PROTOCOL TITLE: Improving Mediolateral Walking Balance with an Assistive Exoskeleton

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1.0 Objectives / Specific Aims

The purpose of this study is to investigate the potential of exoskeleton assistance to improve walking balance using methods that will be accepted by people with stroke. The first specific aim is to characterize the effects of exoskeleton balance assistance on unperturbed walking. The second specific aim is to characterize the effects of exoskeleton balance assistance on perturbed walking.

We hypothesize that exoskeleton assistance will strengthen the relationship between step width and pelvis displacement relative to the stance foot, an important biomechanical strategy for ensuring walking balance. We anticipate that this relationship will be strengthened during both unperturbed and perturbed walking.

2.0 Background

Numerous exoskeletons have been developed with the goal of assisting walking,[1] including some available to consumers.[2] However, most devices (Ekso, HAL, Indego, ReWalk) do not assist balance,[2] preventing normal use of the arms by requiring users to rely on walkers, crutches, or canes. Alternatively, a few devices (Atalante, Rex) prevent falls by essentially carrying patients around,[2] rather than assisting strategies normally used to ensure balance. This approach is not viewed favorably by many patients, who would instead prefer an "exoskeleton to assist and correct their movement rather than walking for them".[3] While some early-stage work has developed exoskeleton control strategies that improve balance responses to anteroposterior pushes or slips,[4,5] mediolateral balance has been largely neglected despite its importance for gait stability and fall prevention.[6–9] We will test whether exoskeleton assistance can restore the normal mediolateral gait stabilization strategy of adjusting step width based on real-time pelvis dynamics.

Beyond the ability of an exoskeleton to alter gait mechanics, it must be accepted by users – which is unlikely if a device is perceived to make walking more difficult or otherwise interfere with the intended gait pattern.[3] This is a particular concern with balance, as individuals at a risk of falls are often resistant to changing their walking pattern,[10] likely because unfamiliarity is perceived as risky. Here, we will assess physiological and psychological indicators of participants' acceptance of the exoskeleton assistance.

In summary, despite the critical importance of walking balance, assistance of mediolateral balance is largely limited to walkers and canes that must be controlled with the arms, limiting performance of real-world tasks. The proposed work will address this gap through testing of an assistive control strategy based on a mechanistic understanding of walking balance.

3.0 Study Endpoints

Our primary outcome measure will be the partial correlation between step width and pelvis displacement at the start of a step (ρ_{SW}).[11] Secondarily, we will quantify the average bilateral gluteus medius activity during the stance and swing phases of the gait cycle. We will also quantify Rating of Perceived Stability[12], a validated psychological measure of balance difficulty. Finally, for trials in which mediolateral pulls are applied, we will quantify the change in mediolateral foot placement relative to unperturbed steps.

4.0 Inclusion and Exclusion Criteria/ Study Population

Participants will be recruited from an MUSC database containing the contact information of stroke survivors who have agreed to be contacted for research participation (Pro00037803). Initial screening will be performed by study staff through a phone call to confirm basic participant characteristics (e.g., timing of stroke) and interest in research participation. The ability of potential participants to meet the more detailed inclusion and exclusion criteria will subsequently be determined in person.

Inclusion Criteria

- Evidence of a stroke at least 6 months prior to participation
- Evidence of dysfunction of the paretic lower limb (Fugl-Meyer lower extremity motor score < 34)
- At least 21 years of age
- Self-reported experience of a fall in the previous year, and/or a fear of falling
- Gait speed of at least 0.2 m/s
- Ability to walk on a treadmill without a cane or walker
- Ability to follow three step commands and communicate with experimenters to answer questions (e.g., regarding their balance confidence)
- Provision of informed consent

Exclusion Criteria

- Resting blood pressure higher than 220/110 mm Hg
- History of unstable cardiac arrhythmias, hypertrophic cardiomyopathy, severe aortic stenosis, angina or dyspnea at rest or during activities of daily living
- Preexisting neurological orders or dementia
- Legal blindness or severe visual impairment
- Presence of neglect
- History of DVT or pulmonary embolism within 6 months
- Uncontrolled diabetes with recent weight loss, diabetic coma, or frequent insulin reactions
- Orthopedic injuries or conditions (e.g., joint replacements) in the lower extremities with the potential to alter the gait pattern

We plan to include a diverse participant population, paralleling the general demographic characteristics of the Charleston area. This will be accomplished using the database referenced above, which currently contains contact information for over 1000 individuals. We will not exclude any sex/gender or racial/ethnic group. This study will not involve any special classes of subjects, including fetuses, neonates, pregnant women, children, prisoners, institutionalized individuals, or other vulnerable populations. Children will not be included because this study focuses on individuals who have experienced a stroke. This is rare among children, and would be expected to involve a different mechanism or pattern of recovery.

