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Gait variability is altered in patients with peripheral arterial disease

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

Methods: Nineteen symptomatic PAD patients (age, 63.6 ± 9.8 years; body mass, 82.1 ± 18.5 kg; 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 with results obtained from 17 matched healthy controls (age, 65.2 ± 12.5 years; body mass, $82.0 \pm 25.9.5$ kg; 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 largest Lyapunov exponent values and coefficient of variation values for all joints, and higher standard deviation values at the ankle and the hip ($P < .05$).

Conclusion: 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 symptomatic PAD patients. (*J Vasc Surg* 2009;49:924-31.)

Peripheral arterial disease (PAD) is a manifestation of atherosclerosis producing blockages in the arteries supplying the lower extremities. PAD affects 8 to 12 million people in the United States, most of whom are elderly.^{1,2} In patients with significant PAD, the blood flow to their legs does not increase during exercise and they experience a combination of ischemic muscle pain and inability to walk normally, called intermittent claudication. Claudicating patients, most of whom 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 to our knowledge, 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 biologic 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 (Fig 1), in a variable manner.^{8,9} Mathematic techniques from chaos theory or nonlinear applications have demonstrated that such variations are not random but have a deterministic pattern.

In a biologic 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. A decrease and an increase in the form of the variability are both 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), whereas 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 arrhythmias¹⁰ and sudden cardiac death syndrome,¹¹ whereas alterations in brain wave variability are associated with ischemic brain syndromes¹² 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 patient's locomotor system. It can allow insight into the intricate strategies PAD patients use to control movement and eventually help develop appropriate prognostic and diagnostic tools.

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Competition of interest: none.

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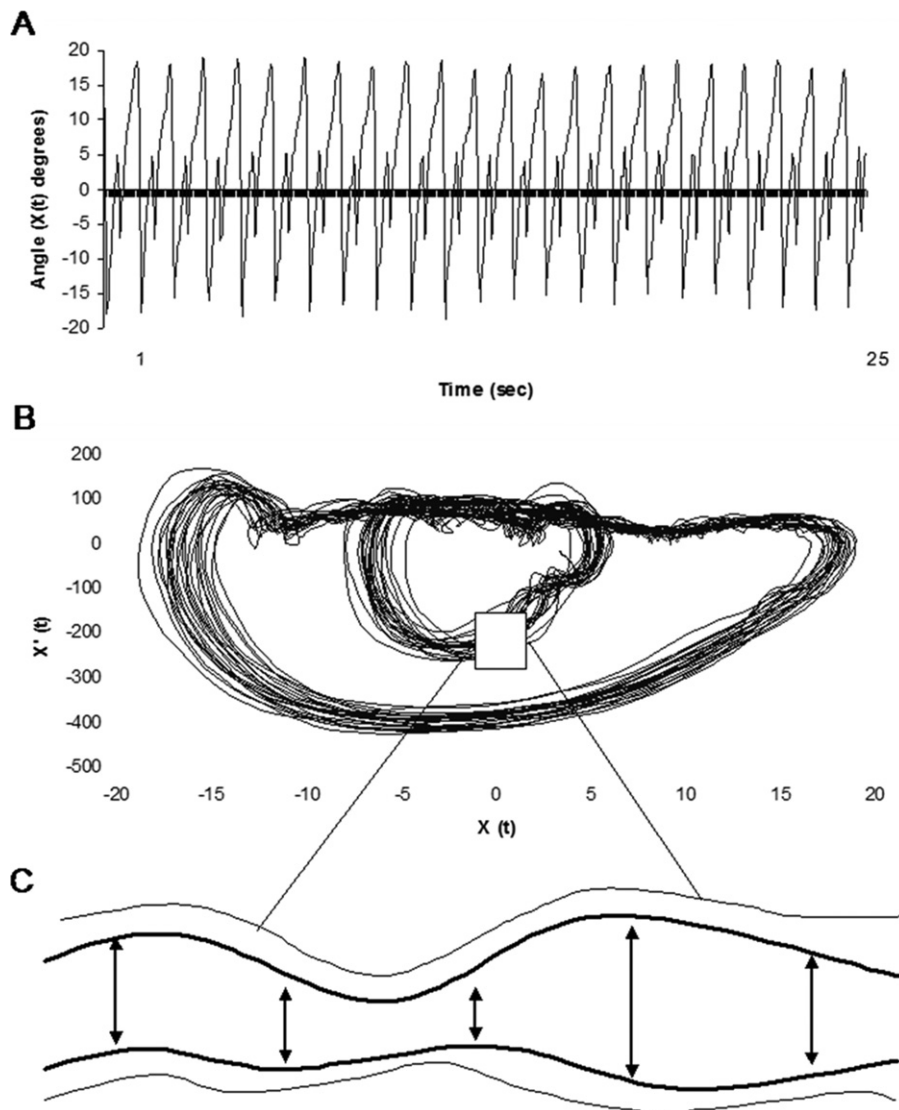


