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Treatment With Pharmacological Agents in Peripheral Arterial Disease Patients Does Not Result in Biomechanical Gait Changes

Jessie M. Huisinga, Iraklis I. Pipinos, Nicholas Stergiou, and Jason M. Johanning

Pharmacological treatment has been used to alleviate the claudication symptoms and improve walking performance in peripheral arterial disease (PAD) patients. However, the effects of claudication treatments on gait mechanics have not been objectively indentified with biomechanical techniques. For this study, 20 PAD patients were assigned to take either pentoxifylline ($n = 11$) or cilostazol ($n = 9$), the two FDA-approved pharmacological therapies used to treat intermittent claudication symptoms. All patients completed a gait evaluation protocol that involved the acquisition of kinematic and kinetic gait data before use of the medication and after 12 weeks of treatment. Results showed that treatment with either pentoxifylline or cilostazol resulted in limited overall improvement in gait parameters including joint angles and joint moments. Walking speed was unchanged, in either treatment group, as a result of the medication. These results suggest that to improve biomechanical walking parameters of PAD patients, clinicians cannot rely on drug therapies alone.

Keywords: locomotion, intermittent claudication, pentoxifylline, cilostazol, joint moments

Peripheral arterial disease (PAD) is a manifestation of atherosclerosis that produces physical activity-induced muscle cramping called *intermittent claudication*. Specifically, the decrease in blood flow due to the arterial occlusion leads to muscle pain and cramping distal to the arterial obstruction. Pain and cramping occur as a result of ischemia in the calf, thigh, or buttocks during walking, when oxygen demand is increased (Aronow, 2004; Scherer et al., 1998). Typically, the superficial femoral and popliteal arteries are most affected by atherosclerosis, so the claudication pain is commonly localized to the gastrocnemius. This muscle has an important role during walking since the ankle joint is responsible for providing a large amount of positive work to transfer the leg from stance phase into the swing phase (Sawicki, Lewis, & Ferris, 2009). However, patients may also experience pain in other muscles of the legs (Aronow, 2004). Several studies have shown that intermittent claudication

in patients with abnormally decreased blood flow to the leg muscles (documented via the ankle-brachial index (ABI), where $ABI < 0.9$ indicates a PAD diagnosis) leads to alterations of gait characteristics (McDermott et al., 2001) and increased risk of poor health outcomes (Gardner et al., 2001).

Prescribed treatment programs for patients with PAD vary from conservative treatment, using exercise and smoking cessation, to pharmacological therapy and more aggressive management, including surgical interventions such as stenting and angioplasty (Antignani, 2003; Aronow, 2004; Christman et al., 2001; Schainfeld, 2001; Shammass & Dippel, 2005). Two pharmacological therapies are currently approved by the FDA for treatment of intermittent claudication associated with PAD. The older of the two, pentoxifylline, acts by altering the hemorheological properties of blood leading to reduced blood viscosity and hypercoagulability (Muller, 1979) and possibly improving blood flow to the leg muscles. Research has found that pentoxifylline can also improve the respiration capacity of the mitochondria, which may result in changes in muscle physiology during physical activity (Pipinos et al., 2002). The other medication, cilostazol, increases the intracellular concentration of cyclic adenosine monophosphate to suppress platelet aggregation and increase arterial dilation for improved blood flow (Aronow, 2004). However, the underlying physiological/neuromechanical mechanisms of both medications with respect to their effect on PAD remain unknown (Dawson, 2001). Compared with placebo, pentoxifylline has shown to increase walking distances in some studies (Accetto, 1982; Bollinger & Frei, 1977; Di Perri & Guerrini, 1983)

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but has also been shown to have no effect (Perhoniemi et al., 1984; Porter et al., 1982; Tonak et al., 1983). Cilostazol, however, has been shown to increase maximum walking distance in patients by 28–100% compared with 10–30% for placebo (Cariski, 2001; Dawson et al., 1998). Cilostazol has also been shown to increase maximum walking distance significantly more than pentoxifylline in patients with intermittent claudication (Dawson et al., 2000). Because the drug therapies appear to improve physical functioning and improve walking distance, it appears likely that the therapeutic action of the drugs is due to the acute effects on platelet function or direct vasodilation (Dawson, 2001). These effects are seen within hours or days of drug administration (Dawson, 2001).

Because PAD affects 10–12 million people in the United States (Scherer et al., 1998), it is not surprising that numerous studies have been completed to categorize the effect of the disease. However assessing the severity of PAD and the effectiveness of treatments has classically been limited to the examination of ABI scores and simple clinical measures such as the Timed Up and Go test, initial claudication distance (walking time up to the occurrence of pain), and absolute claudication distance (maximal distance a patient is able to walk) (Gardner et al., 2001; Dawson, 2001; Dawson et al., 2000; McDermott et al., 2001; Scherer et al., 1998). In addition, studies with PAD patients have incorporated spatial and temporal variables associated with gait, such as step length and step frequency or a 6-min walk distance (Gardner et al., 2001; McDermott et al., 2001; Scherer et al., 1998). These techniques are limited since they do not explain how pathophysiological changes that are known to occur in PAD patients may be translated into walking deficits (Gardner et al., 2001; Scherer et al., 1998). Our investigation attempts to bridge this knowledge gap by utilizing biomechanical measures to quantify changes in walking mechanics that are the result of pharmacological therapy in PAD patients. Studies involving the examination of the biomechanics of gait have been performed on a variety of gait related pathologies providing invaluable insights (Andriacchi, 1990; Andriacchi et al., 2004; Begg & Sparrow, 2006; DeLuca et al., 1997; Devita et al., 1997, 1998a, 1998b; DeVita & Hortobagyi, 2000; Hortobagyi & DeVita, 1999, 2000; Landry et al., 2007; Lee et al., 1992; Messier et al., 2005; Ristanis et al., 2003; Winter et al., 1990). However, only recently have preliminary studies been performed examining changes in joint kinematics and kinetics associated with PAD patients as compared with healthy controls (Chen et al., 2008; Crowther et al., 2007, 2008a, 2008b, 2008c; Scott-Pandorf et al., 2007).

