discovered that the walking deficits of people with post-stroke hemiparesis can be improved on short timescales by adaptation to split-belt treadmill conditions that exaggerate the deficit. The exaggeration drives the nervous system to adapt to correct the deficit, and results in improved walking patterns when the person returns to normal conditions. Here, we plan to investigate how short-term adaptation can be translated into long-term improvement in walking patterns. In addition, we plan to assess economy of gait to determine if there is any reduction in rate of energy use (i.e.- metabolic power) when being trained on a split belt treadmill versus a conventional treadmill. This would allow us to understand whether this training regime, which targets the locomotor pattern, leads to any changes locomotor efficiency. We will study adults with post-stroke hemiparesis before, during and after training for 12-weeks on a split-belt treadmill or conventional treadmill. This pilot study will provide data to power a full scale clinical trial of walking training.

2. Objectives (include all primary and secondary objectives)

The aim of this project is to determine the effects of long term split belt training versus long term conventional treadmill training on spatiotemporal asymmetry, metabolic capacity and functional locomotion after stroke.

3. Background

Recent data shows that walking patterns can be altered through split-belt treadmill training, even after central nervous system damage, and that people with cerebral damage from stroke can benefit in the short-term to correct asymmetric walking patterns (Reisman et al 2007). We have studied short-term adaptation of inter-limb coordination during walking using a split-belt treadmill to control speed of the two legs independently (Reisman et al 2005). Our findings demonstrate that walking patterns are adaptable, and that this process is dependent on cerebellar integrity. Our previous work has focused on short term training and we would like to investigate any effects that could last with even longer training.

4. Study Procedures

a. Study design, including the sequence and timing of study procedures (distinguish research procedures from those that are part of routine care).

If the individual with hemiparesis meets the initial telephone screening criteria we will send a medical clearance letter to the potential participant to give to their doctor. Once we have received written medical clearance from their doctor we will schedule the potential participant to come in for their first baseline visit. We will also ask the patient to provide us with their most recent MRI reading to determine that their stroke did not occur in the cerebellum as well as to determine its exact location.

If it is determined that the subject is eligible based on the telephone screening, the results from their MRI reading and they have medical clearance the subject will be asked to participate in the screening visit to obtain written consent as well as to gather a detailed medical history. This visit will establish that that they have a 10% step length asymmetry and to establish initial measurements for relevant variables and day to day individual subject variability (see step asymmetry testing). If the potential subject does meet the criteria we will continue with the study protocol. If they do not meet this criteria they will not be accrued for the study. We will also use the screening visit to determine the speeds for the treadmill that will be used for the VO_2 walking test for each subject (see VO_2 walking test for details).

There will be two baseline training sessions (Baseline visit 1 and 2, BV1 And BV2). Subjects who are eligible for the study are then randomized to either the split belt training group or the conventional treadmill training group. We will use a stratified randomization based on the initial gait asymmetry to ensure that subjects of similar severity are represented in each group. Testing will be repeated after every 11th training session (training evaluation e.g.- TE1, TE2, etc.) and at one (post training 1, PT1) and 3 months (post training 3, PT3) after the completion of training.

Details of the visits are in the chart below:

Screening	***Visit 1 (Baseline I)***	***Visit 2 (Baseline II) to establish repeatability of outcome measures (within 2 weeks of Visit 1)***	***First block of 11 training sessions (3 x per week- ~ 4 weeks training)***	***Training Evaluation #1 (TE1)***	***Second block of 11 training sessions (3 x per week- ~ 4 weeks training)***
• Gait Evaluation (Step Asymmetry Testing). If NOT met subject will not be accrued for study. • Screening Clinical Exams TOTAL TIME: 1 hr 15 mins	• Gait Evaluation • Clinical testing • VO_2 walking testing and VO_2 peak testing (EKG w/o metabolic cart) TOTAL TIME: 2 hours 15 mins	• Gait Evaluation • Clinical testing • VO_2 walking testing and VO2 peak testing TOTAL TIME: 2 hrs 15 mins.	• Treadmill Training (up to 30 minutes total walking time). This may take up to 1 hour when considering rest breaks. Subject will either do conventional or split belt training depending on the group they were randomly selected to be in. TOTAL TIME: 1 hr	• Gait Evaluation • Clinical Testing • VO_2 walking testing TOTAL TIME: 2 hrs	• Treadmill Training (up to 30 minutes total walking time). This may take up to 1 hour when considering rest breaks. Subject will either do conventional or split belt training depending on the group they were randomly selected to be in. TOTAL TIME: 1 hr