Fig 1. A graphic representation shows the state space of an ankle joint angle time series and the calculation of the largest Lyapunov exponent. **A**, An original ankle plantarflexion-dorsiflexion time series from a control subject. **B**, In this two-dimensional state space created by the position and 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° to 20° for the absolute maximums (*large circle*) and from about -5° to 5° 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

Gait variability can be measured using advanced biomechanical analysis and described by using linear and nonlinear tools. Linear tools measure the magnitude or amount of variation and include the standard deviation and the coefficient of variation. Standard deviation shows how much observations are spread around a mean central point, whereas the 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} The purpose of this study was to determine the gait variability by evaluating the joint kinematic variability of the lower extremities in claudicating patients com-

pared with controls matched for age, height, mass, and gender.

METHODS

Participants. The study recruited 19 symptomatic PAD patients diagnosed with moderate arterial occlusive disease and bilateral claudication from the vascular surgery clinics of the Veterans Affairs Medical Center of Nebraska and Western Iowa and the University of Nebraska Medical Center, Omaha. The patients were 63.6 ± 9.8 years old, their mass was 82.1 ± 18.4 kg, and their height was 1.71 ± 0.06 m. In addition, 17 healthy controls matched for age (65.2 ± 12.5 years) height (1.73 ± 0.08 m), mass (82.0 ± 25.9 kg), and gender were recruited from the community and volunteered to participate. Informed consent was obtained from all participants before 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. The evaluation included a detailed history, physical examination, and direct assessment and observation of the patient's walking impairment. A vascular surgeon observed the patient walking to ensure the limitation was secondary to claudication pain. The study excluded 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, such as arthritis, low back pain, musculoskeletal problems, or peripheral neuropathy.

Control participants had an ankle-brachial index ≥ 1.0 and no subjective or objective ambulatory dysfunction. Controls were screened in a similar fashion to PAD patients and were excluded for the same ambulation-limiting comorbidities or if pain was experienced during walking. The gait of all recruited participants was tested in the biomechanics laboratory.

Experimental procedure and data collection. Before data collection, reflective markers were placed at specific anatomic locations of each participant's lower limb using the systems of Vaughan et al¹⁵ and Nigg et al.¹⁶ Participants wore a tightly fitting running suit to allow markers to be placed as close to the anatomic position as possible. After the markers were placed, participants were allowed to get accustomed to the treadmill before data were recorded. During this familiarization period, participants started walking at 0.45 m/s and were free to increase or decrease the speed until a comfortable speed was found. This speed was identified as the self-selected speed. Participants were given up to 10 minutes to get used to the treadmill; this time has previously been found to be adequate for participants to achieve a proficient treadmill walking pattern.¹⁷ The patient was then allowed to rest to ensure absence of claudication pain before data collection began.