Specifically, Scott-Pandorf et al. (2007) found that PAD patients exhibited increased plantar flexion, increased dorsiflexion, and thus increased total ankle range of motion compared with control subjects during the stance phase of gait. At the knee, however, claudicants exhibited decreased motion or a “stiff knee” gait. Crowther et al. (2007) found that PAD patients exhibited significantly reduced ankle plantar flexion during stance, decreased hip peak extension during stance, and

decreased overall knee range of motion during stance. More recently, Chen et al. (2008) reported that PAD patients, while walking without claudication pain, had decreased hip flexion and increased ankle plantar flexion during early stance and increased ankle dorsiflexion during late stance. Chen et al. (2008) also found that compared with controls, PAD patients showed significantly reduced peak hip extensor moment during early stance suggesting muscle strength decrements in the PAD patients. As evidenced by Chen et al. (2008), employing joint moments may help to elucidate the gait mechanics used by PAD patients to control gait and whether pharmacological therapy can help the patient produce a healthier gait pattern. In addition, by examining changes in joint moment that occur in PAD patients, clinicians may be able to better target different muscle groups for revascularization surgery.

Thus, the purpose of this study was to determine the effects of two different pharmacological therapies on the gait biomechanics of patients with PAD since no prior investigations have explored changes in walking mechanics as a result of drug treatment in this population. Biomechanical parameters have previously been used to identify the effects of pharmacological therapies on musculoskeletal disorders and neurological disorders including osteoarthritis (Shrader et al., 2004) and Parkinson’s disease (Hass et al., 2005). In the current study, we hypothesized that if treatment with either cilostazol or pentoxifylline can improve hemodynamics of the affected arteries, then we will expect that biomechanical gait parameters will be altered in PAD patients administered these drugs for three months. Previous studies (Dawson et al., 1998; Dawson et al., 2000; Dawson, 2001) have shown that cilostazol has a greater effect on improving overall walking distance in PAD patients as compared with pentoxifylline. Based on these studies, we also hypothesized that PAD patients treated with cilostazol would exhibit increased gait changes compared with patients treated with pentoxifylline.

Methods

Subject Inclusion and Exclusion Criteria

Twenty PAD patients (66.7 ± 8.7 yrs) presenting with claudication in at least one leg, and planning to undergo pharmacologic therapy with either the drug pentoxifylline or cilostazol were recruited from the Medical Center and the Veterans Affairs Medical Center vascular surgery clinics. A total of 11 patients were given pentoxifylline while 9 patients were given cilostazol (Table 1). Out of the 11 patients treated with pentoxifylline, 21 limbs were evaluated and of the 9 patients treated with cilostazol, 17 limbs were evaluated. The difference between patient number and limb number is due to the fact that some patients in each group were unilateral while others were bilateral with respect to the limbs affected by PAD. Affected limbs were defined as exhibiting an ABI of less than 0.9 and had symptoms of intermittent claudication. All

Table 1 Group means (SD) for several demographic, functional, and clinical characteristics of the patients and the controls

Characteristic	Pentoxifylline (N = 11), mean (SD)		Cilostazol (N = 9), mean (SD)	
Age (yrs)	66.4 (10.1)		67.0 (7.4)	
Weight pretest (kg)	79.5 (16.5)		81.9 (13.7)	
BMI	27.4 (5.6)		27.5 (4.1)	
Height (cm)	170.2 (4.6)		172.2 (4.8)	
ABI (R/L)	0.56 (0.16) / 0.53 (0.23)		0.55 (0.12) / 0.65 (0.15)	
ACD (m)	Pre-Rx 234.9 (85.2)	Post-Rx 236.8 (149.6)	Pre-Rx 190.6 (82.8)	Post-Rx 209.2 (179.2)
Walking speed (m/s)*	Pre-Rx 1.19 (0.19)	Post-Rx 1.18 (0.19)	Pre-Rx 1.14 (0.19)	Post-Rx 1.14 (0.23)
Change in TUG (s)	+0.20		+0.62	
Diabetes (%)	0		0	
Hypertension (%)	63.6		77.8	
Smoking (%)	63.6		33.3	
Dyslipidemia (%)	45.5		77.8	
CAD (%)	36.4		11.1	

Note. BMI—body mass index; ABI—ankle-brachial index; ACD—absolute claudication distance; CAD—cardiovascular disease; TUG—timed up and go.