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Training Evaluation #2 (TE2)	*Third block of 11 training sessions (3 x per week- ~ 4 weeks training)*	*Training Evaluation #3 (TE3)*	*Post training visit 1 month (PT1)*	*Post training visit 3 month (PT3)*
• Gait Evaluation • Clinical testing • VO_2 walking testing TOTAL TIME: 2 hrs	• Treadmill Training (up to 30 minutes total treadmill walking time). This may take up to 1 hour when considering rest breaks. Subject will either do conventional or split belt training depending on the group they were randomly selected to be in. TOTAL TIME: 1 hr	• Gait Evaluation • Clinical testing • VO_2 walking testing and VO_2 peak testing TOTAL TIME: 2 hrs 30 mins	• Gait Evaluation • Clinical Testing • VO_2 walking testing TOTAL TIME: 2 hrs	• Gait Evaluation • Clinical Testing • VO_2 walking testing TOTAL TIME: 2 hrs

I. Baseline measurements will be taken at the Screening visit, Visit 1, then no more than 2 weeks later at Visit 2 before training. This will be done to determine step asymmetry eligibility as well as repeatability and stability of baseline measures.

II. **Treadmill Training will occur in 3 separate blocks of 11 sessions totaling to 33 total training visits. Each block of 11 sessions will ideally have subjects coming in to the lab 3 times a week during a 4 week period. For each block, the first, second and third weeks will have 3 training sessions and the fourth week will only have two. The Training Evaluations will always be held during the fourth week. The particular days during the week in which they choose to come does not matter and they do not have to be the same days of the week each week (i.e.- a subject could come in Monday, Tuesday Thursday one week and the next week come in Tuesday Thursday Friday the following week). We will try to make sure that the subject comes in the same time of day for each visit but due to scheduling issues we realize this may not be possible. It is possible, due to the patient's schedule, the lab's schedule or even weather, that a visit may not be able to be completed, leaving the subject with completing less than 3 visits in one week. Subjects will not be allowed to have more than three training visits in one week. Subjects will also not be allowed to miss more than 3 training sessions in each of the 3 blocks of 11 sessions. If they do they will be taken out of the study.**

Participants will either train on a conventional treadmill paradigm (belts going the same speed) or they will train on a split-belt treadmill paradigm (one leg moving faster than the other leg).

Participant's assignment to which study group they participate in (conventional treadmill walking or split-belt treadmill walking) will be randomly assigned (like flipping a coin)

III. Training evaluations will occur after each of the 3 blocks of training.

IV. **Post-Training measurements will be taken one month (plus or minus 1 week) after the final training visit and another will be take 3 months (plus or minus one week) after the final training visit.**

Clinical Evaluation

Clinical Testing will include the following:

a) *lower extremity portion of the Fugl-Meyer Scale* which is a test that measures coordination, reflexes and the ability to move in and out of synergy. On day 1 this will also include a monofilament exam of the feet to determine if there is any peripheral sensory loss in the feet.

b) *6 meter walk test* which is a measure of short-distance walking speed. This is performed according to the protocol of Plummer et al. (2007). Subjects will walk along a 10m walkway with time recorded during the middle 6m to allow for acceleration and deceleration. Subjects will perform 2 trials at both their self-selected and fastest speeds.

c) *6 Minute Walk Test* which is a measure of walking endurance. This test records the distance walked in 6 minutes and has been used as an endurance measure in people post-stroke.

d)*Mini Mental State Exam and the Star Cancellation test*- both of these will be completed at the screening visit only. The Mini Metal test is to make sure that the subjects are competent enough to participate in our study and the start cancellation test is to make sure there is no hemi-neglect due to the stroke.

e) *Activities-specific Balance Confidence Scale* which is a 16-item self-report questionnaire that asks individuals to rate their confidence in performing specific balance-challenging activities on a scale (0-100). A score of zero represents no confidence and a score of 100 represents complete confidence. The scores for each item were averaged to produce a total score. The ABC Scale has been reported to have acceptable measurement properties for people post-stroke.

f) *Stroke Impact Scale, version 3.0* is a psychometrically robust measure of stroke-specific outcome. It measures 8 domains (physical problems, memory and thinking, mood and emotions, communication, daily activities, mobility, affected hand, and participation). For this study only data for the mobility and participation domains will be collected and evaluated.

g)*Timed up and go test*- this test times subjects as they rise from a chair, walk a distance, turn around and come back to the chair.