Three-dimensional kinematics were acquired at 60 Hz using EVART software (Motion Analysis Corp, Santa Rosa, Calif) while participants 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 participants into an uncomfortable situation, which may be manifested with increased variability, rather than the more stable state that occurs with the self-selected speed.¹⁸ Patients walked on the treadmill for 3 minutes or until the onset of claudication pain, whichever came first. All kinematic measurements were taken before the onset of claudication symptoms. For safety purposes, blood pressure was monitored before and after the treadmill test.

Data analysis. Data were exported and processed in custom software using MATLAB software (MathWorks Inc, Natick, Mass). 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 of 0.82 to 0.99 and coefficients of multiple comparisons of 0.85 to 0.95.¹⁹ Joint kinematic variability was also examined because variability of stride characteristics, such as stride length and 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 participants, the data were cropped to that number, ensuring each time series included at least 30 gait cycles. All participants were able to complete 30 strides before the onset of claudication pain.

The data were analyzed unfiltered to obtain a more accurate representation of the variability within the locomotor system. Because the same collection system was used for all participants, we assumed a consistent level of measurement noise existed. 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 American Standard Code for Information Interchange (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 participant, as well as standard deviations and coefficients of variation. The calculation of these parameters was performed in MATLAB software. 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 system (Fig 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 series and for both groups. Further descrip-

tion of the actual calculation of this measure is included in the Appendix (online only).^{9,21,23,26}

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 (Fig 1). The largest Lyapunov exponent from a stable system with little to no divergence will be zero (eg, sine wave). Alternatively, the largest Lyapunov exponent for an unstable system that has a high amount of divergence will be positive with a larger value (>0.5).^{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 participant.

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.^{8,9,27} 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 with 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 produce 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 that the variations in the original time series are not randomly derived, but they are deterministic in nature.⁹

Surrogated data sets were created for each original joint angle time series analyzed. This procedure was performed in MATLAB using the pseudoperiodic surrogation algorithm.^{9,27} The pseudoperiodic algorithm is used to determine if additional determinism in the fluctuations is present in a time series that have inherent periodicity (eg, gait cycles). The 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 values were calculated for the ankle, knee, and hip joints for the patient and control groups. Independent *t* tests were used to compare the group means between the two groups. Statistical comparisons were performed using SPSS 12.0 software (SPSS Inc, Chicago, Ill). The level of significance was set at $\alpha = 0.05$.

Table I. Baseline characteristics of peripheral arterial disease patients and healthy control subjects

Characteristics ^a	Patient	Control	P
No. in group	19	17	
Gender			.054
Male	18	12	
Female	1	5	
Age, y	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, y	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, kg/m ²	28.0 ± 5.6	27.2 ± 7.1	.605
Treadmill speed, km/h ^b	0.63 ± 0.13	1.03 ± 0.26	<.001

NA, Not applicable.

^aContinuous data are presented as the mean ± standard deviation.

^bTreadmill speed was self-selected.

Table II. Group means for the largest Lyapunov exponent

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

LyE, largest Lyapunov exponent of the original time series; LyE-S, Lyapunov exponent for the surrogate time series; PAD, peripheral arterial disease.

^aData are reported as mean ± standard deviation.

^bIndicates a significant difference ($P < .05$) between PAD and control groups.

^cIndicates significant differences between the original time series and their surrogate counterparts.

RESULTS

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

For the nonlinear analysis, PAD patients had significantly higher largest Lyapunov exponent values than controls for the ankle, knee, and hip joints (Table II). These findings demonstrate that joint movement patterns in PAD patients were farther apart in consecutive strides (Fig 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 III). 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