*No significant differences were present for walking speeds before vs. after.

participating patients in this study were given informed consent by one of the vascular surgeons when they were seen at the vascular clinic. All procedures were approved by the University and the Veterans Affairs institutional review boards.

The drug assignment was conducted to best optimize therapy based on the patient's medical history and participating medication formulary; therefore, the drug assignment within the study was not random and the investigators were not blinded to the treatment. Past treatment history, such as smoking cessation programs or exercise therapy, was considered by the treating physician when assigning the specific pharmacological agent to each subject and all patients were treatment naïve with regards to both cilostazol and pentoxifylline. PAD patients were recruited at the Veterans Affairs hospital by two board certified vascular surgeons (coauthors I.P., J.J.). For all patients enrolled in this study, personnel at the Veterans Affairs Hospital monitored drug disbursement and refills. Patients were specifically evaluated before enrollment in the study to ensure that walking impairments were secondary to claudication pain. Patients with ambulation limiting cardiac, pulmonary, neuromuscular, or musculoskeletal disease or those who experienced pain or discomfort during walking for reasons other than claudication, such as arthritis, low back pain, or other orthopedic problems, were excluded. Additional exclusion criteria for the PAD patients were severe congestive heart failure, severe hypertension (>180/110), severe lung disease, severe ischemic heart disease, severe arthritis, threatened limb loss (foot ulcers or gangrene), uncontrolled hyperlipidemia or any other process limiting the ability to walk. Patient evaluation included resting ABI (a

measurement below 0.90 was present in all subjects with claudication), detailed history, physical exam, and direct assessment/observation of the patient's walking impairment. A vascular surgeon observed the patient walking and recorded all symptoms and signs affecting ambulation to ensure limitation was secondary to claudication pain.

One of the unique features of this study is that patients were screened for significant comorbidities that could affect gait, such as osteoarthritis, orthopedic problems in the legs, artificial joints, and significant lower extremity trauma. This resulted in "pure" PAD patients. Examination of PAD patients without gait affecting comorbidities is almost never seen in studies examining PAD populations because subjects are only screened for an ankle brachial index of less than 0.90 to ensure that they have PAD (Gardner & Montgomery, 2001a, 2001b; McCully et al., 1999; McDermott et al., 2001, 2003).

Experimental Procedures and Data Collection

For all data collections, subjects wore a form fitting outfit while reflective markers were placed bilaterally according to anatomical position and a modified Helen Hayes marker set (Houck et al., 2005). Patients were asked to walk through the 10 m walk-way at a normal pace without care of the position of the force platform. Once the starting position was determined for each leg, the patient was seated to rest for one minute before the beginning of the data collection. The rest period was to insure that any ischemic condition resulting from walking 10 m would have subsided.

The 3D marker trajectories were captured with a six high-speed real-time camera system (EvaRT 5.0, Motion Analysis Corporation, Santa Rosa, CA) sampling at 60 Hz. The ground reaction force data were acquired with a Kistler force platform sampling at 600 Hz. We collected one limb at a time, as only one force platform was available in the laboratory, so each limb was analyzed separately. The limb collected first was randomly selected to insure fatigue was not a factor in the results. Following the initial trial and the rest period, the subject was asked to walk through the walkway from the determined starting position. Data were collected from heel contact to toe off on the force platform, representing an entire stance phase. Once the walk over was completed, the patient again sat for a one minute rest period. The same process was then repeated at least four more times to obtain five walkovers. Next, the contralateral limb was collected using the same process. Absolute claudication distance was measured at the end of the data collection after a period of five minutes of rest to insure the beginning of testing commenced while the patients were pain-free. Patients walked on a treadmill at a speed of 0.67 m/s and at a grade of 10% according to published clinical guidelines (DiBianco et al., 1984). Patients walked until they were unable to continue due to claudication pain. Absolute claudication distances were based on patient's self-reported, maximum tolerable pain. Thus, once maximum pain was reached, walking was ceased. This is standard clinical protocol for the absolute claudication distance test in PAD patients (Dawson et al., 2000; Dawson, 2001; Money et al., 1998).

The data collection procedure was completed in the same fashion for the patient's baseline data collection, before pharmacological therapy, and for the posttherapy data collection. During the treatment period, patients were not restricted from performing extra training and their physical activity levels were not monitored. The two collection times were separated by at least 3 months

so that the subjects were administered the drug therapy for at least 12 weeks. Treatment periods of 12–24 weeks are standard for pharmacological interventions involving pentoxifylline and cilostazol (Beebe et al., 1999; Dawson et al., 1998, 2000).

From the ground reaction force data and the positions of the markers, joint kinetics and kinematics were calculated from the sagittal plane of motion during the stance phase of walking. A low-pass fourth-order Butterworth filter with a 6 Hz cutoff was used to smooth the marker trajectories during post data processing. Relative joint angles were calculated with the methods described by Vaughan et al. (1999) and Nigg et al. (1993). A custom MatLab program was used to calculate joint kinetics and kinematics of each subject while inverse dynamics were used to calculate the joint moments at each joint throughout the stance phase of the gait cycle. The joint kinetics parameters were scaled to body weight and body height (Winter, 2005).

