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GAIT VARIABILITY IS ALTERED IN PATIENTS WITH PERIPHERAL ARTERIAL DISEASE

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Abstract

Objective. Claudication is the most common presentation of peripheral arterial disease producing significant ambulatory compromise. Claudicating patients, the majority of which are elderly, have reduced mobility and poor health outcomes, including increased risk of falls. The gait of elderly fallers is characterized by increased variability. Increase in the variability of the locomotor system makes gait more noisy and unstable. The purpose of this study is to investigate gait variability in PAD patients.

Design/Methods: Nineteen symptomatic PAD patients (age: 63.6 ± 9.8 years, body mass: 82.1 ± 18.5 kg, body height: 1.71 ± 0.06 m) walked on a treadmill in the absence of pain or claudication symptoms while joint flexion and extension kinematics were captured. Results were compared to those obtained from 17 matched healthy controls (age: 65.2 ± 12.5 years, body mass: 82.0 ± 25.9.5 kg, body height: 1.73 ± 0.08 m). Relative joint angles were calculated for the ankle, knee and hip flexion/extension and the stride to stride variability of joint flexion and extension was calculated from at least 30 consecutive footfalls. Variability was expressed using the largest Lyapunov Exponent, standard deviation and coefficient of variation. Independent t-tests were used to compare gait variability between groups.

Results. Symptomatic PAD patients had significantly higher Lyapunov Exponent values and coefficient of variation values for all joints, and higher standard deviation values at the ankle and the hip ($P < 0.05$).

Conclusions: Symptomatic PAD patients have increased gait variability at the ankle, knee, and hip joints at baseline ambulation in the absence of claudication pain. Our findings indicate significant baseline deterioration in the locomotor system of symptomatic PAD patients. This deterioration results in increased noise and instability of gait and is a potential contributing factor to the falls and mobility problems experienced by the symptomatic PAD patients.

Introduction

Peripheral arterial disease (PAD) is a manifestation of atherosclerosis producing blockages in the arteries supplying the lower extremities. PAD affects eight to twelve million people in the Unites States, the majority of which are elderly [1, 2]. Patients with significant PAD cannot increase the blood flow to their legs during exercise and experience a combination of ischemic muscle pain and inability to walk normally called intermittent claudication. Claudicating patients, most of which are elderly, have reduced mobility and poor health outcomes, including increased risk of falls. Although gait in PAD patients with a history of falls has not been previously investigated, it has been the subject of considerable research in the elderly population. Advanced biomechanical analysis has demonstrated that one of the most important changes noted in the gait of elderly fallers is increased variability [3- 5]. Because PAD patients tend to be older and to fall [6,7] we hypothesized that they also have increased gait variability.

Variability is inherent within all biological systems and can be described as the normal variations that occur in motor performance across multiple repetitions of a specific task. In healthy adults, the way leg joints flex and extend changes from one stride to the next (Figure 1), in a variable manner [8,9]. Mathematical techniques from chaos theory or nonlinear applications have demonstrated that such variations are not random but have a deterministic pattern. In a biological system such as the ambulating normal lower extremities there is an “optimal” amount of variability. This variability has highly organized form and its maintenance at the “optimal” level is associated with health. Both a decrease and an increase in the form of the variability are associated with malfunction and disease. A decrease or loss of form makes the locomotor system more rigid and less adaptable to different perturbations (“robot-like” walking), while an increase

makes the system more noisy and unstable ("drunken-like" walking). Study of variability in different organ systems has demonstrated that alterations in heart rhythm variability can predict arrhythmias [10] and sudden cardiac death syndrome [11], while alterations in brain wave variability are associated with ischemic brain syndromes [12] and epileptic seizures [13] . Similarly, analysis of the variability of the gait patterns of PAD patients may provide a window into the status of the locomotor system of the patient. It can allow insight into the intricate strategies PAD patients use to control movement and eventually help develop appropriate prognostic and diagnostic tools. Gait variability can be measured using advanced biomechanical analysis and can be described by using linear and nonlinear tools. Linear tools measure magnitude or amount of variation and include the standard deviation and the coefficient of variation. Standard deviation shows how much are a series of data spread around a central point (i.e. mean), while coefficient of variation is a normalized measure of this dispersion to the mean. Nonlinear tools measure how variability changes over time (from one stride to the next) and tell us about the structure of variability. A commonly used nonlinear tool is the largest Lyapunov exponent [8.14] [16, 27, 28]. The purpose of this study was to determine the gait variability by evaluating the joint kinematic variability of the lower extremities in claudicating patients as compared to age, height, mass, and gender matched controls.