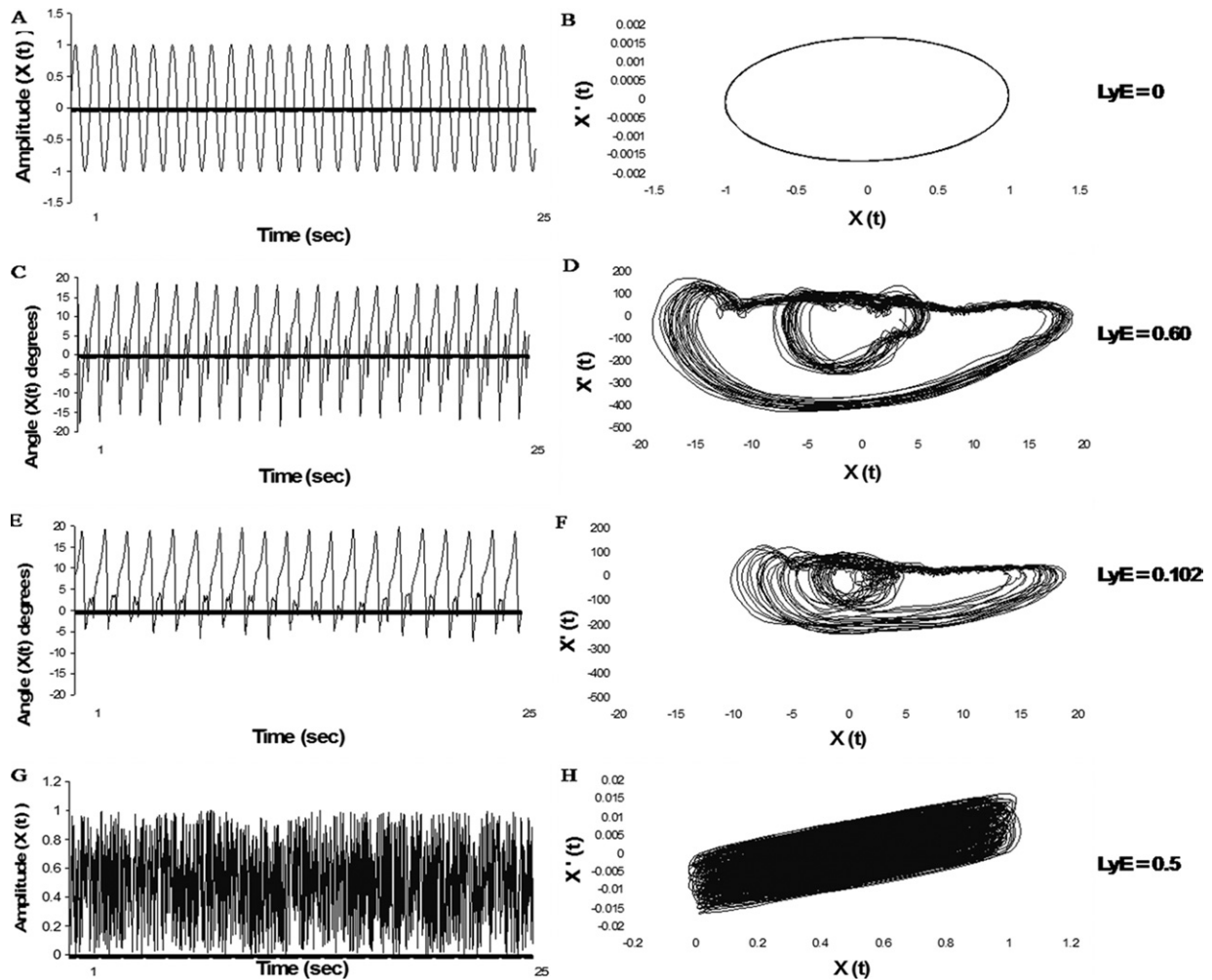


Fig 2. A graphic comparison of variability between a (A) periodic signal (sine wave), (C) control subject ankle joint, (E) PAD ankle joint, and (G) a random signal (*white noise*). Graphs A, C, E, and G are the time series and graphs B, D, F, and H are two-dimensional state spaces created by plotting the position ($X(t)$) vs 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.

in the gait patterns of the PAD patients. Regarding the surrogation analysis, the surrogate data series in the control group had significantly higher largest Lyapunov exponent values than the original data at the ankle and the knee. The surrogated largest Lyapunov exponent values in the PAD group were significantly higher than the original data only for the ankle (Table II).

