

Version Date: 5/22/2015

Project Title: Community-based walking exercise enhanced by orthoses to improve walking ability in patients with peripheral artery disease

Principal Investigator
Ryan J. Mays, PhD, MPH

Co-Investigators
Ryan L. Mizner, PhD, PT; Ashley A. Mays, MD, FACC

A. Background, Hypotheses and Specific Aims

A.1. Background

Peripheral artery disease (PAD) occurs as a result of the development of plaque in the arteries of the lower limbs. The blockages cause a reduced blood flow to the muscles of the legs. This reduction in blood flow may cause PAD patients to experience intermittent claudication (IC), which is characterized by pain, cramping, and/or aching in the muscles of the legs during exertion that resolves with rest.¹ Consequently, walking ability is significantly impaired resulting in a sedentary lifestyle as well as poor patient-reported outcomes.²

Supervised walking exercise programs in hospital settings are an effective therapy for improving walking ability of PAD patients with IC.^{3,4} However, these types of programs currently do not exist outside of research settings primarily due to a lack of insurance reimbursement as well as poor proximity to healthcare facilities.⁵ In contrast to supervised walking exercise programs, community-based walking exercise programs for patients with PAD have met with discouraging results for improving walking ability.^{6,7} Exercise training in the community to treat PAD typically consists of upfront advice from healthcare providers for patients to walk, which is the standard of care. These programs often fail due to a number of reasons, however one of the most prominent barriers is IC experienced by PAD patients during ambulation.^{8,9} **The calf muscle is the most frequently reported location of IC,¹⁰ thus it is critical that new strategies are developed to attenuate calf pain during walking exercise training in community settings.**

The recent development of novel ankle foot orthoses (AFO) have led to significant improvements in walking ability in patients, particularly those with impaired ambulation (e.g., patients with a stroke).^{11,12} The AFO (Figure 1) are made of light-weight, low profile carbon-fiber materials that store elastic energy early in a footstep followed by a release of the stored energy during the propulsive phase of walking that assists calf muscle function.¹¹⁻¹³ These devices are relatively low cost and minimally invasive and may acutely improve PAD patients' ability to walk. **To date, using an AFO to circumvent restrictions to walking (calf pain) in PAD have not been completed and may provide patients with an opportunity to improve their walking ability.** Additionally, the impact of an AFO on biomechanical parameters in PAD patients is unclear as there are few studies examining this important component of ambulation. A full assessment of calf muscle function using motion analysis may provide new insight into the mechanistic limitations PAD patients' experience. **Thus, an AFO used to aid PAD patients' walking ability could potentially lead to a new therapeutic method for PAD patients.**

A.2. Hypothesis and specific aims

We will test the hypotheses that PAD patients using an AFO during a graded exercise test will demonstrate a greater peak walking time (PWT) compared to PWT assessed without the use of the AFO.

Specific Aim 1. Examine the effect of an AFO on the primary outcome of PWT assessed using a graded treadmill test for PAD patients. Determination of PWT (defined as the maximal time a patient walks on a graded treadmill test) with and without the AFO will be important for understanding its potential utility for improving walking ability in PAD. Secondary outcomes will include claudication onset time (COT), defined as the point when leg pain first occurs during walking, functional ability (assessed via the 6-minute walk test) and peak oxygen consumption (VO_{2peak}) with and without the AFO.

Specific Aim 2. Evaluate the capacity of an AFO to assist calf muscle function during walking in patients with PAD and IC. The device may decrease the mechanical demands of the calf, thus patients will receive a motion analysis assessment during walking with and without the AFO. Outcomes will include ankle power during propulsion and calf muscle recruitment analyses using electromyography sensors during walking.

Specific Aim 3. Examine the effects of an AFO following a walking exercise program. The device may improve primary and secondary outcomes following 12 weeks of community walking (standard of care). Outcomes will include PWT, COT, functional ability, VO_{2peak} and patient-reported outcomes assessed with the Walking Impairment Questionnaire (WIQ) and the Medical Outcomes Study Short Form 36-item questionnaire (SF-36).