5.0 Number of Subjects

A total of 21 individuals with chronic stroke will be recruited, all locally.

6.0 Setting

All research, including all recruitment, data collection, and data analysis, will be performed at the MUSC College of Health Professions Research Building at 77 President St. Charleston, South Carolina. North Carolina State University received the center grant funding that supports this center subproject, but is not otherwise involved in conducting the research that is part of this study.

7.0 Recruitment Methods

This study will recruit from the Registry for Stroke Recovery (RESTORE-Pro#00037803, IRB approved 9/6/14), which is a research tool sponsored by the National Institutes of Health (NIH) Center of Biomedical Research Excellence (COBRE) in Stroke Recovery with subjects consented for future contact to support stroke recovery research conducted at MUSC. RESTORE staff will query the registry for potential subjects and provide the Principal Investigator (PI) with the contact information of subjects who meet their criteria. The PI or research staff will contact subjects to further screen for potential enrollment.

8.0 Consent Process

Informed consent will be obtained from participants prior to participation, using a form approved by the MUSC IRB. Participants will first be informed of the purpose of the experiments and possible risks. A member of the study staff will then review the Informed Consent form with the potential participant, ensuring they are given adequate time to review the document. The potential participant will be asked if they have any questions about the study, and asked if they agree to participate. The Informed Consent form will be signed by the participant. Copies of the signed forms will be given to the participant. The consent process will take place in a private room in the MUSC College of Health Professions Building. There will be no set period between informing the prospective participant and obtaining the consent. Participants will be reminded that they may end their participation in the study at any point.

9.0 Study Design / Methods

A total of 21 people with chronic stroke will be recruited for this study. The study will consist of four experimental sessions: Session 1A, Session 1B, Session 2A, and Session 2B.

Session 1A. A trained study team member will assess participants' general function using several common clinical assessments:

- Functional Gait Assessment: a test of walking balance
- Lower Extremity Fugl-Meyer motor score: a test of leg motor function
- Activities-specific Balance Confidence scale: a questionnaire about balance confidence
- Fall history questionnaire: a questionnaire about participant's self-reported fall history and fear of falling
- Psychosocial Impact of Assistive Devices scale: a questionnaire about the effects of an assistive device on functional independence, well-being, and quality of life

For familiarization, participants will don the exoskeleton to be assessed in this study (described in the Devices section below). Participants will perform four 2-minute treadmill walking trials at their self-selected speed while wearing the exoskeleton, which will alternate between not applying forces (transparent mode) and applying assistive forces to help appropriate foot placement location when talking a step.

Session 1B. Participants will perform ten 2-minute treadmill walking trials at their self-selected speed. Two trials will be performed for each of five conditions:

- No Exoskeleton. The participant will not wear the exoskeleton.
- Zero Impedance. The participant will wear the exoskeleton, but it will not provide the user with assistance or resistance.
- Low Impedance. The exoskeleton will assist participants in placing their foot in a mechanically-appropriate location when stepping, with a stiffness of 0.1 Nm/deg and damping of 0.01 Nm/deg*s. This assistance is weak, essentially "nudging" participants toward the target foot placement.
- Medium Impedance. The exoskeleton will assist participants in placing their foot in a mechanically-appropriate location when stepping, with a stiffness of 0.2 Nm/deg and damping of 0.02 Nm/deg*s. This assistance is moderate, as it will be noticeable to participants, but could still be resisted.
- High Impedance. The exoskeleton will assist participants in placing their foot in a mechanically-appropriate location when stepping, with a stiffness of 0.3 Nm/deg and damping of 0.03 Nm/deg*s. This assistance is strong, as it will essentially enforce the target foot placement.

After completing the walking trials in Session 1B, participants will complete the Modified ASSET Psychosocial Measure, a questionnaire that asks participants questions about the exoskeleton.

Aim 1 experiments (Sessions 1A and 1B) for all participants will be completed before progressing to Aim 2 (Sessions 2A and 2B). Therefore, we anticipate that many participants will experience an extended time between Sessions 1B and 2A.