Methods

Subjects

Nineteen symptomatic PAD patients (age: 63.6 ± 9.8 years, body mass: 82.1±18.4 kg, body height: 1.71±0.06 m) diagnosed with moderate arterial occlusive disease and bilateral claudication were recruited from the vascular surgery clinics of the Veterans Affairs Medical Center of Nebraska and Western Iowa and the University of Nebraska Medical Center, Omaha, NE. In addition, seventeen height, mass, gender, and age matched healthy controls (age: 65.2 ± 12.5 years, body mass: 82.0 ± 25.9 kg, body height: 1.73 ± 0.08m) were recruited from the community and volunteered to participate. Informed consent was obtained from all subjects prior to data collection according to the guidelines of the respective institutions' Institutional Review Boards. Patients and controls were screened and evaluated by two board certified vascular surgeons. Patient evaluation included detailed history, physical exam and direct assessment/observation of the patient's walking impairment. A vascular surgeon observed the patient walking to insure limitation was secondary to claudication pain. Those PAD patients with ambulation limiting cardiac, pulmonary, neuromuscular or musculoskeletal disease or those who experienced pain or discomfort during walking for any reason other than claudication (i.e. arthritis, low back pain, musculoskeletal problems, neuropathy) were excluded.

Control subjects had an Ankle Brachial Index ≥ 1.0 and no subjective or objective ambulatory dysfunction. Controls were screened in a similar fashion as PAD patients and were excluded for the same ambulation limiting co-morbidities or if pain was experienced during walking. The gait of all recruited participants was tested in the biomechanics laboratory.

Experimental Procedure and Data Collection

Prior to data collection, reflective markers were placed at specific anatomical locations of each subject's lower limb utilizing the systems used by Vaughan [15] and Nigg [16]. Subjects wore a tightly fitting running suit to allow markers to be placed as close to the anatomical position as possible. Following the marker placement, subjects were allowed to get accustomed to the treadmill prior to recording data. During this familiarization period, subjects started walking at 0.45 m/sec and were free to increase or decrease the speed until a comfortable speed was found; this speed was identified as the self-selected speed. Subjects were given up to 10 minutes to get used to the treadmill, this time has previously been found to be adequate for subjects to achieve a proficient treadmill walking pattern [17]. The patient was then allowed to rest to insure absence of claudication pain before data collection began. Three dimensional kinematics were acquired at 60 Hz using EVART software (Motion Analysis Corp., Santa Rosa CA) while subjects walked on a treadmill at their self-selected speed. Self-selected speed is the most comfortable and natural walking speed and is the optimal speed to evaluate gait variability [18]. A predetermined speed could put subjects into an uncomfortable situation, which may be manifested with increased variability, as opposed to the more stable state that occurs with the self-selected speed [18]. Patients walked on the treadmill for three minutes or until the onset of claudication pain, whichever came first. All kinematic measurements were taken prior to the onset of claudication symptoms. For safety purposes, blood pressure was monitored before and after the treadmill test.

Data Analysis

Data was exported and processed in custom software using Matlab (Mathworks Inc., MA). This software was used to calculate the relative joint angle time series for the ankle, knee and hip flexion/extension. The within and between session repeatability of kinematic gait parameters is high with intraclass correlation coefficients ranging between 0.82 and 0.99, and

coefficients of multiple comparisons ranging from 0.82 to 0.99 [19]. Furthermore, joint kinematic variability was examined, because it has been shown that variability of stride characteristics (i.e. stride length, stride time) offer a less sensitive measure of differences between groups than variability of joint kinematics [20]. A trial with a minimum of 30 footfalls was considered adequate for nonlinear and linear analysis [9, 21-24]. All joint angle time series were graphed and the number of data points required to reach 30 strides was counted. After the minimum data points for 30 strides were determined for all subjects, all data were cropped to that number, insuring each time series included at least 30 gait cycles. All subjects in the study were able to complete 30 strides prior to the onset of claudication pain. The data was analyzed unfiltered to obtain a more accurate representation of the variability within the locomotor system. Because the same collection system was used for all subjects, we assumed a consistent level of measurement noise exists. Therefore any differences between groups could be attributed to the differences in the locomotor system itself [8,25]. Time series of these values were exported in ASCII format and used for further analysis.

Linear analysis

From each time series, range of motion was calculated for every gait cycle for the ankle, knee and hip angles. Means were then calculated for each variable and for each subject, as well as standard deviations and coefficients of variation. The calculation of these parameters was performed in Matlab (Mathworks Inc., MA). This analysis supplemented the nonlinear analysis and provided answers regarding the magnitude of variability present in the gait patterns.

