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Pharmacological Treatment of Intermittent Claudication Does Not Have a Significant Effect on Gait Impairments During Claudication Pain

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Peripheral arterial disease (PAD) is a manifestation of atherosclerosis resulting in intermittent claudication (IC) or leg pain during physical activity. Two drugs (cilostazol and pentoxifylline) are approved for treatment of IC. Our previous work has reported no significant differences in gait biomechanics before and after drug interventions when PAD patients walked without pain. However, it is possible that the drugs are more efficacious during gait with pain. Our aim was to use advanced biomechanical analysis to evaluate the effectiveness of these drugs while walking with pain. Initial and absolute claudication distances, joint kinematics, torques, powers, and gait velocity during the presence of pain were measured from 24 patients before and after 12 weeks of treatment with either cilostazol or pentoxifylline. We found no significant improvements after 12 weeks of treatment with either cilostazol or pentoxifylline on the gait biomechanics of PAD patients during pain. Our findings indicate that the medications cilostazol and pentoxifylline have reduced relevance in the care of gait dysfunction even during pain in patients with PAD.

Keywords: peripheral arterial disease, locomotion, biomechanics, cilostazol, pentoxifylline

Peripheral arterial disease (PAD) is a manifestation of systemic atherosclerosis, characterized by atherosclerotic blockages of the arteries supplying the legs, affecting up to 12 million elderly in the United States (Hirsch & Hiatt, 2001; McDermott et al., 2001; Nehler et al., 2003). Intermittent claudication, the most common manifestation of PAD, is defined as activity induced dysfunction and muscle pain (claudication pain) relieved by rest. When patients with intermittent claudication start walking, their leg muscles have adequate blood flow and they experience no leg pain. With continued walking, the metabolic needs of the exercising limb rapidly increase. However, the blood flow required to support these needs cannot be delivered due to blockages in the arterial system. As exercise continues, the muscles become progressively more ischemic and painful, forcing the patient to eventually stop walking (Regensteiner et al., 1988). Studies have demonstrated that patients with PAD walk with decreased gait velocity, cadence, step length and increased stance time as compared with controls (Gardner et al., 2001). Recently, biomechanical investigations have revealed that PAD patients demonstrate abnormal ground reaction forces and altered joint kinetics and kinematics, before and after the onset of claudication pain as compared with healthy controls (Celis et al., 2009; Chen et al., 2008; Crowther et al., 2007; Koutakis et al., 2010a; Scott-Pandorf et al., 2007).

Treatments for PAD range from risk factor management (e.g., exercise, smoking cessation) to more aggressive surgical interventions (e.g., surgical bypass and endovascular revascularization; Antignani, 2003; Aronow, 2007; Christman et al., 2001; Schainfeld, 2001). Currently, two pharmacological agents are approved by the United States Food and Drug Administration for treatment of PAD. The first approved drug, pentoxifylline, a xanthine derivative, acts as a competitive nonselective phosphodiesterase inhibitor (PMID 11692087) and a nonselective adenosine receptor antagonist (PMID 3588607). The second approved medication, cilostazol, is a phosphodiesterase inhibitor that has antiplatelet and

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vasodilatory effects (Lipsitz & Kim, 2008; Regensteiner & Stewart, 2006). The objective for the use of the two medications is to improve the walking function of patients with claudication by improving blood flow at all times. In most studies evaluating effects of medications on claudication, walking function has been evaluated with the measurement of the initial claudication distance (distance walked before the onset of claudication symptoms) and of the absolute claudication distance (maximal distance the patient can walk). Certain studies have demonstrated improved walking distances with pentoxifylline (Accetto, 1982; Cesarone et al., 2002; De Sanctis et al., 2002; Dettori et al., 1989; Di Perri et al., 1984; Perhoniemi et al., 1984) and cilostazol treatment (Beebe et al., 1999; Dawson et al., 1998; Robless et al., 2008; Thompson et al., 2002). Conversely, studies have also found no changes in walking distances with either pentoxifylline (Reilly et al., 1987) or cilostazol (O'Donnell et al., 2009). Moreover, in a trial comparing the two medications to each other and to placebo, cilostazol shows significant improvements in absolute claudication distance and initial claudication distance while no significant differences were found between the pentoxifylline and placebo groups (Dawson et al., 2000).