Group means of the joint kinetics and kinematics were calculated for each testing condition (pre and post conditions) and by medication group (cilostazol or pentoxifylline) by combining all legs of each group. Thus, an N of 21 limbs was generated for the pentoxifylline group and an N of 17 limbs for the cilostazol group. To extend the normality assumption to the currently studied pathological population, all investigated variables were tested for normality using the Shapiro-Wilk (*W*) procedure. The average *W* values across all subjects are listed in Tables 2 and 3. The *W* values suggest a strong tendency for normality among the subjects. Thus, a 2 × 2 mixed ANOVA was performed for the within (pre vs. post test) and the between (cilostazol vs. pentoxifylline) factors using SPSS software (SPSS 14.0, Chicago, IL). For any significant interactions, a Tukey's post hoc test was performed. Due to the large number of comparisons, a Bonferroni correction was employed and the α -level

Table 2 Joint angle results

Degrees	Cilostazol		Pentoxifylline		Test	P-Values		Shapiro-Wilk <i>W</i>
	Pre-Rx	Post-Rx	Pre-Rx	Post-Rx		Treatment	Interaction	
ADM	14.71	14.56	13.68	12.57	0.460	0.078	0.573	.986
APM	-4.83	-4.97	-5.33	-6.61	0.320	0.201	0.427	.980
AROM	19.54	19.53	19.01	19.19	0.870	0.638	0.853	.977
KFM	13.75	13.90	11.45	10.21	0.560	0.123	0.448	.975
KEM	4.37	4.86	1.32	0.44	0.430	0.001†	0.152	.963
KROM	9.38	9.05	10.13	10.64	0.830	0.409	0.313	.982
HFM	24.51	23.39	23.67	25.14	0.830	0.727	0.129	.979
HEM	-11.79	-13.16	-13.34	-12.14	0.900	0.762	0.078	.975
HROM	36.30	36.55	37.01	37.28	0.540	0.625	0.988	.974

Note. All mean values are in degrees of motion. ADM—Peak dorsiflexion during stance; APM—Peak plantar flexion during stance; AROM—Ankle range of motion; KFM—Peak knee flexion during stance; KEM—Peak knee extension during stance; KROM—Knee range of motion; HFM—Peak hip flexion during stance; HEM—Peak hip extension during stance; HROM—Hip range of motion.

†Significance, $p < 0.003$.

Table 3 Joint moment results

%BW × BH	Cilostazol		Pentoxifylline		Test	P-Values		Shapiro Wilk W
	Pre-Rx	Post-Rx	Pre-Rx	Post-Rx		Treatment	Interaction	
ADMM	-3.53	-3.58	-3.44	-3.17	0.450	0.356	0.292	.972
APMM	14.88	14.89	15.51	15.87	0.530	0.059	0.552	.968
KFMM	2.53	1.55	1.92	2.03	0.120	0.897	0.050	.972
KEMM	-6.90	-7.89	-7.44	-7.10	0.340	0.922	0.044	.970
HFMM	7.99	7.23	9.28	9.51	0.520	0.038	0.234	.978
HEMM	-8.30	-8.74	-9.45	-9.55	0.330	0.224	0.530	.972

Note. ADMM—Peak ankle dorsiflexion moment during early stance; APMM—Peak ankle plantar flexion moment during late stance; KFMM—Peak knee flexion moment during stance; KEMM—Peak knee extension moment during stance; HFMM—Peak hip flexion moment during late stance; HEMM—Peak hip extension moment during early stance.

†Significance, $p < 0.003$.

was set at 0.003 (0.05/15). For both medication groups, a within group analysis was performed using paired t tests to investigate changes in absolute claudication distance and walking speed.

Results

For the pentoxifylline group, there was an average improvement in absolute claudication distance (ACD) of only 1.95 ± 166.8 m [pretherapy (234.9 ± 85.2 m) and posttherapy (236.8 ± 149.6 m)]. For the cilostazol group, there was an average improvement in ACD of 25.7 ± 105.9 m [pretherapy (190.6 ± 82.8 m) and posttherapy (209.2 ± 179.2 m)]. However due to the large within subject variability, there was no significant difference (pentoxifylline, $p = .970$; cilostazol, $p = .642$) between absolute claudication distance pre- and posttherapy for either treatment group. There was no significant change in walking speed for the pentoxifylline group ($p = .848$) or the cilostazol group ($p = .993$).

No significant differences were found due to test (pre versus post) in all the joint angle parameters (0 out of 9 comparisons; Table 2). Due to treatment (cilostazol versus pentoxifylline), only one parameter was found to be significant (1 out of 9 comparisons; Table 2). Peak knee extension (KEM) was significantly less in the pentoxifylline group as compared with those assigned to cilostazol ($p = .001$). No significant interactions were found between test and treatment for the joint angle parameters evaluated.

Due to test (pre vs. post) no significant differences were found in all joint moment parameters evaluated (0 out of 6 comparisons). Due to treatment (cilostazol vs. pentoxifylline), no significant differences were found in all joint moment parameters evaluated (0 out of 6 comparisons). No significant interactions were found between test and treatment for joint moment parameters (Table 3).

Interestingly, even if we did not adopt a more stringent α -value (0.003) and we used an α -value of 0.05, our results would have stayed the same (Tables 2 and 3).