Step Asymmetry Testing

This will be done to determine if subjects meet the 10% step asymmetry criteria for inclusion in the study. Spatiotemporal gait characteristics will be measured using the GaitRite System (Havertown, PA). The GaitRite system automates measuring temporal (timing) and spatial (distance) gait parameters via an electronic walkway connected to

the serial port of a personal computer. The GaitRite electronic walkway contains six sensor pads encapsulated in a roll up carpet to produce an active area 24 inches (61cm) wide and 144 inches (366cm) long. In this arrangement the active area is a grid, 48 sensors by 288 sensors placed on .5 inch (1.27 cm) centers, totaling 13824 sensors. Participants will walk across the electronic walkway at their self-selected comfortable walking speed (SSWS) for 10 trials and at their fastest possible, safe walking speed for 5 trials, totaling 15 trials during each evaluation session. Rest breaks will be provided between each trial.

VO_2 walking testing

We plan to assess the economy of gait for baseline visit 1 and , training evaluation 1- 3 (end of training), 1 and 3 month follow-ups. Economy of gait refers to the amount of metabolic power that is required when walking at a particular speed. In this study we will be investigating the effects of conventional treadmill walking versus split belt walking on the economy of gait to see if there are any cardiovascular effects that are influenced by either types of training. In order to do this we will record oxygen consumption / carbon dioxide production while having the subjects stand as well as while they walk on the treadmill at their comfortable over ground speed. (described below). All subjects, for this test, will walk on the treadmill with both belts moving at the same speed, regardless of whether they are in the split belt or conventional treadmill group. This walking and standing data will allow for a determination of economy of gait.

We will use motion analysis to track movement while we do this test. Prior to testing we will place small (dime sized) markers that will be placed bilaterally on the foot (5^{th} metatarsal head), ankle (lateral malleolus), knee (lateral joint space), hip (greater trochanter), pelvis (iliac crest) and shoulder (acromion process). These markers emit an infrared light, which our sensors can track in 3D. A Northern Digital OPTOTRAK movement measurement system (with 2, 3D position sensors) will be used to collect the 3-dimensional location of each marker. Marker position and analog data (treadmill belt speeds) will be time locked using OPTOTRACK software, and sampled simultaneously at 100 Hz and 1000 Hz respectively. This will be used to record each subject's movement on the treadmill.

For the VO_2 testing, we will first acclimate the subject to the mouthpiece to make sure that it is a proper fit. We will then continue with the metabolic set up by fitting them with the head piece and then attaching the remaining equipment to the subject.

To begin testing we will have the subject stand in place for 5 minutes and record their kinematics as well as their metabolic data. Then, all subjects will be monitored as they walk on the treadmill with both belts moving at the same speed. Each subject will walk for 3-5 minutes at their comfortable walking speed and at their fast walking speed (both determined at baseline visit 1), depending on how quickly it takes our VO2 measure to reach steady state. These speeds will be the same across the study we can evaluate whether their VO_2 value changes due to a change in their economy of gait, not because of a change in treadmill speed.

VO_2 peak testing

For Baseline Visit 1 we will have the subjects come in to do a stress test. This test will be done similarly to Baseline Visit 2 and Training Evaluation 3.

For Baseline Visit 1, the purpose of this test is to make sure the subject understands how the test will work, check their EKG, and make sure that the subject will be able to complete the test. We will not record VO_2 on this visit since spirometry testing requires a mouth piece to be in during the entire test, making communication between the subject and the researchers limited. We will teach the subject different hand signals as we do this test so the subject will know how to communicate with the researchers when we do the test with the mouthpiece in place. EKG leads will be placed and monitored by a nurse from the Kennedy Krieger Department of Nursing. It will be read by a cardiologist.

The speed of the treadmill will be set to 75% of their comfortable self-selected over ground speed as tested in 6 meter walk (Macko et al., 2001). Patients will be instructed to minimize handrail support to what is necessary for them to keep their balance while walking on the treadmill.