Due to conflicting results found regarding both pharmacological treatments, there is a need for more sensitive measures to quantify the functional outcomes of these pharmacological interventions. Using advanced biomechanical analysis, investigators have been able to characterize gait abnormalities in several pathologies (Barker et al., 2006; Basford et al., 2003; Chang et al., 2006; Tenore et al., 2006). Specifically, joint moments can determine the net response of all muscle groups in the lower extremities and the crucial PAD-related adaptations and deficits in muscle function during gait (Winter, 2005). Joint powers can then determine the contribution of the torque-producing muscle groups to the fundamental biomechanical processes of energy generation and energy dissipation through concentric and eccentric contractions of skeletal muscles (Winter, 2005). Our laboratory has used this approach to define baseline gait deficit in PAD patients (Celis et al., 2009; Koutakis et al., 2010a). Furthermore, we recently investigated the effect of therapy with pentoxifylline and cilostazol on biomechanical gait parameters in PAD patients walking before the onset of claudication pain (Huisinga et al., 2010a, 2010b). Specifically, Huisinga et al. (Huisinga et al., 2010a) compared patients with PAD that were treated with either one of the pharmacological agents with healthy controls. Patients were not grouped separately by pharmacological treatment (i.e., were compared as one group to the controls) and they were tested only under a pain free condition. Therefore, this research design did not explore the separate effects of the two agents. Thus, in a follow-up study Huisinga et al. (Huisinga et al., 2010b) separated patients with PAD into two groups that were exposed to the two agents. Then, the authors compared the two groups under a pain free condition. Collectively, these two studies showed that post 3 months of treatment no identifiable biomechanical alterations were produced as compared with the aged-matched controls (Huisinga et al., 2010a). Further, when patients with PAD were separated to two groups based on treatment, no significant differences were found between the two groups for either treatment (before vs. after 12 weeks of therapy) for gait velocity, absolute claudication distance, joint kinematic and peak joint torque values (Huisinga et al., 2010b). These results indicate that three months of pharmacological therapy did not have an effect on joint kinematic or kinetic parameters of PAD patients while they are walking before they experience claudication pain. These findings also suggest that for improvements in functional outcomes of patients walking before the onset of claudication pain, physicians cannot rely solely on pharmacological interventions.

On the other hand, it may be possible that pharmacological treatment produces appreciable effects in the biomechanics of patients mainly while they are walking with claudication pain, when blood flow is restricted and limbs suffer from ischemia. These pharmacological treatments are even marketed as being able to improve pain in PAD patients. Further, it is known that walking with claudication pain does significantly impact biomechanical gait parameters, with the ankle musculature demonstrating the greatest deficits (Koutakis et al., 2010b). As stated before, patients with PAD experience a cycle of ischemia and reperfusion. It is possible that the effects of pentoxifylline and cilostazol may help to improve blood flow specifically during activity and potentially attenuate the patient's ischemic state. As the metabolic demand increases with exertion, the two medications may be able to support aerobic metabolism with an increased supply of oxygen and glucose (Carman & Fernandez, 2006).

Therefore, the purpose of the current study was to investigate the effects of pharmacological treatments on the biomechanics of gait of PAD patients while experiencing claudication pain. Joint kinetic and kinematic parameters were used to evaluate gait impairments after the onset of claudication pain. This evaluation was performed before pharmacological treatment and 12 weeks after the commencement of treatment. We hypothesize that treatment with the medications will have a positive effect on patients' gait parameters post treatment. The drugs have been designed to increase blood flow upon exertion and even during continued walking and sustained metabolic demand. Therefore, improvements could be noted as we know decrements in gait during walking with pain are present (Koutakis et al., 2010b). If improvements are demonstrated, then there would be reason to believe that improved gait mechanics would eventually lead over time to improved maximal walking distances, thus, warranting use of these drugs. However, if no improvements in gait mechanics and/or walking distances can be found, then prescription of such pharmacological agents may not be warranted. In addition, it is expected that cilostazol will have more of an impact than pentoxifylline. This is due to findings in which cilostazol demonstrated significant

increase in walking distances as compared with pentoxifylline (Dawson et al., 2000).