Discussion

The purpose of this study was to determine the effects of two different pharmacological therapies on the gait biomechanics of patients with PAD. Gait of PAD patients was evaluated with joint angles and moments which provide information regarding specific changes at each of the joints of the lower extremities and identify specific responses and contributions at each joint as related to normal, over-ground walking. We hypothesized that if treatment with either cilostazol or pentoxifylline can improve hemodynamics of the affected arteries, then we would expect biomechanical gait parameters to be altered in PAD patients administered these drugs for three months. Because cilostazol has already been shown to affect overall walking distance to a greater extent than placebo or pentoxifylline (Dawson et al., 1998, 2000; Dawson, 2001), we also expected the PAD patients treated with cilostazol would exhibit increased gait changes compared those patients treated with pentoxifylline.

The first hypothesis, that PAD patients would exhibit significant gait changes as a result of pharmacological therapy, was not supported by our results. There were no significant differences in either joint angles or joint moments due to the pharmacological therapy (before vs. after). Due to treatment, there was only one significant difference in the joint angle at the knee. Peak knee extension was higher in the cilostazol group than the pentoxifylline group. However, the lack of interaction between test and treatment for this variable indicates that knee extension was different between the two treatment group both before and after treatment. Joint angle differences between the two treatment groups could be indicative of different walking strategies employed by each group, but the lack of significant changes indicates that both groups had gait parameters that were similar before and after therapy.

The examination of the efficacy of these two pharmacological therapies is not new but the use of these biomechanical tools to examine this population of patients is novel. Previously, Dawson et al. (2000) quantified the

effect of the drug cilostazol and pentoxifylline on the maximal walking distance of patients with PAD. The authors concluded that only cilostazol treatment improved maximal walking distance (107 ± 158 m) over a 24 week treatment period while pentoxifylline was no different than placebo for increasing mean maximal walking distance in patients with intermittent claudication. The current study did not find that cilostazol provided larger improvements instead it found a nonsignificant increase on absolute claudication for both the pentoxifylline group (1.95 ± 166.8 m) and the cilostazol group (25.7 ± 105.9 m). In the previous studies examining walking distance (Dawson et al., 2000; Dawson, 2001), the number of subjects that participated in each study was much larger than the number of subjects who participated in the current study. This difference is significant since increasing the number of subjects in the current study could possibly affect the outcome of the absolute claudication distance measurements. In addition, in the Dawson et al. (2000) study, pharmacotherapy was provided for almost 6-months, while in the current study, we only used 3 months. It is possible that after 6-months, the results of the pharmacotherapy could be augmented and differences can be observed in biomechanical parameters as well. This hypothesis will be explored in future studies. The rationale for using only 3 months of treatment in the current study is based on the most commonly used time of pharmacotherapy for PAD patients by clinicians.

The present study found that there were no significant differences in biomechanical gait parameters which revealed that there were no changes in the walking mechanics or how the patients walk as a result of pharmacological therapy. Scott-Pandorf et al. (2007) and Chen et al. (2008) found that PAD patients ambulate differently than controls even in the absence of pain. The medication should improve hemodynamics and increase blood flow regardless of the presence of pain. Thus, the pain-free condition should hypothetically exhibit improvements in gait mechanics. However, due to the physiological changes at the muscle fibers described by Pipinos et al. (2006), the altered hemodynamics may not be sufficient to reverse the mitochondrial damage seen in PAD patients. Because the muscle fibers have been physiologically altered as a result of PAD, the altered hemodynamics caused by the pharmacological therapy may not be able to reverse mitochondrial damage and elicit normal muscle function and thus, normal gait mechanics.

Besides the differences in study methods and number of patients, the lack of significant findings in the current study may also stem from the fact that previous studies have measured pharmacological therapy effects after a 12 week treatment period using simple spatial and temporal walking parameters (Wang et al., 2006; Hiatt et al. (1990). Such measures cannot identify specific joint muscular responses and contributions during walking. The results of the current study for the joint angle values are in agreement with previously published values for PAD patients by Chen et al. (2008) and Crowther et al. (2007), while joint moment values were also in agreement with those

published by Chen et al. (2008). It should also be noted that because these medications are the only drugs approved by the FDA to treat intermittent claudication related symptoms in PAD, many doctors prescribe the drugs to help patients "walk better." However, the examination of biomechanical changes as a result of the medications has not previously been investigated. Thus, for physicians prescribing these drugs, it is important to be aware that there may be no underlying changes to gait mechanics and instead only changes to walking distance. While the patients may walk farther, as illustrated by Dawson et al. (1998), Dawson et al. (2000), and Dawson (2001), our results show walking mechanics are unchanged, so the response to these drugs may be patient specific with respect to improving the overall walking pattern.