B. Study Design and power calculation

B.1. Study design

The proposal will utilize a prospective cohort design. We will recruit a total of 15 male and female patients with PAD and IC who are ≥ 40 years of age. Patients will be diagnosed with PAD at the vascular clinics of the International Heart Institute (IHI) within St. Patrick Hospital and its affiliated outreach sites within their network of providers or will be screened per standard guidelines if not receiving care from IHI (see **D.2.d. Ankle-brachial index assessment**).

B.2. Power calculation

Sample size was calculated to evaluate differences in PWT with the AFO vs. without during graded exercise testing. The estimates were based on data from a previously conducted clinical trial¹⁴ composed of 25 PAD patients who were randomized to a new detailed community-based walking program or the standard of care (upfront advice to exercise). Based on an effect size of 0.94, a sample of 12 patients is estimated to provide 80% power at $\alpha=0.05$ to detect a significant difference in PWT. To account for a 20% attrition rate, 3 additional patients are needed (total sample $n=15$).

C. Patient recruitment and inclusion/exclusion criteria

Primary recruitment sites will be from the IHI clinics in Missoula, MT as well as IHI's clinical outreach sites throughout Western Montana and Idaho. This includes the following locations: 1) IHI at Community Hospital Anaconda, MT, 2) IHI-Butte, MT, 3) IHI at Powell County Medical Center, Deer Lodge, MT, 4) IHI at Marcus Daly Memorial Hospital, Hamilton, MT, 5) IHI-Helena, MT, 6) IHI-Plains, MT, 7) IHI at St. Joseph Medical Center, Polson, MT, 8) IHI at St. Luke Community Clinic, Ronan, MT, 9) IHI at Steele Memorial Hospital, Salmon, ID, 10) IHI at Seeley-Swan Medical Center, Seeley Lake, MT, 11) IHI at Life Span Medical Clinic, Stevensville, MT and 12) IHI at Thompson Falls, MT. Additionally patients will be recruited from the physical therapy clinics at the University of Montana and in the local community via posted advertisements and emails to the University and hospital communities. The study doctor and Co-Investigator Ashley Mays, MD will medically approve all patients for inclusion into the trial.

Patients will be provided a copy of the consent. Patients will meet with the study staff who will explain the study to them and discuss their primary reasons and motivation for wanting to volunteer in the trial. The study team will also discuss any practical problems such as planned vacations that could interfere with completion of the trial in a timely manner. Any questions the patients have regarding the trial will be answered and the patients must demonstrate their ability to provide informed consent by describing in detail their understanding of the study goals and what is expected of them. Patients are given a signed copy of the consent form, with signed copies placed in separate study charts (separate from PHI). A HIPAA authorization form will also be obtained from patients during the first study visit. All research study team members have completed relevant protection of human subjects' modules per regulatory standards.

C.1. Exclusion criteria

- Lower extremity amputation(s) which interfere(s) with walking.
- Critical limb ischemia (i.e., ischemic rest pain, ulcers/gangrene on the lower extremities).
- Non-atherosclerotic PAD (e.g., popliteal entrapment syndrome, Takayasu's arteritis)
- Major surgical procedures that are contraindicated to an exercise program (e.g., recent organ transplant) or coronary artery bypass graft within 6 months prior to screening.
- Primarily limitations to exercise due to chronic obstructive pulmonary disease, angina or heart failure.
- Myocardial infarction within 3 months prior to screening.
- Acute coronary syndrome symptoms diagnosed at time of screening.
- Significant ischemic changes (documented on the 12-lead electrocardiogram) which horizontal or down-sloping ST-segment depression ≥ 0.5 mm at rest and >1 mm with exercise in 3 beats for 2 contiguous leads, relative to the PR-segment (or ST-segment elevation ≥ 1 mm).
- Transient ischemic attack or stroke 3 months prior to screening.
- New left bundle branch block or sustained ventricular tachycardia of >30 seconds during screening.
- Uncontrolled hypertension defined as ≥ 180 systolic or ≥ 100 diastolic resting blood pressure during screening.
- Woman who are pregnant (women of childbearing potential, a pregnancy test will be performed at screening).
- Individuals currently incarcerated.
- Evidence of acute impairment from alcohol or other illicit drugs.
- Lack of diabetes control (glycated hemoglobin $>12\%$).
- Patients who are anemic (Hgb <11 g·dL⁻¹ for women and <10 g·dL⁻¹ for men).