Methods

Subject Inclusion and Exclusion Criteria

Patients presenting with intermittent claudication of at least one lower limb and intended to undergo pharmacological treatment were recruited from the vascular surgery clinics of the University of Nebraska and the Western Iowa–Nebraska Veterans' Affairs Medical Centers. The institutional review boards of the two institutions approved all procedures. All participants provided informed consent before enrollment into the study. A total of 24 PAD patients were enrolled (67.8 ± 9.6 years); 14 participants were prescribed cilostazol and 10 participants were prescribed pentoxifylline. Drug assignment was nonrandomized, nonblinded, and based upon each patient's past medical history and current medication profile.

Patients were specifically evaluated by two board-certified vascular surgeons before enrollment in the study to ensure that walking impairments were secondary to claudication pain. Patients were excluded if they demonstrated ambulation limiting cardiac, pulmonary, neuromuscular, or musculoskeletal disease or those who experienced pain or discomfort during walking for reasons other than claudication. Patient evaluation included resting ankle brachial index (ABI; a measurement below 0.90 defined PAD), detailed history, and physical exam. Affected limbs were identified if the ABI was less than 0.9 and expressed symptoms of intermittent claudication.

Experimental Procedures and Data Collection

Reflective markers were placed on anatomical locations, bilaterally, according to a modified Helen Hayes marker set (Houck et al., 2005). To induce claudication pain, subjects were asked to walk on a treadmill at 0.67 m/s at a 10% incline until the presentation of claudication symptoms (DiBianco et al., 1984). The constant work load protocol has been shown to be reliable in inducing claudication pain (Labs et al., 1999). Claudication symptoms were self-reported by the patient. Before the treadmill protocol, subjects were asked what their normal claudication symptoms were like, pain and/or cramping in the buttock, thigh, and/or leg. Research staff asked specific questions regarding claudication pain once every minute until patients reported claudication symptoms similar to what they would experience in daily life. For instance, patients would be asked, "Are you having any pain or cramping in your legs?" and once the patient reported yes, the research staff would inquire as to where the pain was and what type. The onset of claudication symptoms was defined, when the patient reported that they felt it was similar to their daily claudication symptoms or asked to stop. Once the onset of claudication symptoms was felt by the subject, they were immediately removed from the treadmill and walked through a 10 m walkway. Five trials were collected for each affected limb; 10 trials total if they presented with bilateral PAD. Participants were not allowed to rest during the data collection to provide for experimental data to be collected while the patient was experiencing claudication pain. The 3D marker trajectories were collected with a digital high-speed eight-camera system (EvaRT 5.0.4, Motion Analysis Corp., Santa Rosa, CA) sampling at 60 Hz. Ground reaction force data from heel contact to toe-off was collected using a piezoelectric force plate (Kistler Instrument Corp., Winterthur, Switzerland) sampling at 600 Hz. To ensure that a complete stance phase would be collected during each overground walking trial during claudication pain, starting positions for each limb were determined before having the subject walk on the treadmill to induce pain. It has been shown that step lengths do not change from the pain-free to pain condition and thus patients would maintain similar spatial gait patterns between the two conditions (Koutakis et al., 2010b).

Initial claudication distance and absolute claudication distance were measured at the end of the data collection session. Patients were required to rest for a minimum of 5 min and until all claudication pain had subsided after all overground walking trials were collected. Once patients were pain free, they were asked to walk on the treadmill at a speed of 0.67 m/s at a 10% incline until they were unable to continue due to claudication pain (DiBianco et al., 1984). Initial claudication distances were based upon the patient's first report of claudication pain. Absolute claudication distances were based on the patient's self-reported maximum tolerable pain.

Data collection was completed before the administration of pharmacological treatments and again at 12 weeks after treatment commenced. This time frame is appropriate since 12 weeks is the minimum amount of time allotted before declaring a patient as unresponsive to a medication (Carman & Fernandez, 2006). During the treatment period, patients were not restricted from performing extra training and their physical activity levels were not monitored. Gait kinematics and kinetics were calculated from the sagittal plane of motion during the stance phase of walking for each subject after intermittent claudication was exhibited in the affected limb(s). No swing phase data were analyzed. A low-pass, fourth-order Butterworth filter with a 7 Hz cutoff was used to smooth the marker trajectories before data processing. Custom MatLab programs (MatLab 2007, Mathworks, Inc., Concord, MA) were used for calculation of all dependent variables. Using the methods described by Vaughn et al. (1992) and Nigg et al. (1993), relative joint angles were calculated. Joint range of motion was defined as the maximum range of the joint angle during the stance phase of walking. Inverse dynamics were used to calculate joint torques of each joint and were scaled to body weight and height (Winter, 2005). Extensor torques were represented by positive torque values while negative torque values represent flexor torques. Joint powers were

calculated as the product of the net joint torque and angular velocity. Positive joint power values indicate power generation while a negative joint power values indicate power absorption. Peak torques and peak powers were recorded for the hip, knee, and ankle.