Largest Lyapunov Exponent

The largest Lyapunov exponent quantifies the mean rate of divergence of neighbored state-space trajectories and estimates the amount of variability in the ~~a~~ system (Figure 1). The calculation of

the largest Lyapunov Exponent takes into consideration the entire time series of the joint angle (it does not occur at a specific time point in each time series). It was calculated for all joint angle time series and for both groups.

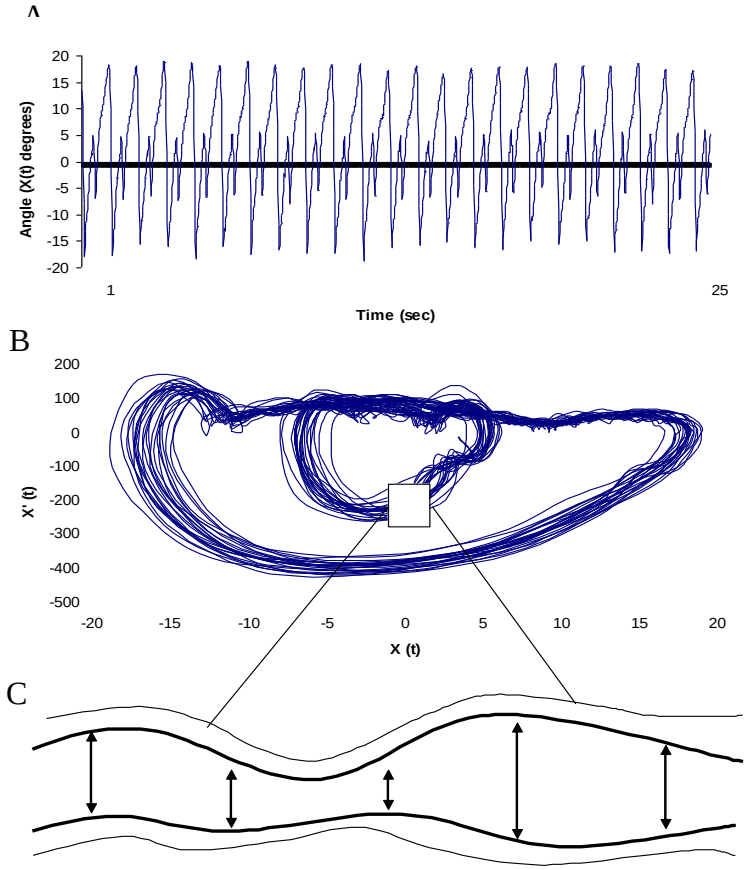

Figure 1. A graphical representation of the state space of an ankle joint angle time series and the calculation of the largest Lyapunov Exponent. (A) An original ankle plantarflexion-dorsiflexion time series from a control subject. (B) A two-dimensional state space created by the position and velocity time series from the same ankle angle. Each step (from heel touchdown to heel touchdown in the same foot) includes both a large and a small circle. The large circle corresponds to the maximum ankle plantarflexion and dorsiflexion positions around toe off, while the small circle corresponds to the relatively smaller ankle plantarflexion and dorsiflexion positions around heel touchdown. This becomes apparent by comparing the maximum and minimum values from part A to the position values from part B. They range from about -20 degrees to 20 degrees for the absolute maximums (large circle) and from about -5 degrees to 5 degrees for the local maximums (small circle). (C) A section of the state space where the divergence of neighboring trajectories is outlined. The largest Lyapunov exponent is calculated as the slope of the average logarithmic divergence of the neighboring trajectories [9].

Further description of the actual calculation of this measure is included in Appendix A. The largest Lyapunov Exponent quantifies the exponential separation of nearby trajectories in the reconstructed state space of the joint angle time series. As nearby points of the state space separate, they diverge rapidly and can produce instability (Figure 1). The largest Lyapunov Exponent from a stable system with little to no divergence will be zero (e.g. since wave). Alternatively, the largest Lyapunov Exponent for an unstable system that has a high amount of divergence will be positive with a larger value (above 0.5; Figure 2) [8-9,23]. The *Chaos Data*

Analyzer (professional version, American Institute of Physics [21] was used to numerically calculate the largest Lyapunov Exponent for each joint angle time series for each subject.