- Any other clinically significant diseases (e.g., pulmonary, renal, psychiatric, immunological) that are not stabilized or may otherwise confound the results of the study.
- Individuals meeting exclusion criteria may still be recruited into trial with the approval for participation by a physician.

D. Methods

D.1. AFO: We will provide patients with two AFO devices (one for each leg). Prior mechanical analysis of walking in PAD revealed deficits in both limbs for ankle power production for those who experience IC.¹⁵ We will use a standard carbon-fiber AFO model (see Figure 1) that is commercially available to enhance the clinical meaningfulness of the pilot trial (see section G. Measures to minimize potential risks and discomforts below for patient fitting details). The design of this AFO provides considerable energy storage potential to maximize the effect of the calf muscle augmentation in this initial pilot project.



Figure 1. Example of carbon-fiber AFO for use in walking exercise

D.2. Assessments and Outcomes

D.2.a. Health history and physical exam: Patients will complete a health history form (attached). Questions pertaining to their health and any recent adverse events will be discussed with each patient. The initial health history examination is important for reviewing inclusion/exclusion criteria for the study. Height and weight will be recorded, followed by a physical exam conducted by a physician/PA/NP (unless extensive medical records in EPIC available). Calf and quadriceps muscle circumferences will be measured at baseline and at 12 week outcome visits using a constant tension spring loaded tape.

D.2.b. Vital signs: Vital signs will be assessed at all outcome assessment study visits. This will include resting heart rate (beats·min⁻¹), standing systolic and diastolic blood pressure (mmHg) and sitting blood pressure using a standard electronic or manual sphygmomanometer. Patients will be asked to breathe normally while the study team performs the assessments.

D.2.c. Blood draws: Patients will be asked to fast for 10 hours prior to outcomes assessment visits. Six teaspoons of blood will be drawn from the patient to assess the following: 1) complete blood count, 2) glycated hemoglobin, and 3) lipid panel.

D.2.d. Ankle-brachial index (ABI) assessment: ABIs will be performed prior to the initial graded exercise test according to published methods for screening purposes and standard outcome assessment.¹⁶ Measurements will be of the left and right systolic pressures for 1) brachial arteries, 2) dorsalis pedis arteries, and 3) posterior tibial arteries. The method utilizes a Doppler ultrasound to detect the systolic blood pressure. The highest of the arm pressures is used as the denominator. The numerator for the ABI of each ankle is derived from the highest of the dorsalis pedis or posterior tibial pressures. The leg with the lowest ABI is identified as the index leg. *Note that in the event a patient has not been diagnosed with PAD, a separate ABI assessment may need to be completed prior to fitting the patient for the AFO devices.*

D.2.e. Graded exercise tests: The graded exercise tests will be conducted on a treadmill using the Gardner protocol as previously described¹⁷ with continuous electrocardiogram monitoring in the Montana Peripheral Artery and Cardiac Exercise (PACE) Laboratory (directed by Dr. Ryan Mays) at IHI. Patients will complete two separate outcome assessment visits within 1 week. Outcomes will be assessed with the AFO and without the AFO over the first 2 baseline visits (order randomized to avoid test bias). PWT (min) will be recorded as the maximal time the patient can walk on the treadmill before having to stop due to severe leg pain (**Specific Aim 1**). COT (min) will be obtained with the patient pointing to the pain scale at the initial presentation of leg pain. An open-circuit respiratory-metabolic system will be used to measure VO_{2peak} (ml·kg⁻¹·min⁻¹).