Session 2A. This session will repeat the procedures for Session 1B, serving to identify each individual participant's optimum assistance level for subsequent use in Session 2B.

Session 2B. Participants will perform ten 2-minute treadmill walking trials. In one trial, participants will not wear the exoskeleton. The remaining nine trials will consist of every combination of three exoskeleton conditions and three perturbation conditions.

The exoskeleton conditions are:

- Zero Impedance. The participant will wear the exoskeleton, but it will not provide the user with assistance.
- Group Optimum Assistance: The exoskeleton will provide assistance using the parameters found to produce the largest group-average positive effect in Aim 1.
- Individual Optimum Assistance: The exoskeleton will provide assistance using the parameters identified as optimum for each individual participant in Session 2A.

The perturbation conditions are:

- Speed Perturbations: The treadmill speed will follow a sinusoidal pattern, gradually changing from 0.2 m/s less than their self-selected speed to 0.2 m/s greater than their self-selected speed and back over a period of 20 seconds.
- Vision Perturbations: While walking, participants will turn their heads to look at visual targets 45^{o} to the left and right of their heading direction, as cued every 10 seconds.
- Mediolateral Pull Perturbations: While walking, participants will experience mediolateral pulls delivered at the level of the sacrum[13]. These perturbations will be delivered at the start of the swing phase with a peak magnitude of 12% body weight and a duration of 200 ms.

To eliminate the risk of participants falling while experiencing perturbations, participants will wear a harness attached to an overhead rail during all treadmill and overground walking trials. This harness will not support body weight, but would prevent participants from falling in the case of a loss of balance. The adhesive used to secure the LED markers and EMG electrodes to the skin may produce the risk of minor skin irritation. We will reduce this risk by asking participants if they have had any previous experience of skin irritation in reaction to specific gel or tape types, and by checking the participants' skin after each experiment.

In return for participants' time and effort, they will be paid $200 for participation in the study. If they do not complete the study, they will be paid $50 for each completed visit. Payments that participants receive from MUSC for participating in a research study are considered taxable income per IRS regulations. Payment types may include, but are not limited to: checks, cash, gift certificates/cards, personal property, and other items of value. If the total amount of payment a participant receives from MUSC reaches or exceeds $600 in a calendar year, they will be issued a Form 1099.

10.0 Data Management

For Aim 1, all statistical comparisons will involve data collected in Session 1B. For our primary analysis, we will use paired t-tests (α=0.0125 to account for multiple comparisons; using non-parametric methods if appropriate) to compare ρ_{SW} values for normal walking

trials with each exoskeleton condition. Secondary analyses with the same structure will be performed to investigate potential differences across trials in average stance and swing phase gluteus medius activity, and Rating of Perceived Stability.

For Aim 2, all statistical comparisons will involve data collected in Session 2B. Each perturbation type will be analyzed separately. For speed and vision perturbations, we will use paired t-tests (α=0.025 to account for multiple comparison) to compare ρ_{SW} values between the zero impedance condition and each exoskeleton assistance condition. Secondarily, we will perform the same analyses with stance and swing phase gluteus medius activity and Rating of Perceived Stability. For mediolateral pull perturbations, we will perform an analysis with the same structure to compare the changes in mediolateral foot placement (relative to unperturbed steps).

The sample size is based on a power analysis using data from previous studies in our lab, which revealed an effect size of assistance of 0.9.[14] For Aim 1, with an alpha value of 0.0125, the sample size of 21 will provide 90% power. For Aim 2, with an alpha value of 0.025, a sample size of 18 (in case of dropout) will provide 90% power.

Steps will be taken to minimize the risk of loss of confidentiality. Participants will be assigned a code, and all collected study data will be associated with this code, not with the participant's identity. The only links between participant code and identity will be in a study binder stored in a locked filing cabinet and an electronic enrollment document stored on a password protected server. All published data will be de-identified, and will not include any identifiable data. All data will be stored on a password-protected secure server that is backed-up nightly.

The RESTORE registry (Pro#00037803), from which this study will recruit subjects, also serves as a data analysis tool by which interdisciplinary teams may share data across projects and provide MUSC's stroke recovery research community with a more complete registry with key stroke elements. Some subjects may have participated or will participate in other stroke related research studies at MUSC. Sharing data from this and other stroke research studies with RESTORE will allow for more targeted recruitment efforts in the future and could reduce the burden placed on subjects by reducing the duplicative efforts of collecting common data and physical function assessments requested by multiple studies and storing them in one centralized and secure location.