On Baseline Visit 1, the stress test will be done without open circuit spirometry. Before testing we will have the subject seated for two minutes and then standing for two minutes to allow us to get resting blood pressure readings. The subject will then walk for 2 minutes at 0% incline, then 2 minutes at a 4% incline. After this point the treadmill will increase its incline by 2% every minute until the subject says they can no longer continue or the treadmill reaches its maximum incline at 14%. There are no breaks during this test as the purpose of it is to determine when the subject reaches fatigue and can no longer continue or they reach the 14% incline. If they reach 14% we will have the subject continue to walk until either they become fatigued, the cardiologist and/or study team nurse determine it is no longer safe to continue or the subject's VO_2 values plateau.

A nurse will check blood pressure (BP) with the subject seated and standing before this test, as well as every 2 minutes during recovery until it returns within 10mmHG of the baseline reading. By not performing the open circuit spirometry this allowed for optimal communication with the subjects for safety purposes. The EKG reading from this stress test will be sent to a study team cardiologist for review to determine whether the subject will be healthy enough to participate in our study.

Baseline Visit 2 and Training Evaluation 3 will involve the open circuit spirometry. The subject will be connected to the spirometer, EKG machine and the kinematic markers as was described previously. The VO_2 peak will be measured the same way described for Baseline Visit 1 but with the inclusion of the open circuit spirometry. BP and EKG will be monitored as in Baseline visit 1. Researchers and the subject will be in constant communication during the test using agreed upon hand signals to allow the researchers if the subject is able or unable to continue with the test.

Gait Evaluation

Gait Evaluation will be completed on baseline visit #1 and #2, Training Evaluation #1-3 and 1 and 3 month post training follow-ups.

We will have the subject walk over ground on the GaitRite mat which measures footfalls in space and time. This is the same system that will be used to complete the initial screening with each subject to make sure that they have a large enough step asymmetry to participate in our study. The variables that will be measured are step length, double support, stance time and single limb support. Participants will walk across the electronic walkway at their self-selected comfortable walking speed (SSWS) for 10 trials and at their fastest possible, safe walking speed for 5 trials, totaling 15 trials during each evaluation session. Rest breaks will be provided between each trial.

Treadmill Training

Subjects will train on a Woodway split-belt treadmill in one of two conditions: 1) split-belt, with the paretic leg on the slow belt or 2) conventional treadmill with belts tied at the same speed.

Treadmill belt speeds will be determined based on a subject's over ground walking speed. For split-belt training, the fast belt will be set to the subject's fast over ground walking speed as measured during the 6 meter walk test and the slow belt will be half of this speed. We will choose which leg trains on the fast belt based on the step length asymmetry of the subject. If the paretic leg takes a shorter step, that leg will be trained on the fast belt and vice versa if it takes a longer step. This perturbation leads to after-effects that restore symmetry by increasing the fast trained step length and slightly decreasing the slow trained leg. For conventional training, the average speed will be 75% of the fast over ground walking speed. If it seems that this speed is too fast for the subject (based on a higher than expected heart rate or blood pressure value) we will decrease the belt speed by 10%. For split belt training both the slow and fast belt speeds will be decreased by 10%. Our goal will be to try to get the subject up to their overground speed as quickly as possible but we will only increase the speed when the Borg rate drops to or below 9.

Progression of training speed will occur based on the Borg rating scale. When the subject's average Borg rate for a single training session drops to 9 or below we will reassess the 6 meter *fast* walk test to determine if their split belt speeds can be progressed. If the Borg rating drops below a 9 but the subject's over ground walking speed does not seem to have changed when they do the 6 meter fast walk test their treadmill speed will be increased by 10% in order to bring them to a Borg rating above 9. The fast belt speed will equal the new fastest walking speed (or the 10% increase from the previous speed that the fast belt was going at) and the slow belt speed will be half of that speed.

Subjects will train on the treadmill with a goal of at least 20 minutes, but not more than 30 minutes each session. Treadmill training will be immediately followed by 10 minutes of over ground walking in 2 five minute bouts. This amount of training time is commonly utilized in post-stroke locomotor training interventions and is feasible in a clinical setting. During over ground walking the subject will be instructed to focus on

equal step length and stance time while walking. Twelve weeks was chosen because, based on preliminary testing, 4 weeks did not appear to maximize improvement and previous studies of treadmill training that have examined changes in spatiotemporal characteristics have found changes following 36 sessions (Plummer et al., 2007; Silver et al, 2000).