Our results should also be viewed under certain limitations. Most obviously, there was not randomization of the assigned medication and therefore, there were not an equal number of patients in each treatment group. The differences between groups should be better controlled in future studies by randomizing the assignment of each medication, which was not done in this study. However, because no differences were found between groups in BMI, age, or walking speed, there is no indication that lack of randomization affected the kinematic and kinetic gait results. Next, as mentioned above, the medication was administered for a minimum of 12 weeks which is half the administration time as previous studies comparing cilostazol and pentoxifylline (Dawson et al., 2000). Twelve weeks, however, is the same amount of time that Dawson et al. (1998) used where absolute claudication distance was examined and was compared with patients who received placebo. Cilostazol treated subjects increased absolute claudication distance by 63% after 12 weeks as compared with baseline. This illustrated that 12 weeks should have been enough time for PAD patients treated with this medication to effectively increase their absolute claudication distance. This supports our selection for using 12 weeks for our experimental design. Finally, any extra training for the patients was not monitored. However, patients did not report any changes to their level of activity while enrolled in the study. Because there were no changes in activity level before, after, or during the study, there should be no effect of activity level on gait changes.

In conclusion, this study found that treatment with the two primary drug therapies for intermittent claudication symptoms in PAD patients resulted in minimal outcome changes in gait kinematics and kinetics. This study found that neither cilostazol nor pentoxifylline had an overall significant effect on walking parameters in PAD patients. These findings should be substantiated with longer randomized studies using larger patient populations to objectively determine whether drug therapy can result in changes in the gait mechanics of PAD patients. In addition, future studies should be performed to determine the effect of medication in improving gait mechanics while patients are experiencing claudication pain in a manner that parallels the work by Celis et al. (2009).

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References

- Accetto, B. (1982). Beneficial hemorheologic therapy of chronic peripheral arterial disorders with pentoxifylline: Results of double-blind study versus vasodilator-nylidrin. *American Heart Journal*, 103(5), 864–869.
- Andriacchi, T.P. (1990). Dynamics of pathological motion: Applied to the anterior cruciate deficient knee. *Journal of Biomechanics*, 23(Suppl. 1), 99–105.
- Andriacchi, T.P., Mundermann, A., Smith, R.L., Alexander, E.J., Dyrby, C.O., & Koo, S. (2004). A framework for the in vivo pathomechanics of osteoarthritis at the knee. *Annals of Biomedical Engineering*, 32(3), 447–457.
- Antignani, P.L. (2003). Treatment of chronic peripheral arterial disease. *Current Vascular Pharmacology*, 1(2), 205–216.
- Aronow, W.S. (2004). Management of peripheral arterial disease of the lower extremities in elderly patients. *The Journals of Gerontology. Series A, Biological Sciences and Medical Sciences*, 59(2), 172–177.
- Beebe, H.G., Dawson, D.L., Cutler, B.S., Herd, J.A., Strandness, D.E., Bortey, E.B., et al. (1999). A new pharmacological treatment for intermittent claudication: Results of a randomized, multi-center trial. *Archives of Internal Medicine*, 159, 2041–2050.
- Begg, R.K., & Sparrow, W.A. (2006). Aging effects on knee and ankle joint angles at key events and phases of the gait cycle. *Journal of Medical Engineering & Technology*, 30(6), 382–389.
- Bollinger, A., & Frei, C. (1977). Double blind study of pentoxifylline against placebo in patients with intermittent claudication. *Pharmatherapeutica*, 1, 557.
- Cariski, A.T. (2001). Cilostazol: A novel treatment option in intermittent claudication. *International Journal of Clinical Practice. Supplement*, 119, 11–18.
- Celis, R., Pipinos, I.I., Scott-Pandorf, M.M., Myers, S.A., Stergiou, N., & Johanning, J.M. (2009). Peripheral arterial disease affects kinematics during walking. *Journal of Vascular Surgery*, 49(1), 127–132.