One of the assumptions made when calculating the largest Lyapunov Exponent is that the source of the variation in a given time series is actually deterministic in nature [8-9,26]. A deterministic time series is one that has an ordered pattern (each point in the series is related to its preceding points). Therefore, to ensure our time series met this assumption, we used the method of surrogation. Surrogation compares the original time series data set to an equivalent random data set with similar structure. Essentially, surrogation removes the deterministic characteristics from the actual joint angle data set by shuffling the data to ~~and~~ produce~~s~~ a random series with the same mean, variance and power spectra as the original data. The surrogated data set includes the same values as the original time series, but the values are in a different order, so that the points are no longer related with each other (random). Significant differences in largest Lyapunov Exponent values between the original and surrogate counterparts reveal ~~show~~ that the variations in the original time series are not randomly derived, but they are deterministic in nature [9]~~[17]~~.

Surrogated data sets were created for each original joint angle time series analyzed. This procedure was performed in Matlab (Mathworks Inc, MA) using the pseudoperiodic surrogation algorithm [9,26]~~.~~ The pseudoperiodic algorithm is used to determine if there is additional determinism in the fluctuations present in a time series that have inherent periodicity (e.g. gait cycles). Largest Lyapunov Exponent values were calculated for both the surrogated and original joint angle time series data and compared using a dependent t-test (alpha=0.05). Significant differences between data sets indicate that the variations present in the original data set are not random, but they are deterministic in nature.

Statistical Analysis

Means for the standard deviation and the coefficient of variation of the range of motion and the largest Lyapunov Exponent were calculated for the ankle, knee and hip joints for both patient and control groups. Independent t-tests were used to compare the group means between the two groups. Statistical comparisons were performed using SPSS (SPSS Inc., 12.0). The level of significance was set at $\alpha = 0.05$.

Results

Group means for age (P=.986), height (P=.281), weight (P=.397) and body mass index (BMI; P=.605) did not differ between patients and controls, verifying that the two groups were well matched (Table 1), whereas clinical characteristics of the two groups were quite different (Table 1).

Table 1. Baseline characteristics of PAD patients and healthy control subjects.

	Patient (N= 19)	*Control (N=17)*	*P values*
Clinical characteristics			
Gender (Male/Female)	18/1	12/5	.054
Age (years)	63.6 ± 9.8	65.2 ± 12.5	.986
Body mass (kg)	82.1 ± 18.4	82.0 ± 25.9	.397
Body height (m)	1.71 ± 0.06	1.73 ± 0.08	.281
Disease duration (years)	6.25 ± 3.84	0	NA
Ankle Brachial Index			
Right limb	0.52±0.22	1.1±0.10	<.001
Left limb	0.50±0.25	1.1±0.09	<.001
Smokers (%)	73.68	0	<.001
Hypertension (%)	84.21	13.33	<.001
Diabetes mellitus (%)	21.05	6.67	.199
Hyperlipidemia (%)	89.47	6.67	<.001
Body Mass Index	28.0 ± 5.6	27.2 ± 7.1	.605
Self-selected treadmill speed (km/hr)	0.63 ± 0.13	1.03 ± 0.26	<.001

For the nonlinear analysis, PAD patients had significantly higher largest Lyapunov Exponent values than controls for the ankle, knee and hip joints (Table 2). These findings demonstrate that joint movement patterns in PAD patients were farther apart in consecutive strides (Figure 2) and indicate altered neuromuscular organization. For the linear analysis, PAD patients had higher coefficient of variation values than controls for all three joints (Table 3 ~~2~~). PAD patients also had significantly higher standard deviation values than controls for the ankle

and the hip. Thus, the linear analysis indicated an increased amount of variability in the gait patterns of the PAD patients. Regarding the surrogation analysis, in the control group the surrogate data series had significantly higher largest Lyapunov Exponent values than the original data at the ankle and the knee (Table 2). In the PAD group, the surrogated largest Lyapunov Exponent values were significantly higher than the original data only for the ankle (Table 2).

Table 2. Group means for the Lyapunov Exponent of the original time series (LyE) and the surrogate time series (LyE-S) for Peripheral Arterial Disease (PAD) and control groups.

Group	Ankle	Knee	Hip
PAD LyE (n=16)	.105 ± 0.02*	.098 ± 0.01*	.095 ± 0.02*
Control LyE (n=17)	.078 ± 0.02	.074 ± 0.02	.078 ± 0.01
PAD LyE-S	.118 ± 0.02^{+}	.103 ± 0.01	.092 ± 0.02
Control LyE-S	.088 ± 0.02^{+}	.093 ± 0.02^{+}	.081 ± 0.03

Data are reported as Mean ± SD. Significant differences ($P < 0.05$) between PAD and control groups are marked with an asterisk (*). Significant differences between the original time series and their surrogate counterparts are marked with a plus sign ($^{+}$).