D.2.f. Functional ability and patient-reported outcomes: Patients will complete the 6-minute walk test with and without the AFO during the two separate outcome assessment visits to evaluate the immediate effect of the AFO. Patients will walk in a 50 foot corridor at the hospital as previously reported.¹⁸ Maximal walking distance achieved in 6-minutes and COT will be assessed at each outcome time point. The WIQ and SF-36 questionnaires will be administered as previously described.^{19,20}

D.2.g. Three-dimensional gait analysis of self-paced walk: Motion analysis testing for lower extremity joint kinetics (forces) and kinematics (motion) during self-paced walking will be performed using an eight-camera motion analysis system with two force plates (**Specific Aim 2**). Anatomical landmarks for the trunk, pelvis, thigh, and shank (part of the leg between the knee and ankle) will be placed per Dr. Mizner's published methods involving gait analysis of

patients with total knee arthroplasty.^{21,22} Recruitment levels for the calf during propulsion will be measured via surface electromyography sensors and analyzed using established methods.²³ Multiple trials of walking with and without the AFO will be compiled for analysis (~1 hour). The outcomes to be measured are ankle power during propulsion and calf muscle recruitment.

D.3. Standard of care enhanced by AFO: Following baseline assessments, patients will complete 12 weeks of walking exercise in the community. We will advise patients to walk as much as possible for several days per week. Patients will be provided the AFO to use during walking exercise as well as during daily activities requiring ambulation. Patients will again complete two study visits within 1 week (two separate days) following the 12 week time period to assess outcomes following usage of the AFO. We will compare outcomes with a historical cohort of PAD patients (**Specific Aim 3**) who were previously given the standard of care for walking in the previous clinical trial conducted by Dr. Ryan Mays.¹⁴ Please see Table 1 below for outcome assessment time points and schedule of visits.

Table 2. Schedule of visits for the trial

Procedures	Initial visits			Community walking	Follow-up	
	Visit 1	Visit 2	Visit 3 (1 week after Visit 2)	12 weeks	Visit 4 [†]	Visit 5 (1 week after Visit 4)
Timeline (MM/DD/YR)						
Length of Visits	30 min	3 hours	3 hours	--	3 hours	3 hours
Informed consent/HIPAA	X					
AFO fittings	X					
Health history forms		X				
Physical exam		X*				
Calf and quadriceps measurements		X			X	
Heart rate and blood pressure	X	X	X		X	X
Blood draws		X			X	
Finger stick		X ^Δ	X ^Δ		X ^Δ	X ^Δ
Questionnaires			X		X	
Ankle-brachial index	X**	X			X	
ECG		X	X		X	X
Graded exercise test		X	X		X	X
6 minute walk test		X	X		X	X
Upfront walking advice using AFO				X		
Motion analyses at University of Montana		X			X	

^ΔFor patients with diabetes; *Only if no electronic medical records available; [†]Indicates 12 weeks after Visit 3

**For patients who have not been previously diagnosed with PAD

List of abbreviations

AFO, ankle-foot orthoses; ECG, electrocardiogram; HIPAA, health insurance portability and accountability act

E. Assurance of privacy and confidentiality

As previously mentioned, the study will be primarily conducted at the Montana PACE Laboratory at IHI in Suite 356A. Initial fittings of the AFO will occur at a local off-site location (with a certified prosthetist/orthotist), with motion analyses to be completed at the University of Montana Movement Science Laboratory (directed by Dr. Ryan Mizner). Consent will be obtained in a quiet room at the prosthetist/orthotist location, with the door closed to ensure privacy for the patient. Additionally, all clinical study visits will be conducted in a private exercise testing room and within hallways at IHI. Testing at the Movement Science Laboratory will ensure privacy of the patients as the laboratory regularly conducts research trials with human subjects (e.g., private testing area within the University). Additionally, confidentiality of patient data will be maintained. Paper documents for the study will be stored in a locked cabinet located within the PI's office at the IHI. Study data will be maintained for a period of 7 years after IRB acknowledgement of study closure (per standard HIPAA regulations). After that time, any material that could potentially be used to identify a patient will be discarded in a locked, confidential files disposal unit.