- Chen, S.J., Pipinos, I., Johanning, J., Radovic, M., Huisinga, J.M., Myers, S.A., et al. (2008). Bilateral claudication results in alterations in the gait biomechanics at the hip and ankle joints. *Journal of Biomechanics*, 41(11), 2506–2514.
- Christman, S.K., Ahijevych, K., & Buckworth, J. (2001). Exercise training and smoking cessation as the cornerstones of managing claudication. *The Journal of Cardiovascular Nursing*, 15(4), 64–77.
- Crowther, R.G., Spinks, W.L., Leicht, A.S., Quigley, F., & Golledge, J. (2007). Relationship between temporal-spatial gait parameters, gait kinematics, walking performance, exercise capacity, and physical activity level in peripheral arterial disease. *Journal of Vascular Surgery*, 45(6), 1172–1178.
- Crowther, R.G., Spinks, W.L., Leicht, A.S., Quigley, F., & Golledge, J. (2008a). Intralimb coordination variability in peripheral arterial disease. *Clinical Biomechanics (Bristol, Avon)*, 23(3), 357–364.
- Crowther, R.G., Spinks, W.L., Leicht, A.S., Quigley, F., & Golledge, J. (2008b). Lower limb movement variability in patients with peripheral arterial disease. *Clinical Biomechanics (Bristol, Avon)*, 23(8), 1080–1085.
- Crowther, R.G., Spinks, W.L., Leicht, A.S., Sangla, K., Quigley, F., & Golledge, J. (2008c). Effects of a long-term exercise program on lower limb mobility, physiological responses, walking performance, and physical activity levels in patients with peripheral arterial disease. *Journal of Vascular Surgery*, 47(2), 303–309.
- Dawson, D.L. (2001). Comparative effects of cilostazol and other therapies for intermittent claudication. *The American Journal of Cardiology*, 87(12A), 19D–27D.
- Dawson, D.L., Cutler, B.S., Hiatt, W.R., Hobson, R.W., 2nd, Martin, J.D., Bortey, E.B., et al. (2000). A comparison of cilostazol and pentoxifylline for treating intermittent claudication. *The American Journal of Medicine*, 109(7), 523–530.
- Dawson, D.L., Cutler, B.S., Meissner, M.H., & Strandness, D.E., Jr. (1998). Cilostazol has beneficial effects in treatment of intermittent claudication: Results from a multicenter, randomized, prospective, double-blind trial. *Circulation*, 98(7), 678–686.
- DeLuca, P.A., Davis, R.B., 3rd, Ounpuu, S., Rose, S., & Sirkin, R. (1997). Alterations in surgical decision making in patients with cerebral palsy based on three-dimensional gait analysis. *Journal of Pediatric Orthopedics*, 17(5), 608–614.
- DeVita, P., & Hortobagyi, T. (2000). Age causes a redistribution of joint torques and powers during gait. *Journal of Applied Physiology*, 88(5), 1804–1811.
- DeVita, P., Hortobagyi, T., & Barrier, J. (1998a). Gait biomechanics are not normal after anterior cruciate ligament reconstruction and accelerated rehabilitation. *Medicine and Science in Sports and Exercise*, 30(10), 1481–1488.
- Devita, P., Hortobagyi, T., Barrier, J., Torry, M., Glover, K.L., Speroni, D.L., et al. (1997). Gait adaptations before and after anterior cruciate ligament reconstruction surgery. *Medicine and Science in Sports and Exercise*, 29(7), 853–859.
- DeVita, P., Lassiter, T., Jr., Hortobagyi, T., & Torry, M. (1998b). Functional knee brace effects during walking in patients with anterior cruciate ligament reconstruction. *American Journal of Sports Medicine*, 26(6), 778–784.
- Di Perri, T., & Guerrini, M. (1983). Placebo controlled double blind study with pentoxifylline of walking performance in patients with intermittent claudication. *Angiology*, 34(1), 40–45.
- DiBianco, R., Morganroth, J., Freitag, J.A., Ronan, J.A., Jr., Lindgren, K.M., Donohue, D.J., et al. (1984). Effects of nadolol on the spontaneous and exercise-provoked heart rate of patients with chronic atrial fibrillation receiving stable dosages of digoxin. *American Heart Journal*, 108(4 Pt 2), 1121–1127.
- Gardner, A.W., Forrester, L., & Smith, G.V. (2001). Altered gait profile in subjects with peripheral arterial disease. *Vascular Medicine*, 6(1), 31–34.
- Gardner, A.W., & Montgomery, P.S. (2001a). Impaired balance and higher prevalence of falls in subjects with intermittent claudication. *The Journals of Gerontology. Series A, Biological Sciences and Medical Sciences*, 56(7), M454–M458.