There may be stroke survivors who are not able to complete a total of 30 minutes of treadmill walking on the first day. These subjects will be progressed as quickly as possible to achieve the full 30 minutes. For each session, the amount of time trained will be recorded, allowing us to track the total training time for each subject. This information can then be used to preliminarily examine the relationship between amount of training time and outcome. In order to minimize loss of follow-up data, all follow-up sessions will be scheduled before the last training day. Subjects will either receive a reminder email or call (which ever they prefer) at least one week before their follow-ups to confirm that they are still able to come in on the dates that were arranged before their last training day.

The training will take place in either the Motion Analysis Laboratory at the Kennedy Krieger Institute or the Outpatient Center of the Kennedy Krieger Institute, whichever is available for that particular subject for that particular week. Participants are required to complete 33 sessions in no more than 16 weeks and to miss not more than 3 sessions (Plummer et al, 2007).

During the training sessions, the Borg Scale of perceived exertion (RPE) will be measured every 2 minutes and heart rate will be continuously monitored. For all sessions, the guidelines set forth by the American College of Sports Medicine (ACSM) for individuals in phase III or IV of cardiac rehabilitation will be followed. Based on these guidelines, a session will be terminated if any of the following conditions occur: a) Drop in systolic blood pressure of $\geq$ 10mmHg from baseline (resting for that day) despite increase in workload, b) Hypertensive response with a systolic blood pressure >240 mmHg and diastolic blood pressure >110, c) Presence of nervous system symptoms: ataxia, dizziness, or near syncope, d) Any chest pain or angina symptoms, e) Signs of poor perfusion such as cyanosis or pallor, f) Excessive fatigue, excessive shortness of breath, leg cramps, claudication. If any of the above occurs, the subject's physician will be contacted and informed of the subject's response to the activity. Subjects can also terminate any session or training bout by stating their desire to stop. An exercise bout will be stopped by the Researcher if a subject reports a rate of perceived exertion of 15 or greater or if their heart rate exceeds his/her Target Heart Rate (THR). The next five minute training bout will start when all of the following criteria are met: 1) subject states readiness; 2) at least 5 min of seated rest has occurred; and 3) RPE of $\leq$8.

Subjects will wear a safety harness during all treadmill training. During over ground walking, subjects will be guarded by the researcher.

Returning Subjects

In this pilot study, we would like to allow subjects to cross over to the other treatment arm (i.e. split-belt or conventional treadmill training). The protocol would be identical (e.g. subject would be cleared by physician, meet inclusion criteria) with one exception – we will not require the stress test for baseline visit 1 if the subject returns to the study within 6

months of finishing the other treatment arm. If a subject would like to wait more than 6 months to return, we will ask that they do the stress test again to make sure there is no change in their EKG.

b. Study duration and number of study visits required of research participants.
The study will take place over 41 total visits. There will be 1 screening visit, 2 baseline visits, with no more than a two week span between the two, 3 blocks of 11 training sessions (totaling 33 training sessions), 3 training evaluation sessions followed, 1 one month follow up and 1 three month follow up.

c. Blinding, including justification for blinding or not blinding the trial, if applicable.
The clinician performing testing will not be blinded as to subject group assignment (conventional vs. split-belt treadmill training) since this is a pilot study. However, subjects will be blinded to our hypothesis and their group assignment (though the split belt group will undoubtedly realize that they are training at 2 different speeds).

d. Justification of why participants will not receive routine care or will have current therapy stopped.
All subjects will receive standard care and current therapy will not be stopped. However, we will ask that they not change their previous therapy or activity level during the course of the study.

e. Justification for inclusion of a placebo or non-treatment group.
There will not be a placebo or non-treatment group—all subjects will receive training. The inclusion of a conventional treadmill training group will let us begin to assess whether split-belt treadmill training is in any way superior to standard treadmill training.

f. Definition of treatment failure or participant removal criteria.
A subject will be removed from the study if they miss 3 training session visits within a block of 11 training sessions.

g. Description of what happens to participants receiving therapy when study ends or if a participant's participation in the study ends prematurely.
If a subject's participation in the study is ended prematurely, discontinuation of the treadmill training will not be harmful to them. If the participant completes the training we will follow up with them 1 week, 1 month and 3 months after they have completed the training program to assess treatment effect and retention.