F. Potential risks and discomforts

- Confidentiality and privacy: The use of patient-reported questionnaires, compiling personal medical information, attendance at the off-site prosthetist/orthotist setting and walking in the community pose minor risks to confidentiality and privacy and may cause embarrassment.
- Blood draws: There is a small risk of local hematoma, infection, and thrombosis associated with intravenous blood sampling.
- ABI: There is a small risk of bruising and discomfort where the blood pressure cuff is placed on the arm and ankles.
- ECG: An initial skin prep (using NuPrep gel) poses a small risk of irritation and discomfort of the skin. Additionally, the electrodes are “sticky” and there could be mild discomfort when electrodes are removed (e.g., like a piece of tape being removed from the skin). Additionally, in the event a patient has a high volume of hair on the upper torso, there is minor discomfort potentially with the required shaving needed to ensure adequate impedance levels are obtained with the electrocardiogram system.
- Graded exercise test and exercise training: Graded exercise tests are standard procedure conducted in hospital settings (thousands of advanced cardiovascular patients every year receive these tests). The cardiac event rate in a mixed adult population (includes acute myocardial infarction, ventricular fibrillation, hospitalization and death) is approximately 6 per 10,000 tests.²⁴ Other minor risks of the graded exercise test include dryness of the mouth/throat or slight bleeding of the gums due to the respiratory-metabolic analyzer mouthpiece. The risks associated with the standard of care for walking exercise and PAD are minimal as virtually healthcare providers encourage patients to adopt a walking exercise program.
- AFO: There is a small risk of discomfort and skin wear from the AFO where it contacts the lateral and/or medial part of the ankle. The strapping that holds the shin plate in place can also apply some pressure leading to potential discomfort and areas of wear on the skin. Additionally, there may be a risk of falling while using the devices.
- Motion analysis: The only risk associated with the motion analysis tests is minor skin irritation or discomfort when removing the adhesive tape that is used to hold reflectors and sensors to the skin.

G. Measures to minimize potential risks and discomforts

- Confidentiality and privacy: Personal identifying information will not be included, when possible, and study visits will be conducted in a private setting. Potential embarrassment during community-based exercise will be minimized, as patients can choose where they exercise (e.g., park, neighborhood) in addition to the AFO being a low-profile device (unlike walking canes or strollers).
- Blood draw: Standard methods for extracting blood samples for subsequent analysis will be followed. Samples will be obtained from trained phlebotomists at St. Patrick Hospital.
- ABI: To ensure appropriate assessment of patient's arm and ankle pressures, standard procedures will be conducted per published methods. We will not inflate the cuff above 220 mmHg and the rate of pressure decrease will be in accordance with best practices.
- Graded exercise test: Dr. Ryan Mays (PI) has extensive experience in clinical exercise testing and training for patients with PAD. The IHI has a full complement of Advanced Cardiovascular Life Support (ACLS) certified healthcare providers (e.g., cardiologists, physician assistants, nurse practitioners) to monitor exercise stress test electrocardiograms for patients enrolled into the trial. Dr. Ashley Mays is the study doctor for this trial and will provide oversight of stress testing. IHI has necessary resuscitative equipment (e.g. crash carts) and trained personnel available if a patient experiences an adverse event during exercise testing. Additionally, in the event of an acute myocardial infarction during exercise testing, the IHI Cardiac Catheterization laboratory is ~50 meters from the Montana PACE lab. The stress tests are critically important for determining the safety of any exercise activity the patients will complete. The likelihood of an adverse event caused by exercise training is most likely to occur during the stress test when the critical equipment and personnel are available to respond to such an event. Patients who are unable to safely complete the graded exercise test due to an abnormal event will be categorized as high risk and excluded from participation in the trial. The dryness of the mouth and throat will be minimized by allowing the patient to drink water prior to the test as needed. A thorough description of the device will be explained to patients' (informed the mouthpiece is similar to "snorkel" or “mouth guard”) and that slight bleeding of the gums from contact with the mouthpiece is not serious and common during use.
- Vulnerable populations: Pregnant woman may not be included in this study. Pregnancy testing will be requested if their menstrual cycle is more than one week overdue or if they suspect they are pregnant. We don't anticipate this

being a concern, as the average age of PAD patients is in the mid-60's and thus the vast majority of women PAD patients are post-menopausal.