Table 3. Group means for the standard deviation (SD) and coefficient of variation (CoV) for Peripheral Arterial Disease (PAD) and control groups.

Group	Ankle	Knee	Hip
PAD SD (n=18)	3.99 ± 2.08*	2.44 ± 0.82	2.09 ± 0.76*
Control SD (n=17)	2.84 ± 1.06	2.03 ± 0.79	1.47 ± 0.45
PAD CoV	18.80 ± 10.31*	5.16 ± 2.29*	6.60 ± 2.54*
Control CoV	8.29 ± 5.60	3.61 ± 1.44	3.98 ± 1.38

Data are reported as Mean ± SD. Significant differences ($P < 0.05$) between groups are marked with an asterisk (*).

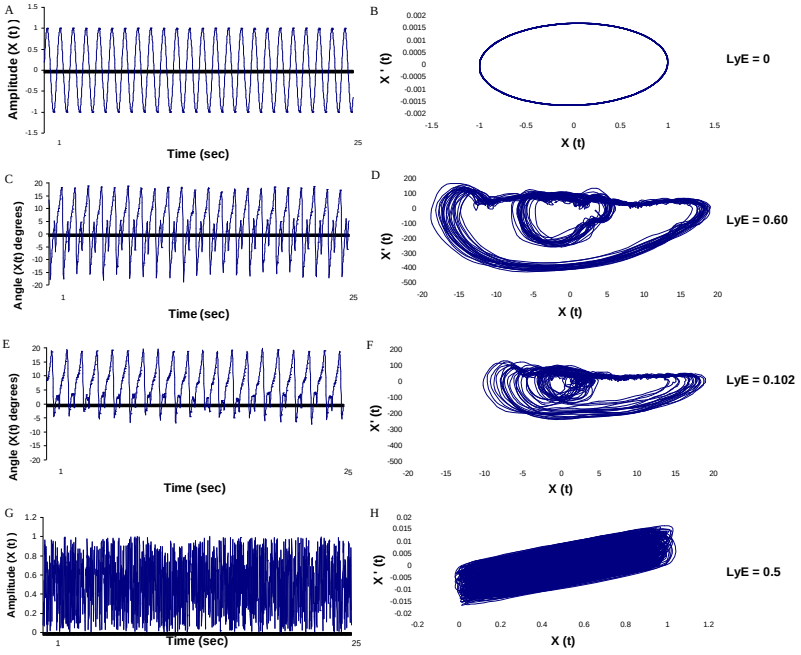

Figure 2. A graphical comparison of variability between a (A) periodic signal (sine wave), (C) Control subject ankle joint, (E) PAD ankle joint, and (G) a random signal (white noise). Graphs A, C, E, and G are the time series and graphs B, D, F, and H are two-dimensional state spaces created by plotting the position (X(t)) versus the velocity (X' (t)) from the corresponding signals. The largest Lyapunov Exponent (LyE) for each signal is also shown. It is clear that the PAD patient has much more divergence in the movement trajectories which results in a larger Lyapunov Exponent.

Discussion

The purpose of this study was to determine the kinematic variability of the lower extremities in symptomatic PAD patients while walking in the absence of claudication pain and to compare them to controls matched for age, height, mass, and gender. Our data demonstrate that the gait of claudicating patients is abnormal even when walking in the absence of claudication symptoms. Literally the gait of PAD patients is abnormal from the first step they take [27]. The character of PAD gait is disorganized with the changes becoming apparent at the level of all lower extremity joints (ankle, knee and hip) suggesting multilevel neuromuscular deterioration in the locomotor system. For the linear measures of variability, five out of six comparisons were significantly different, indicating a significant increase in the gait variability of PAD patients. Furthermore, for our nonlinear analysis all comparisons were significantly different indicating an increase in the noise and randomness of the PAD gait and instability in the locomotor system [5]. This increased noise in the neuromuscular system may result in inability to correctly select the required response when faced with a perturbation. Similar findings in the elderly and in patients with Parkinson's and Huntington's disease have been linked to increased risks of falling and decreased physical function [3,8,25]. Likewise, the altered variability may be contributing to the increased rate of falls and mobility problems in patients with PAD.