Group means of each dependent variable was calculated for the therapy (before and after) group and for the treatment group (cilostazol and pentoxifylline) by combining all legs of each group. Out of the 14 participants given cilostazol, 26 limbs were evaluated because two patients had unilateral claudication only and of the 10 participants given pentoxifylline, all 20 limbs were evaluated. All dependent variables were tested for normality using the Shapiro-Wilk procedure. There was a strong tendency for normality and thus a repeated-measures 2 × 2 ANOVA was performed for the within (before vs. after) and the between (cilostazol vs. pentoxifylline) factors using SPSS software (SPSS 16.0, SPSS, Inc., Chicago, IL). Due to a large number of comparisons, a Bonferroni correction was employed. Mean difference was calculated for each dependent variable using effect size, which is the mean of the pre-therapy minus the mean of post-therapy divided by the standard deviation of the pre-therapy. The significance level was set at $p < .0025$ (0.05 divided by 20 (20 dependent variables presented in Table 1)).

Results

No significant main effects were found due to therapy or treatment group for gait velocity, initial claudication distance, absolute claudication distance, joint range of motions, joint torque parameters, or joint powers (Table 1). In addition, no significant interactions were found between therapy and treatment group for these variables. Importantly, if a less conservative p-value was adopted ($p < 0.05$), only 6 out of the total 60 F-ratios would have been significant (Table 1). Due to therapy there were only 2 out of 60 F-ratios that were significant. These two were the variables of knee power absorption in early stance and hip power generation in late stance (Table 1). Due to treatment group there were again 2 out of 60 F-ratios that were significant. These two were the variables of gait velocity and ankle power generation in late stance (Table 1). The two variables that were significant due to therapy were not the same for the treatment, further strengthening this point.

Discussion

The purpose of this study was to investigate the effect of pharmacological treatment on the gait abnormalities exhibited by PAD patients while they walk with claudication pain. It was hypothesized that a 12-week course of pharmacological treatment would have a positive effect on patients' gait parameters post treatment. Further, it was expected that cilostazol would attenuate gait parameters more so than pentoxifylline. The current findings refute these hypotheses as we now accept the null hypothesis.

These data presented in this study demonstrate that neither treatment group (pentoxifylline vs. cilostazol) nor therapy (before vs. after) had a significant effect on gait impairment in patients with PAD. Due to the large number of dependent variables evaluated in this study, a more stringent p-value ($p < 0.0025$) was employed to accommodate for the number of comparisons performed (Table 1). Interestingly, if a less stringent p-value ($p < 0.05$) would have been used, only 6 of 60 F-ratios calculated would have reached significance (Table 1). The lack of significant changes in gait parameters indicates that 12 weeks of treatment with cilostazol or pentoxifylline produce no appreciable improvements in the gait biomechanics of claudicating patients. In addition, our measurements of walking distances demonstrate changes in absolute claudication distance in the cilostazol group (improvement) and in the pentoxifylline group (decrement) but neither of the two changes reached statistical significance. Our findings from advanced biomechanical analysis of PAD gait are further supported by studies in which it has been found that these medications do not improve claudication distances (O'Donnell et al., 2009; Reilly et al., 1987). Reilly et al. (1987) have stated that pentoxifylline has limited effect on blood flow properties and no effect on claudication distances. Further, O'Donnell et al. (O'Donnell et al., 2009) have shown that despite improvements in quality of life after 24 weeks of cilostazol treatment, no significant differences were demonstrated in walking distances. Taken together, the findings from the current study and those reported by Huisinga et al. (2010a, 2010b) suggest that the medications cilostazol and pentoxifylline have limited application in the clinical treatment of the gait dysfunction of patients with peripheral arterial disease regardless of the presence of claudication pain.