- AFO: The devices will be fitted and sized by a certified prosthetist/orthotist experienced with using carbon fiber orthotics. The AFO selected for this study is commercially available to patients and has been in use for an extended period of time. The AFO is purposefully designed with a lateral and/or medial positioned strut to connect the shin and foot plate thus eliminating the most common source of skin irritation on the medial portion of the foot and ankle. Commonly practiced safeguards to monitor the skin's response to the AFO will be offered to the patient by the certified prosthetist/orthotist. Examples of such safeguards include introducing a progressive wear schedule for conditioning patients to the use of the AFO, screening for areas of diminished skin sensation, using felt or soft foam materials to cushion potential areas of contact, and teaching patients to visual inspect their skin after use. Patients with PAD are familiar with such inspections as they are commonly asked to monitor their skin response to new activities or purchasing new shoes. Additionally, Dr. Ashley Mays will be consulted with relevant medical questions or concerns. To reduce strap pressure, the brace is designed with two bands instead of one to share the load across a broad contact area. Patients will be trained in how to adjust the straps to ensure adequate fit for keeping the brace on between steps, but not at a level of pressure to constrict blood flow. The bulk of contact pressure experienced by the patient with the AFO is only on the anterior shin in the late phase of gait during propulsion and represents approximately 30 pounds of force for an instant. Regarding fall risk while using the devices, patients will have ample amounts of practice with the AFO in addition to being monitored directly during the graded exercise tests. Any gait abnormalities while walking with the devices will be addressed with patients.
- Motion analysis: The tape used in the motion analysis collection is specifically designed to be hypoallergenic and represents a level of risk that is similar to the application of a Band-Aid.

H. Implications of the study

AFO devices have demonstrated success in neurologically impaired children and adults who present with similar difficulties in calf muscle performance.^{12,13,25} Because PAD represents a significant morbid condition in ~8-12 million adults in the U.S. alone, new methods and ways to treat patients are needed. Augmenting muscular effort with an over the counter device could potentially be a useful approach to treating PAD when used as an adjunct to the standard of care. The proposed project represents the unique opportunity to combine differing yet complimentary approaches of Dr. Ryan Mays' clinical exercise physiology and vascular medicine research expertise and Dr. Mizner's clinical biomechanics focus. This will also facilitate and build upon an existing consortium between the two primary research institutions in Western Montana- the University of Montana and St. Patrick Hospital in order to compliment the standard of care treatment for PAD which is a potentially ground-breaking approach. If a new method (i.e., AFO) for assisting PAD patients in their walking ability can be developed and implemented both acutely via testing in laboratories as well as in community settings, healthcare costs could decline and patient's may ultimately improve their overall health and well-being.

I. Adverse Event Reporting

Any adverse events that occur during the study that the investigator believes are serious AND qualify as an unanticipated adverse device effect OR are related to study-specific procedures as defined above will be reported to the JIRB in a timely manner. The investigator or a research staff member will submit a detailed written report to the JIRB no later than 5 days after the investigator discovers the event.

J. References

1. Norgren L, Hiatt WR, Dormandy JA, Nehler MR, Harris KA, Fowkes FG. Inter-society consensus for the management of peripheral arterial disease (TASC II). *J Vasc Surg* 2007;45 Suppl S:S5-67.
2. Golomb BA, Dang TT, Criqui MH. Peripheral arterial disease: Morbidity and mortality implications. *Circulation* 2006;114(7):688-99.
3. Hiatt WR, Regensteiner JG, Hargarten ME, Wolfel EE, Brass EP. Benefit of exercise conditioning for patients with peripheral arterial disease. *Circulation* 1990;81(2):602-9.
4. Fakhry F, van de Luijngaarden KM, Bax L, den Hoed PT, Hunink MG, Rouwet EV, et al. Supervised walking therapy in patients with intermittent claudication. *J Vasc Surg* 2012;56(4):1132-42.