The data from the surrogation analysis demonstrate that the largest Lyapunov Exponent values of the original data series were significantly different than their surrogate counterparts for the ankle and knee in the control group. For the PAD group when surrogation was applied, we found that only the ankle showed significant differences from its surrogate counterpart. Our findings indicate that the variability present in healthy controls is deterministic, and that this is much less the case with the PAD patients. The deterministic properties of the normal gait are

important because they allow individuals to successfully adapt to changing environmental conditions (i.e. slippery surfaces, obstacles) during walking. This degradation of the variability structure in the PAD patients is further evidence of the effect of the disease on the gait patterns of these patients. These results are in agreement with Buzzi et al. [8], which found significant differences between the original and surrogate data sets for all three joints in healthy elderly individuals. Buzzi et al. [8] also hypothesized that the deterministic behavior of joint angle variability may degrade with disease, which is precisely what happened in the patients with PAD. It should be noted that lack of significant differences between original and surrogate data series at the hip in controls could be due to limitations in calculating the hip angle. This includes marker placement at the hip area that has a large amount of adipose tissue which increases marker movement. Also, the markers used for hip calculations are sometimes covered up by the arms as they swing in front of them blocking the cameras views. Then, their location has to be interpolated using mathematical algorithms since the actual coordinate data are lost.

The current study compared gait variability between patients with PAD and matched healthy controls. Although the groups are different, the trends of increasing variability found in this study are similar to those found between healthy young and elderly [3,8], healthy elderly and elderly fallers and in studies comparing healthy subjects with Parkinson's and Huntington's disease patients [25]. Healthy (optimal) joint angle variability reflects a coordinated neuro-musculo-skeletal system able to make flexible adaptations to demands placed on the body. Based on this notion, the altered gait variability present in PAD patients demonstrates that symptomatic PAD degrades the ability of the locomotor system to make adaptations to perturbations and may be responsible for the increased rate of falls in this group of patients.

Similarly, because of the high prevalence of PAD among the elderly it is also possible that PAD is one of the underlying comorbidities predisposing older people to falls.

It has previously been shown that patients with PAD have impaired balance and increased risk of falls [6,7], mobility problems [28,29] and altered gait patterns [30,21] as compared to healthy individuals. Specifically functional outcomes measures such as the six minute walk test, physical activity level, chair rises, etc. have repeatedly shown PAD patients to have diminished functioning as compared to those without PAD [2,29], however the mechanisms for these changes are unclear. Previous studies have suggested that muscle weakness or lack of endurance, abnormal muscle metabolism and muscle denervation as caused by chronic muscle ischemia or the onset of claudication pain itself maybe the reason for these impairments [28,31]. The results of the current study suggest that gait is altered prior to the onset of claudication pain, and is not caused by the pain itself. Our data provide considerable support for a well described muscle metabolic myopathy [32,33] and an axonal polyneuropathy in the lower extremities of PAD patients [34]. Specifically, a number of reports have documented a metabolic myopathy in the PAD muscle that appears to be secondary to defective mitochondrial bioenergetics and related oxidative damage to skeletal muscle structures and components [35]. Mitochondria in PAD muscle have abnormal ultrastructure, damaged DNA, altered enzyme expression and activity, and abnormally high intermediates of oxidative metabolism [32,33]. Most importantly, evaluation of claudicating muscle mitochondrial bioenergetics demonstrates specific defects in the complexes of the electron transport chain with associated compromised mitochondrial respiration and ATP production [35-37] that is very similar to those seen in mitochondrial myopathies [32,33]. Recent work also demonstrates that the mitochondriopathy of PAD muscle is associated with evidence of significant oxidative damage to the myofibers [35]. Furthermore, there is

accumulating evidence suggesting that chronic ischemia in PAD patients results in a consistent pattern of electrodiagnostic abnormalities indicating axonal nerve loss [34]. Therefore, the impairments in gait variability prior to the onset of pain likely reflect a combination of myopathy and neuropathy in limbs with PAD. The nature of these myopathic and neuropathic changes and the way they are associated to the clinical and biomechanical findings of leg dysfunction should be the focus of intense future investigation and may hold the key to understanding PAD pathophysiology.

A potential limitation of our study is that the present findings are limited to PAD patients with intermittent claudication and may not be applicable to patients with different symptoms and presentations of the disease. However, our study is unique because detailed screening was used to exclude patients with any gait dysfunction other than claudication. Therefore, our data accurately reflect gait variability changes due to the presence only of PAD, and not of other comorbidities such as neurogenic claudication or osteoarthritis [38,39].