Subjects are informed in the consent process if they enroll into the RESTORE registry, their data from this study will be shared. Subjects will be asked to sign an authorization stating their health information may be disclosed to MUSC investigators requiring their data for their research projects upon approval by an Institutional Review Board.

11.0 Provisions to Monitor the Data to Ensure the Safety of Subjects

The study PI will be responsible for reviewing the collected data on a weekly basis to ensure data quality. All negative health events will be reported to the PI within one day of occurrence, for determination whether they qualify as adverse events.

Any adverse events will be recorded, monitored, and promptly reported to the IRB, following policy HRPP 4.7. Our exclusion criteria will minimize the risk of enrolling participants with severe cardiovascular risk. Scheduled rest breaks will be provided between trials during experimental testing, as well as whenever requested. Minimization of

risk of adverse events will be accomplished by monitoring vital signs during trials in which subjects are performing potentially demanding exercise.

12.0 Withdrawal of Subjects

Participants will be withdrawn from the study without their consent if study staff determine that the participants are at risk of negative health events (e.g., large change in blood pressure from the initial screening assessment; consistent inability to maintain balance while walking on the treadmill). If a participant voluntarily withdraws from the study, their results will not be included in our data analysis, as our sample size accounts for anticipated dropout.

13.0 Risks to Subjects

Potential risks for participation in this study are low. Participants will wear an exoskeleton that can exert moderate sideways forces on their legs while walking. The exoskeleton has both software and hard mechanical stops that prevent the device from approaching the ends of the physiological range of motion. This device has been safely used to influence step width while walking with no negative effects.[15] In some trials, participants will be mechanically perturbed while performing walking trials, thus creating the risk of a loss of balance. To mitigate the risk of possible negative effects of a loss of balance, participants will wear a safety harness attached to an overhead rail. The harness is designed to eliminate the consequences of falling as the device "catches" the subject should they trip or stumble. Additionally, in all walking trials, an investigator will be near the participant to provide assistance in the event of a loss of balance. To this point, over 100 people with chronic stroke (and many more neurologically-intact adults) have participated in studies investigating the effects of our perturbation devices. No adverse events related to the participants' interaction with these devices have occurred.

There is also the risk of minor muscle soreness due to the exercise of walking. This risk will be mitigated by walking only at speeds that are comfortable for each participant, and allowing rest breaks if participants ever indicate they are fatigued.

General post-stroke function will be assessed using several commonly-used clinical tests. There is a risk of a loss of balance during the Functional Gait Assessment, in which individuals perform various functional gait tasks. We will mitigate this risk by having a trained clinician always next to participants, as is common in a clinical context. The other clinical tests either involve verbal questions or are of minimal physical risk.

All research studies have the risk of loss of participant confidentiality. Our Data Management Plan (see above) will minimize this risk.

14.0 Potential Benefits to Subjects or Others

We do not anticipate any direct benefit to participants in this study. However, we anticipate that the results of this study will contribute to the development of an assistive device with the potential to improve the functional mobility and quality of life of future users with chronic stroke. As the risks to participants are low, we believe that the risks are reasonable with respect to the anticipated future benefits.

15.0 Sharing of Results with Subjects

Research will be in the form of research data, and will not be shared with participants or others while the study is ongoing. Once the study is completed, de-identified data will be shared with the scientific community and study participants.

16.0 Drugs or Devices

This study involves a non-invasive exoskeleton that was developed at North Carolina State University, in collaboration with this study's PI (Dean). This device has two degrees of freedom at the hip, allowing passive motion for hip flexion/extension while applying joint torques in the hip abduction/adduction direction.[15] The peak hip torque that can be produced is 57 Nm, approximately half of the average torque that can be produced voluntarily by neurologically-intact individuals,[16] and thus does not risk producing excessively large joint torques. The torques are generated using admittance control, which prevents rapid torque fluctuations that may be destabilizing. The device interfaces with participants through cloth straps designed for comfort. The device itself is attached to an overhead rail, which would support the weight of the device in case the user experiences a loss of balance. This device has been approved by the North Carolina State University Institutional Review Board, and was deemed to be a Nonsignificant Risk Device. This study also involves a non-invasive perturbation device used to apply mediolateral pulls to participants while they walk on a treadmill, which was developed by this study's site PI (Dean).the perturbation device has been judged by the MUSC IRB to meet the criteria for a Nonsignificant Risk Device (as in the protocols Pro00062108, Pro00101810).

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