5. Regensteiner JG, Stewart KJ. Established and evolving medical therapies for claudication in patients with peripheral arterial disease. *Nat Clin Pract Cardiovasc Med* 2006;3(11):604-10.
6. Mays RJ, Rogers RK, Hiatt WR, Regensteiner JG. Community walking programs for treatment of peripheral artery disease. *J Vasc Surg* 2013;58(6):1678-87.
7. Al-Jundi W, Madbak K, Beard JD, Nawaz S, Tew GA. Systematic review of home-based exercise programmes for individuals with intermittent claudication. *Eur J Vasc Endovasc Surg* 2013;46(6):690-706.
8. Galea MN, Bray SR, Ginis KA. Barriers and facilitators for walking in individuals with intermittent claudication. *J Aging Phys Act* 2008;16(1):69-83.
9. Remijnse-Tamerius HC, Duprez D, De Buyzere M, Oeseburg B, Clement DL. Why is training effective in the treatment of patients with intermittent claudication? *Int Angiol* 1999;18(2):103-12.
10. Creager MA, Libby P. *Peripheral artery diseases*, In: Bonow RO, et al., Editors. *Braunwald's heart disease: A textbook of cardiovascular medicine*. Philadelphia, PA: Elsevier; 2011. p. 1338-58.
11. Bregman DJ, Harlaar J, Meskers CG, de Groot V. Spring-like ankle foot orthoses reduce the energy cost of walking by taking over ankle work. *Gait Posture* 2012;35(1):148-53.
12. Dufek JS, Neumann ES, Hawkins MC, O'Toole B. Functional and dynamic response characteristics of a custom composite ankle foot orthosis for charcot-marie-tooth patients. *Gait Posture* 2014;39(1):308-13.
13. Desloovere K, Molenaers G, Van Gestel L, Huenaerts C, Van Campenhout A, Callewaert B, et al. How can push-off be preserved during use of an ankle foot orthosis in children with hemiplegia? A prospective controlled study. *Gait Posture* 2006;24(2):142-51.
14. Mays RJ, Hiatt WR, Casserly IP, Rogers RK, Main DS, Kohrt WM, et al. Community-based walking exercise for peripheral artery disease: A pilot study. *Vascular Medicine (in review)* 2014.
15. Koutakis P, Johanning JM, Haynatzki GR, Myers SA, Stergiou N, Longo GM, et al. Abnormal joint powers before and after the onset of claudication symptoms. *J Vasc Surg* 2010;52(2):340-7.
16. Kim ES, Wattanakit K, Gornik HL. Using the ankle-brachial index to diagnose peripheral artery disease and assess cardiovascular risk. *Cleve Clin J Med* 2012;79(9):651-61.
17. Gardner AW, Skinner JS, Cantwell BW, Smith LK. Progressive vs single-stage treadmill tests for evaluation of claudication. *Med Sci Sports Exerc* 1991;23(4):402-8.
18. Montgomery PS, Gardner AW. The clinical utility of a six-minute walk test in peripheral arterial occlusive disease patients. *J Am Geriatr Soc* 1998;46(6):706-11.
19. Regensteiner JG, Steiner JF, Panzer RJ, Hiatt WR. Evaluation of walking impairment by questionnaire in patients with peripheral artery disease. *J Vasc Med Biol* 1990;2:142-52.
20. Ware JE, Sherbourne CD. The MOS 36-item short-form health survey (SF-36). I. Conceptual framework and item selection. *Med Care* 1992;30(6):473-83.
21. Mizner RL, Snyder-Mackler L. Altered loading during walking and sit-to-stand is affected by quadriceps weakness after total knee arthroplasty. *J Orthop Res* 2005;23(5):1083-90.
22. Yoshida Y, Mizner RL, Ramsey DK, Snyder-Mackler L. Examining outcomes from total knee arthroplasty and the relationship between quadriceps strength and knee function over time. *Clin Biomech (Bristol, Avon)* 2008;23(3):320-8.

23. Davidson BS, Judd DL, Thomas AC, Mizner RL, Eckhoff DG, Stevens-Lapsley JE. Muscle activation and coactivation during five-time-sit-to-stand movement in patients undergoing total knee arthroplasty. *J Electromyogr Kinesiol* 2013;23(6):1485-93.
24. ACSM. *ACSM's guidelines for exercise testing and prescription*. 9th ed. Baltimore, MD: Lippincott Williams and Wilkins; 2014.
25. Danielsson A, Sunnerhagen KS. Energy expenditure in stroke subjects walking with a carbon composite ankle foot orthosis. *J Rehabil Med* 2004;36(4):165-8.