5. Inclusion/Exclusion Criteria

Inclusion	Exclusion
• chronic stroke involving cerebral cortical regions (>6 months post stroke). • completion of all acute rehabilitation therapy. • Ambulatory but with residual gait deficit (including those who use a cane or walker). • 10% or greater asymmetry in step length • age 20-80 • Written medical clearance • MRI reading with no cerebellar involvement	• any neurologic condition other than stroke • Folstein Mini-Mental State exam ≤ 23 for those with 9th grade education; ≤ 18 for those with education to 8th grade or less. • unstable angina • heart failure • uncontrolled hypertension (> 190/110 mmHg) • severe aphasia • total joint replacement in the lower extremities • orthopedic or pain conditions that limit walking • cerebellar signs (e.g. ataxic hemiparesis) • neglect (star cancellation test) failure (score < 44 indicates failure) • Pregnancy • Non- English speakers • Any EKG characteristics that would make this study unsafe for the patient to participate as deemed by the study team cardiologist

6. Drugs/ Substances/ Devices

a. The rationale for choosing the drug and dose or for choosing the device to be used. **We are using a new type of treadmill with two belts (one for each foot) that allows us to make the legs move at different speeds. We have found that short-term training on this device temporarily improves walking symmetry in stroke survivors. Here we will use this device in a long term study to try to make long lasting changes in walking symmetry. We are also using a Parvomedics metabolic cart to measure oxygen consumption and determine if any changes in the gait pattern from training improve each individuals economy of gait.**

b. Justification and safety information if FDA approved drugs will be administered for non-FDA approved indications or if doses or routes of administration or participant populations are changed. **N/A**

c. Justification and safety information if non-FDA approved drugs without an IND will be administered. **N/A**

7. Study Statistics

a. Primary outcome variable.
The primary outcome variables for this study will be step symmetry and economy of gait. Step symmetry is defined as the difference in the right and left step lengths and tells us how even the stepping pattern is. We define the economy of gait as the metabolic power, which is derived from the rate of O2 consumption and CO2 production, and normalized to the mass of the subject. This tells us the metabolic cost of walking. We predict that as subjects learn to take even steps, the metabolic cost of walking will go down.

b. Secondary outcome variables.
The secondary outcome variables for this study will be standard clinical measures including: over ground walking speed, the timed up and go test, 6 minute walking test, 6 meter walking test, and functional gait. We will also use two scales to assess how subjects feel about their balance and overall ability-- the Activities Specific Balance Confidence Scale and the Stroke Impact Scale.

c. Statistical plan including sample size justification and interim data analysis.
This is a pilot study of long-term training on the split-belt treadmill. We estimate that we need a minimum of 7 individuals per group to have enough between-subject and between-group variance for a valid power analysis.

d. Early stopping rules.

None

8. Risks

a. Medical risks, listing all procedures, their major and minor risks and expected frequency.
The potential risks in this study are very low. This study is entirely non-invasive. There is a slight risk that a subject might have an allergic reaction or be sensitive to the tape we use to stick the markers and surface electrodes to their skin.

During the neurological exam, the clinical exam and the walking and balance tests there is a slight risk of the subject losing their balance and falling.

During the treadmill tests, subjects may become fatigued during walking, may have slight muscle soreness after walking, and may lose their balance during treadmill walking. Since this is not an aerobic conditioning study, the cardiovascular risks are no greater than for normal walking.

For VO_2 walking testing subjects will have a mouthpiece attached to a tube that will allow us to measure the air they breathing in and exhaling. There is a slight chance of claustrophobia or discomfort with the mouthpiece in place.

For VO_2 peak testing risks are minimal but include fainting, dizziness, chest pain and cardiac dysrythmias. Myocardial infarctions are also considered a risk but we will monitor the patient with an EKG machine during the test.

For EKG testing there are very minimal risks according to the Mayo Clinic. There is a possibility of minor discomfort when removing the electrodes, much like when removing a band aid. It is rare that the electrodes may cause redness or swelling. There is no risk of electrocution as these electrodes only read the electrical activity of the heart. They do not emit any electricity.

There is a slight risk to the subject due to the time lost from work and school.

There is a risk to the subject's confidentiality of sensitive information.

b. Steps taken to minimize the risks.
Subjects will be given ample rest periods to avoid fatigue. Testing will be stopped if the subject becomes too fatigued to continue performing the movement comfortably.

Each subject will wear a gait belt during walking and balance tests; one or two investigators will be close by to assist and guard the subject at all times.

If subjects are aware that their skin is sensitive to tape or their skin becomes irritated by the tape, after we place the marker, we will use a stretchy stocking over the skin and then place the marker on the stocking. We will only use this technique if a subject is sensitive to the tape because placement of the marker directly to the skin provides more precise placement.