Our results demonstrate that PAD patients have increased and abnormal gait variability at baseline ambulation in the absence of claudication pain. The larger Lyapunov Exponent values observed in the PAD patients indicate increased randomness in their gait patterns and loss of motor control. The surrogation analysis indicated that PAD patients also exhibit a degradation of the deterministic and nonlinear characteristics in their gait patterns. The pathophysiology of PAD includes damage to muscle and nerves of the lower extremities which maybe interfering with the cooperative strategies of the locomotor system producing altered gait variability in patients with PAD. Collectively these results indicate decline of the overall health of the locomotor system, which may contribute to falls and mobility limitations seen in PAD patients. The current study provides the basis for future work that will examine specific mechanisms

contributing to gait abnormalities in PAD patients, including the effect of claudication pain and the role of myopathic and neuropathic changes.

References

1. Menard JR, Smith HE, Riebe D, Braun CM, Blissmer B, Patterson RB. Long-term results of peripheral arterial disease rehabilitation. J Vasc Surg. 2004 Jun;39(6):1186-92.

2. Nehler MR, McDermott MM, Treat-Jacobson D, Chetter I, Regensteiner JG. Functional outcomes and quality of life in peripheral arterial disease: Current status. Vasc Med. 2003 May;8(2):115-26.

3.Maki BE. Gait changes in older adults: Predictors of falls or indicators of fear. J Am Geriatr Soc. 1997 Mar;45(3):313-20.

4. Hausdorff JM. Gait dynamics, fractals and falls: Finding meaning in the stride-to-stride fluctuations of human walking. Hum Mov Sci. 2007 Aug;26(4):555-89.

5. Kurz MJ, Stergiou N. The aging human neuromuscular system expresses less certainty for selecting joint kinematics during gait. Neurosci Lett. 2003 Sep 18;348(3):155-8.

6. Gardner AW, Montgomery PS. The relationship between history of falling and physical function in subjects with peripheral arterial disease. Vasc Med. 2001 Nov;6(4):223-7.

7. Gardner AW, Montgomery PS. Impaired balance and higher prevalence of falls in subjects with intermittent claudication. J Gerontol A Biol Sci Med Sci. 2001 Jul;56(7):M454-8.

8. Buzzi UH, Stergiou N, Kurz MJ, Hageman PA, Heidel J. Nonlinear dynamics indicates aging affects variability during gait. Clin Biomech (Bristol, Avon). 2003 Jun;18(5):435-43.

9. Stergiou, N. Buzzi, UH, Kurz, MJ, Heidel J. Nonlinear tools in human movement. In: Stergiou N, editor. Innovative analysis of human movement. Champaign, IL: Human Kinetics; 2004. p. 63-90.

10. Goldberger AL, West BJ. Applications of nonlinear dynamics to clinical cardiology. Ann N Y Acad Sci. 1987;504:195-213.

11. Goldberger AL, Rigney DR, Mietus J, Antman EM, Greenwald S. Nonlinear dynamics in sudden cardiac death syndrome: Heartrate oscillations and bifurcations. Experientia. 1988 Dec 1;44(11-12):983-7.

12. Freeman WJ. Simulation of chaotic EEG patterns with a dynamic model of the olfactory system. Biol Cybern. 1987;56(2-3):139-50.

13. Glanz J. Do chaos-control techniques offer hope for epilepsy? Science. 1994 Aug 26;265(5176):1174.

14. Hausdorff JM. Gait variability: Methods, modeling and meaning. J Neuroeng Rehabil. 2005 Jul 20;2:19.

15. Vaughan C, Davis B, O'Connor J. *Dynamics of human gait*. Cape Town, South Africa: Kiboho Publishers; 1999.

16. Nigg BM, Cole GK, Nachbauer W. Effects of arch height of the foot on angular motion of the lower extremities in running. J Biomech. 1993 Aug;26(8):909-16.

17. Matsas A, Taylor N, McBurney H. Knee joint kinematics from familiarised treadmill walking can be generalised to overground walking in young unimpaired subjects. Gait Posture. 2000 Feb;11(1):46-53.

18. Sekiya N, Nagasaki H, Ito H, Furuna T. Optimal walking in terms of variability in step length. J Orthop Sports Phys Ther. 1997 Nov;26(5):266-72.

19. Yavuzer G, Oken O, Elhan A, Stam HJ. Repeatability of lower limb three-dimensional kinematics in patients with stroke. Gait Posture. 2008 Jan;27(1):31-5.

20. Barrett R, Noordegraaf MV, Morrison S. Gender differences in the variability of lower extremity kinematics during treadmill locomotion. J Mot Behav. 2008 Jan;40(1):62-70.

21. ~~33.~~ Sprott J, Rowlands G. Chaos data analyzer: The professional version. 1995.