- Gardner, A.W., & Montgomery, P.S. (2001b). The relationship between history of falling and physical function in subjects with peripheral arterial disease. *Vascular Medicine*, 6(4), 223–227.
- Hass, C.J., Waddell, D.E., Fleming, R.P., Juncos, J.L., & Gregor, R.J. (2005). Gait initiation and dynamic balance control in parkinson's disease. *Archives of Physical Medicine and Rehabilitation*, 86(11), 2172–2176.
- Hiatt, W.R., Regensteiner, J.G., Hargarten, M.E., Wolfel, E.E., & Brass, E.P. (1990). Benefit of exercise conditioning for patients with peripheral arterial disease. *Circulation*, 81(2), 602–609.
- Hortobagyi, T., & DeVita, P. (1999). Altered movement strategy increases lower extremity stiffness during stepping down in the aged. *The Journals of Gerontology. Series A, Biological Sciences and Medical Sciences*, 54(2), B63–B70.
- Hortobagyi, T., & DeVita, P. (2000). Muscle pre- and coactivity during downward stepping are associated with leg stiffness in aging. *Journal of Electromyography and Kinesiology*, 10(2), 117–126.
- Houck, J.R., Duncan, A., & De Haven, K.E. (2005). Knee and hip angle and moment adaptations during cutting tasks in subjects with anterior cruciate ligament deficiency classified as noncopers. *The Journal of Orthopaedic and Sports Physical Therapy*, 35(8), 531–540.
- Landry, S.C., McKean, K.A., Hubley-Kozey, C.L., Stanish, W.D., & Deluzio, K.J. (2007). Knee biomechanics of moderate OA patients measured during gait at a self-selected and fast walking speed. *Journal of Biomechanics*, 40(8), 1754–1761.
- Lee, E.H., Goh, J.C., & Bose, K. (1992). Value of gait analysis in the assessment of surgery in cerebral palsy. *Archives of Physical Medicine and Rehabilitation*, 73(7), 642–646.
- McCully, K., Leiper, C., Sanders, T., & Griffin, E. (1999). The effects of peripheral vascular disease on gait. *The Journals of Gerontology. Series A, Biological Sciences and Medical Sciences*, 54(7), B291–B294.
- McDermott, M.M., Guralnik, J.M., Greenland, P., Pearce, W.H., Criqui, M.H., Liu, K., et al. (2003). Statin use and leg functioning in patients with and without lower-extremity peripheral arterial disease. *Circulation*, 107(5), 757–761.
- McDermott, M.M., Ohlmler, S.M., Liu, K., Guralnik, J.M., Martin, G.J., Pearce, W.H., et al. (2001). Gait alterations associated with walking impairment in people with peripheral arterial disease with and without intermittent claudication. *Journal of the American Geriatrics Society*, 49(6), 747–754.
- Messier, S.P., DeVita, P., Cowan, R.E., Seay, J., Young, H.C., & Marsh, A.P. (2005). Do older adults with knee osteoarthritis place greater loads on the knee during gait? A preliminary study. *Archives of Physical Medicine and Rehabilitation*, 86(4), 703–709.
- Money, S.R., Herd, J.A., Isaacsohn, J.L., Davidson, M., Cutler, B., Heckman, J., & Forbes, W.P. (1998). Effect of cilostazol on walking distances in patients with intermittent claudication caused by peripheral vascular disease. *Journal of Vascular Surgery*, 27, 267–274.
- Muller, R. (1979). Pentoxifylline—a biomedical profile. *Journal of Medicine*, 10(5), 307–329.
- Nigg, B.M., Cole, G.K., & Nachbauer, W. (1993). Effects of arch height of the foot on angular motion of the lower extremities in running. *Journal of Biomechanics*, 26(8), 909–916.
- Perhoniemi, V., Salmenkivi, K., Sundberg, S., Johnsson, R., & Gordin, A. (1984). Effects of flunarizine and pentoxifylline on walking distance and blood rheology in claudication. *Angiology*, 35(6), 366–372.
- Pipinos, I.I., Boska, M.D., Shepard, A.D., Anagnostopoulos, P.V., & Katsamouris, A. (2002). Pentoxifylline reverses oxidative mitochondrial defect in claudicating skeletal muscle. *The Journal of Surgical Research*, 102(2), 126–132.
- Pipinos, I.I., Judge, A.R., Zhu, Z., Selsby, J.T., Swanson, S.A., Johanning, J.M., et al. (2006). Mitochondrial defects and oxidative damage in patients with peripheral arterial disease. *Free Radical Biology & Medicine*, 41(2), 262–269.
- Porter, J.M., Cutler, B.S., Lee, B.Y., Reich, T., Reichle, F.A., Scogin, J.T., et al. (1982). Pentoxifylline efficacy in the treatment of intermittent claudication: Multicenter controlled double-blind trial with objective assessment of chronic occlusive arterial disease patients. *American Heart Journal*, 104(1), 66–72.
- Ristanis, S., Giakas, G., Papageorgiou, C.D., Moraiti, T., Stergiou, N., & Georgoulis, A.D. (2003). The effects of anterior cruciate ligament reconstruction on tibial rotation during pivoting after descending stairs. *Knee Surgery, Sports Traumatology, Arthroscopy*, 11(6), 360–365.
- Sawicki, G.S., Lewis, C.L., & Ferris, D.P. (2009). It pays to have spring in your step. *Exercise and Sport Sciences Reviews*, 37(3), 130–138.
- Schainfeld, R. M. (2001). Management of peripheral arterial disease and intermittent claudication. *Journal of the American Board of Family Practice*, 14(6), 443–450.
- Scherer, S.A., Bainbridge, J.S., Hiatt, W.R., & Regensteiner, J.G. (1998). Gait characteristics of patients with claudication. *Archives of Physical Medicine and Rehabilitation*, 79(5), 529–531.
- Scott-Pandorf, M.M., Stergiou, N., Johanning, J.M., Robinson, L., Lynch, T.G., & Pipinos, I.I. (2007). Peripheral arterial disease affects ground reaction forces during walking. *Journal of Vascular Surgery*, 46(3), 491–499.
- Shammas, N.W., & Dippel, E.J. (2005). Evidence-based management of peripheral vascular disease. *Current Atherosclerosis Reports*, 7(5), 358–363.
- Shrader, M.W., Draganich, L.F., Pottenger, L.A., & Piotrowski, G.A. (2004). Effects of knee pain relief in osteoarthritis on gait and stair-stepping. *Clinical Orthopaedics and Related Research*, 421, 188–193.
- Tonak, J., Knecht, H., & Groitl, H. (1983). Treatment of circulatory disturbances with pentoxifylline: A double blind study with Trental. *Pharmatherapeutica*, 3(1), 126–131.
- Vaughan, C., Davis, B., & O'Connor, J. (1999). *Dynamics of human gait*. Cape Town, South Africa: Kiboho Publishers.
- Wang, J., Zhou, S., Brinks, R., Graham, J., & Myers, S. (2006). Effects of supervised treadmill-training on strength and endurance of the calf muscles of individuals with peripheral arterial disease. *Clinical Journal of Sport Medicine*, 16(5), 397–400.
- Winter, D.A. (2005). *Biomechanics and motor control of human movement* (3rd ed.). New York: John Wiley & Sons.
- Winter, D.A., Patla, A.E., Frank, J.S., & Walt, S.E. (1990). Biomechanical walking pattern changes in the fit and healthy elderly. *Physical Therapy*, 70(6), 340–347.