It is logical to conclude that based on the findings in the current study, cilostazol and pentoxifylline are unable to provide a sufficient change in the dynamics of the neuromuscular system of the lower extremities to improve functional outcomes during claudication pain. Myopathy and neuropathy (PMID 18390972 and PMID 18166628) that is present in patients with peripheral arterial disease is a key factor to the pathogenesis of this disease (Pipinos et al., 2007). It has been shown that skeletal muscle tissue in patients with PAD is vastly different than healthy controls. PAD patients suffer from various levels of oxidative stress resulting in mitochondrial abnormalities (Pipinos et al., 2003, 2006), besides shifts in muscle fiber types (Regensteiner et al., 1993), and neuropathy (Pasini et al., 1996; Weber & Ziegler, 2002). This myopathy is possibly related to function, for instance, muscle weakness due to inability to produce energy as a result of mitochondrial changes. Future therapeutic approaches focusing on the neuro-myopathy of PAD may produce improved gait and reduced impairment associated with the disease.

These data presented in study are in line with previous findings within patients with PAD. Normative data for the range of motion for the three joints are typically approximately 40, 18 and 18 degrees for the hip, knee

Table 1 Statistical results reported for each dependent variable

								Therapy		Group		Interaction	
Dependent Variable	**Pre Cilostazol**	**Post Cilostazol**	***ES***	**Pre-Pentoxifylline**	**Post-Pentoxifylline**	***ES***	***df***	***F***	***p***	***F***	***p***	***F***	***p***
Gait Velocity (m/s)	1.05 ± 0.14	0.97 ± 0.11	0.57	1.11 ± 0.16	1.08 ± 0.13	0.12	1,44	4.030	0.051	8.116	0.007	0.870	0.356
Intermittent claudication distance (m)	57.7 ± 39.4	95.0 ± 43.6	0.95	47.6 ± 15.3	53.5 ± 15.4	0.39	1,22	0.964	0.337	1.035	0.320	0.505	0.485
Absolute claudication distance (m)	219.8 ± 38.1	255.3± 49.9	0.93	201.0 ± 28.0	140.4 ± 22.0	2.2	1,22	0.279	0.663	1.642	0.213	4.863	0.038
Ankle ROM (degrees)	20.18 ± 1.09	19.67 ± 0.58	0.47	19.79 ± 0.73	19.80 ± 0.65	0.01	1,44	0.434	0.513	0.402	0.529	0.239	0.627
Knee ROM (degrees)	9.64 ± 1.30	9.69 ± 1.31	0.04	9.96 ± 1.72	9.28 ± 1.42	0.40	1,44	0.603	0.442	0.009	0.923	0.410	0.525
Hip ROM (degrees)	35.29 ± 1.50	35.83 ± 1.28	0.36	35.93 ± 2.11	35.38 ± 1.83	0.27	1,44	0.744	0.393	0.021	0.887	0.778	0.383
ADT (N/kg)	-0.35 ± 0.02	-0.28 ± 0.04	3.5	-0.32 ± 0.03	-0.27 + 0.4	1.7	1,44	0.160	0.691	1.831	0.183	0.078	0.781
APT (N/kg)	1.24 ± 0.06	1.12 ± 0.08	2.0	1.36 ± 0.08	1.32 ± 0.06	0.5	1,44	1.054	0.310	0.790	0.379	0.012	0.912
KET (N/kg)	0.66 ± 0.06	0.73 ± 0.10	1.17	0.82 ± 0.12	0.67 ± 0.06	1.25	1,44	0.023	0.880	1.322	0.256	0.868	0.356
KFT (N/kg)	-0.17 ± 0.05	-0.14 ± 0.07	0.60	-0.11 ± 0.04	-0.06 ± 0.03	1.25	1,44	0.093	0.762	3.504	0.068	0.566	0.456
HET (N/kg)	0.84 ± 0.06	0.82 ± 0.10	0.33	0.89 ± 0.06	0.88 ± 0.10	0.17	1,44	0.096	0.758	0.132	0.718	0.028	0.868
HFT (N/kg)	-0.85 ± 0.10	-1.08 ± 0.17	2.3	-0.89 ± 0.11	-0.94 ± 0.07	0.45	1,44	1.191	0.281	0.004	0.953	0.088	0.768
A1 (W/kg)	-0.38 ± 0.06	-0.32 ± 0.03	1.0	-0.40 ± 0.06	-0.45 ± 0.12	0.83	1,44	1.994	0.165	0.000	0.986	0.020	0.889
A2 (W/kg)	2.02 ± 0.16	1.70 ± 0.14	2.0	2.54 ± 0.17	2.47 ± 0.18	0.41	1,44	1.332	0.255	6.880	0.012	0.699	0.408
K1 (W/kg)	-0.73 ± 0.09	-0.81 ± 0.13	0.89	-0.66 ± 0.11	-0.74 ± 0.14	0.72	1,44	3.870	0.055	0.352	0.556	0.422	0.519
K2 (W/kg)	0.33 ± 0.06	0.42 ± 0.09	1.5	0.51 ± 0.11	0.35 ± 0.06	1.72	1,44	0.228	0.635	0.530	0.471	0.698	0.408
K3 (W/kg)	-0.59 ± 0.06	-1.36 ± 0.27	12.8	-0.69 ± 0.09	-0.66 ± 0.09	0.33	1,44	7.418	0.009	3.108	0.085	4.755	0.035
H1 (W/kg)	0.54 ± 0.05	0.59 ± 0.13	1.0	0.50 ± 0.08	0.55 ± 0.12	0.63	1,44	1.184	0.282	0.106	0.746	0.000	0.998
H2 (W/kg)	-0.64 ± 0.09	-0.96 ± 0.16	3.6	-0.75 ± 0.11	-0.74 ± 0.06	0.10	1,44	1.006	0.321	0.119	0.732	1.327	0.256
H3 (W/kg)	0.51 ± 0.06	0.79 ± 0.12	4.7	0.68 ± 0.08	0.71 ± 0.08	0.38	1,44	7.206	0.010	0.055	0.816	1.471	0.232