When on the treadmill, all subjects are placed in a safety harness that is connected to a ceiling mounted safety track. Subjects will also have a safety cutoff button and will be tethered to a magnetic safety cut-off switch, which when pulled, stops the treadmill (e.g. if they move too far back on the treadmill). All subjects will hold onto a handrail through the

duration of all experiments and are asked to practice stopping the treadmill with the safety button. An experimenter stands in front of the treadmill at all times.

For VO_2 recordings we will always have a researcher who will not only be in charge of the metabolic cart computer (which is next to the subject while they are on the treadmill) but we will also have that researcher constantly checking to make sure that the subject is feeling comfortable. We have different sized mouth pieces and will be sure to fit the appropriate one to each subject. All mouth piece and tubing is cleaned after each subject uses them that way every subject will be given clean materials to prevent any spreading of germs from saliva.

For VO_2 peak testing we will have a nurse present at all times conducting the EKG machine. The EKG will then be read by the cardiologist on our study team to determine if the abnormality will prevent the subject from further participating in our study and will be present during this particular test. The cardiologist will also view the patient's EKG from baseline visit 1 to determine if they are even eligible for the study to begin with.

With EKG testing we will be sure to remove the electrodes carefully to minimize any discomfort or redness. We will also ask subjects if they have any known allergies to the adhesives that are found on the electrodes before proceeding with the EKG.

Subjects will also wear a heart rate monitor during testing, and blood pressure will be monitored every 5 minutes at a break. We will use 80% of the age-predicted maximum heart rate or a Borg scale of perceived exertion of 15 for each subject as a threshold for stopping the treadmill to give a rest break.

We have a physician on the study team who has an office in our lab. He will always be aware of when we are bringing in a patient to do the VO_2 peak testing in case of an emergency.

This is not a cardiovascular aerobic training study since subjects walk at a normal pace on the treadmill. However, when the belts move at different speeds it can be slightly more demanding. Therefore, subjects will obtain medical clearance from their primary physician via a standard letter and form.

Subjects will be allowed to stop any test at any time, or rest between tests.

We will be flexible in scheduling appointments with the subject to reduce the risk of time lost from school and work.

All research materials will be kept confidential and all subject identification will be removed for analyses and presentations. Data will be presented in the aggregate without identifying information.

Subject's files and/or data diskettes will be kept in a locked file cabinet and access will be available only to members of the research team. Subject files will be identified by code numbers and letters. There will be a master list kept linking the subjects' names to the unique codes. This list will be kept on a double password protected computer and only the PI, co-investigators and research coordinator will have access to the list. All research materials will be kept confidential and all subject identification will be removed for

analyses and presentations. Data will be presented in the aggregate without identifying information.

c. Plan for reporting unanticipated problems or study deviations.
Adverse events and protocol deviations will be reported to the primary investigator, to the KKI Office of Research Compliance, JHM IRB, and to the sponsor using the appropriate adverse event reporting form.

d. Legal risks such as the risks that would be associated with breach of confidentiality.
Legal risks that would be associated with breach of confidentiality are minimal because all appropriate steps will be taken to maintain patient confidentiality as described in section 8b.

e. Financial risks to the participants.
None

9. Benefits

a. Description of the probable benefits for the participant and for society.

i. Individual participant
There are no known medical benefits for participants at this time.
Subjects will be informed that there may or may not be an improvement in their walking pattern from the treadmill training. The methods of the study should provide sensitive objective measures of motor deficits, which would be useful in diagnosis and in monitoring progress or the lack of it across time and therapy. This will be explained to all subjects.

ii. Society
This study is an important step towards developing new treadmill training treatments for people with hemiparesis. The potential benefits of this study are that we may understand whether specific types of long term locomotor training can help walking performance of people with hemiparesis. The risks to the subjects are minimal, and the benefit to society could be substantial.

10. Payment and Remuneration

a. Detail compensation for participants including possible total compensation, proposed bonus, and any proposed reductions or penalties for not completing the protocol.
We currently will not be able to pay subjects for their participation. They will receive free valet parking.

11. Costs

a. Detail costs of study procedure(s) or drug (s) or substance(s) to participants and identify who will pay for them.
There will be no cost to the subject; however, subjects will be responsible for the cost of meals they eat while at the Kennedy Krieger Institute.