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 compare them with 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.²⁸ 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 of six comparisons were significantly different, indicating a significant increase in the gait variability of PAD patients.

Furthermore, all comparisons for our nonlinear analysis 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 and Huntington disease have been linked to increased risks of

Table III. Group means for the standard deviation and coefficient of variation

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

CoV, Coefficient of variation; SD, standard deviation.

^aData are reported as mean ± standard deviation.

^bIndicates a significant difference ($P < .05$) between groups.

falling and decreased physical function.^{3,8,25} The altered variability may likewise 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. When surrogation was applied in the PAD group, 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, such as slippery surfaces and 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 who found significant differences between the original and surrogate data sets for all three joints in healthy elderly individuals. They also hypothesized that the deterministic behavior of joint angle variability may degrade with disease, which is precisely what happened in the patients with PAD.

The 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, which has a large amount of adipose tissue that increases marker movement. Also, the markers used for hip calculations are sometimes covered by the arms as they swing in front of them and block the camera views. Then, their location has to be interpolated using mathematic algorithms because 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 participants with Parkinson and Huntington disease patients.²⁵

Healthy (optimal) joint angle variability represents a coordinated neuromusculoskeletal system able to make flexible adaptations to demands placed on the body. From this notion comes the hypothesis that 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.

Previous studies have shown that patients with PAD have impaired balance and increased risk of falls,^{6,7} mobility problems,^{29,30} and altered gait patterns^{31,32} compared with healthy individuals. Specifically, functional outcomes measures such as the 6-minute walk test, physical activity level, and chair rises have repeatedly shown that PAD patients have diminished functioning compared with participants without PAD^{2,30}; however, the mechanisms for these changes are unclear. Muscle weakness or lack of endurance, abnormal muscle metabolism, and muscle denervation caused by chronic muscle ischemia, or the onset of claudication pain itself, may be the reason for these impairments.^{29,32}

The results of the current study suggest that gait is altered before 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^{33,34} and an axonal polyneuropathy in the lower extremities of PAD patients.³⁵ 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.³⁶ Mitochondria in PAD muscle have abnormal ultrastructure, damaged DNA, altered enzyme expression and activity, and abnormally high intermediates of oxidative metabolism.^{33,34}

Most important, evaluation of mitochondrial bioenergetics in claudicating muscle demonstrates specific defects in the complexes of the electron transport chain, with associated compromised mitochondrial respiration and adenosine triphosphate production³⁶⁻³⁸ that is very similar to what is seen in mitochondrial myopathies.^{33,34} Recent work also demonstrates that the mitochondriopathy of PAD muscle is associated with evidence of significant oxidative damage to the myofibers.³⁶

Accumulating evidence suggests that chronic ischemia in PAD patients results in a consistent pattern of electrodiagnostic abnormalities that indicate axonal nerve loss.³⁵ Therefore, the impairments in gait variability in limbs with PAD before the onset of pain likely reflect a combination of myopathy and neuropathy. The nature of these myopathic and neuropathic changes and the way they are associated with 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. Our data therefore accurately reflect gait variability changes due to the presence only of PAD and not of other comorbidities such as neurogenic claudication or osteoarthritis.^{39,40}

CONCLUSIONS

Our results demonstrate that PAD patients have increased and abnormal gait variability at baseline ambulation prior to the onset 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 that maybe interfering with the cooperative strategies of the locomotor system, thus 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.