22. Kaplan D, Glass L. Understanding nonlinear dynamics. New York, NY: Springer-Verlag; 1995.

23. Abarbanel HDI. Analysis of observed chaotic data. New York: Springer-Verlag; 1996.

24. Keenan S, Stergiou N. The reliability of the lyapunov exponent during treadmill walking. Proceedings of the fourth world congress of biomechanics meeting. 2002.

25. Hausdorff JM, Cudkowicz ME, Firtion R, Wei JY, Goldberger AL. Gait variability and basal ganglia disorders: Stride-to-stride variations of gait cycle timing in parkinson's disease and huntington's disease. Mov Disord. 1998 May;13(3):428-37.

26. Miller DJ, Stergiou N, Kurz MJ. An improved surrogate method for detecting the presence of chaos in gait. J Biomech. 2006;39(15):2873-6.

27. Chen SJ, Pipinos II, Johanning JM, Radovic M, Huisinga JM, Myers SA, et al. Bilateral intermittent claudication results in alterations in the gait biomechanics at the hip and ankle joints during gait. Journal of Biomechanics. In Press, 2008.

28. McDermott MM, Greenland P, Ferrucci L, Criqui MH, Liu K, Sharma L, et al. Lower extremity performance is associated with daily life physical activity in individuals with and without peripheral arterial disease. J Am Geriatr Soc. 2002 Feb;50(2):247-55.

29. McDermott MM, Greenland P, Liu K, Guralnik JM, Criqui MH, Dolan NC, et al. Leg symptoms in peripheral arterial disease: Associated clinical characteristics and functional impairment. JAMA. 2001 Oct 3;286(13):1599-606.

30. McDermott MM, Ohlmiller SM, Liu K, Guralnik JM, Martin GJ, Pearce WH, et al. Gait alterations associated with walking impairment in people with peripheral arterial disease with and without intermittent claudication. J Am Geriatr Soc. 2001 Jun;49(6):747-54.

31. Gardner AW, Forrester L, Smith GV. Altered gait profile in subjects with peripheral arterial

383 disease. Vasc Med. 2001;6(1):31-4.
384 32Pipinos II, Judge AR, Selsby JT, Zhu Z, Swanson SA, Nella AA, et al. The myopathy of
385 peripheral arterial occlusive disease: Part 1. functional and histomorphological changes and
386 evidence for mitochondrial dysfunction. Vasc Endovasc Surg. 2007 Dec-2008 Jan;41(6):481-9.
387 33. Pipinos II, Judge AR, Selsby JT, Zhu Z, Swanson SA, Nella AA, et al. The myopathy of
388 peripheral arterial occlusive disease: Part 2. oxidative stress, neuropathy, and shift in muscle
389 fiber type. Vasc Endovascular Surg. 2008 Apr-May;42(2):101-12.
390 34. Weber F, Ziegler A. Axonal neuropathy in chronic peripheral arterial occlusive disease.
391 Muscle Nerve. 2002 Oct;26(4):471-6.
392 35. Pipinos II, Judge AR, Zhu Z, Selsby JT, Swanson SA, Johanning JM, et al. Mitochondrial
393 defects and oxidative damage in patients with peripheral arterial disease. Free Radic Biol Med.
394 2006 Jul 15;41(2):262-9.
395 36. Pipinos II, Shepard AD, Anagnostopoulos PV, Katsamouris A, Boska MD. Phosphorus 31
396 nuclear magnetic resonance spectroscopy suggests a mitochondrial defect in claudicating skeletal
397 muscle. J Vasc Surg. 2000 May;31(5):944-52.
398 37. Pipinos II, Sharov VG, Shepard AD, Anagnostopoulos PV, Katsamouris A, Todor A, et al.
399 Abnormal mitochondrial respiration in skeletal muscle in patients with peripheral arterial
400 disease. J Vasc Surg. 2003 Oct;38(4):827-32.
401 38. Issa SN, Sharma L. Epidemiology of osteoarthritis: An update. Curr Rheumatol Rep. 2006
402 Feb;8(1):7-15.
403 39. Norgren L, Hiatt WR, Dormandy JA, Nehler MR, Harris KA, Fowkes FG, et al. Inter-society
404 consensus for the management of peripheral arterial disease (TASC II). J Vasc Surg. 2007 Jan;45
405 Suppl S:S5-67.

406 40. Kurz MJ, Stergiou N, Heidel J, Foster ET. A template for the exploration of chaotic

407 locomotive patterns. Chaos, solitons and fractals. 2005;23:485-93.