Note. Results are reported in mean ± *SD*. ES = effect size.

Joint ROM: A positive value indicates joint flexion and a negative value is extension. Range of motion is defined as the range from lowest degree to highest. **Joint torque:** All values are normalized to body mass in kilograms. A positive value for the ankle indicates plantar flexion torque and negative values indicate dorsiflexion torque. For the hip and knee, a positive value indicates extension torque and negative values indicate flexion torque. Peak variables used in analysis are ankle dorsiflexor torque (ADT), ankle plantar flexor torque (APT), knee extensor torque (KET), knee flexor torque (KFT), hip extensor torque (HET), and hip flexor torque (HFT). **Joint power:** All values are normalized to body mass in kilograms. The peak variables identified for joint powers were ankle power absorption in midstance (A1), ankle power generation in late stance (A2), knee power absorption in early stance (K1), knee power generation in early stance (K2), knee power absorption in late stance (K3), hip power generation in early stance (H1), hip power absorption in midstance (H2) and hip power generation in late stance (H3).

and ankle respectively during the stance phase of walking (Celis et al., 2009). Our findings are also consistent with other studies that found decreased range of motion at the hip and knee with increased range of motion at the ankle in patients with PAD as compared with controls (Celis et al., 2009; Huisinga et al., 2010a). In addition, joint torque and power values were compared with published literature in which similarly aged healthy controls were reported (Koutakis et al., 2010b). The data from this study demonstrate that all joint torque and power magnitudes (absolute value) reported were decreased as compared with controls, with the exception of peak knee flexor torque. This is also consistent with previous findings for patients with PAD (Huisinga et al., 2010a; Koutakis et al., 2010b). Our data are similar to published values that have been normalized to body weight (Eng & Winter, 1995; Nadeau et al., 2003).

Overall, our data demonstrate that a 12-week treatment of PAD with either cilostazol or pentoxifylline does not result in biomechanical changes in the gait biomechanics of claudicating patients. The lack of changes in gait improvement suggests that underlying myopathy and neuropathy may limit the ability of the medications to produce improvements in gait biomechanics; consequently, reducing the relevance of the use of these two medications in the clinical care of gait dysfunction in peripheral arterial disease. Future studies should focus on evaluating surgical revascularization and supervised exercise as therapies with established and more marked positive effects in the walking ability of PAD patients. The use of advanced biomechanical analysis in such studies would allow identification of the particular joint muscular responses and contributions that lead to improvement in the ambulation of patients with claudication.

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