AUTHOR CONTRIBUTIONS

Conception and design: JJ, NS, IP
 Analysis and interpretation: JJ, NS, IP, SM
 Data collection: JJ, IP, SM, LR, RC
 Writing the article: SM, IP
 Critical revision of the article: JJ, NS, IP, SM, LR, RC
 Final approval of the article: JJ, NS, IP, SM, LR, RC
 Statistical analysis: SM
 Obtained funding: SM, JJ, NS, IP
 Overall responsibility: JJ, NS, IP

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Appendix (online only). Calculation procedures of largest Lyapunov exponent

To reconstruct the state space, a state vector was created from the joint angle time series. This vector is composed of mutually exclusive information about the dynamics of the system.^{2,3,26}

$$y(t) = [x(t), x(t - T_1), x(t - T_2), \dots] \quad (1)$$

where $y(t)$ is the reconstructed state vector, $x(t)$ is the original joint angle data and $x(t - T_i)$ is the time delay copies of $x(t)$. The time delay (T_i) for creating the state vector was determined by estimating when information about the state of the system at $x(t)$ is different from the information contained in its time-delayed copy.

If the time delay is too small, then no additional information about the dynamics of the system will be contained in the state vector. Conversely, if the time delay is too large, then information about the dynamics of the system may be lost and can result in random information.^{2,3} Selection of the appropriate time delay was performed by using an average mutual information algorithm^{2,3}:

$$I_{x(t), x(t+T)} = \sum P(x(t), x(t+T)) \times \log_2 \left[\frac{P(x(t), x(t+T))}{P(x(t))P(x(t+T))} \right] \quad (2)$$

where T is the time delay, $x(t)$ is the original joint angle data, $x(t+T)$ is the time delay data, $P(x(t), x(t+T))$ is the joint probability for measurement of $x(t)$ and $x(t+T)$, $P(x(t))$ is the probability for measurement of $x(t)$, and $P(x(t+T))$ is the probability for measurement of $x(t+T)$. The probabilities were constructed from the frequency of $x(t)$ occurring in the joint angle time series. Average mutual information was iteratively calculated for various time delays and the selected time delay occurred at the first local minimum of the iterative process.^{9,23} This selection is based on previous investigations that have determined that the time delay at the first local minimum contains sufficient information about the dynamics of the system to reconstruct the state vector.^{2,3}

It was also important to determine the number of embedding dimensions to unfold the dynamics of the system in an appropriate state space. An inappropriate number of embedding dimensions may result in a projection of the dynamics of the system that has orbital crossings in the state space that are due to false neighbors and not the actual dynamics of the system.^{2,3} To unfold the state space, we

systematically inspected $x(t)$ and its neighbors in various dimensions (eg, dimension = 1, 2, 3, . . . etc). The appropriate embedding dimension occurs when neighbors of the $x(t)$ stop being unprojected by the addition of further dimensions of the state vector:

$$y(t) = [x(t), x(t+T), x(t+2T), \dots x(t+(d_E-1)T)] \quad (3)$$

where d_E is number of embedding dimensions, $y(t)$ is the d_E -dimensional state vector, $x(t)$ is the original joint angle data, and T is the time delay. A global false nearest-neighbors algorithm with the time delay determined from the local minimum of the average mutual information was used to determine the number of necessary embedding dimensions to reconstruct the joint angle time series.^{2,3} The calculated embedding dimension indicates the number of governing equations that are necessary to appropriately reconstruct the dynamics of the system.^{2,3} Custom MATLAB (MathWorks Inc, Natick, Mass) software was used to calculate the embedding dimension.

After calculating the appropriate time delay and embedding dimension and reconstructing the joint angle time series, the largest Lyapunov Exponent was calculated using the *Chaos Data Analyzer* (professional version, American Institute of Physics).²¹ The *Chaos Data Analyzer* calculates the rate of divergence between two vectors^{2,3}:

$$\lambda = \frac{1}{t_M - t_0} \sum_{k=1}^M \ln \frac{L'(t_k)}{L(t_{k-1})} \quad (4)$$

where $y(t)$ is the d_E -dimensional state vector and serves as the reference trajectory. $L(t_0)$ is the distance between $y(t)$ and its nearest neighbor. $L'(t_1)$ is the distance between the $y(t)$ and its nearest neighbor after moving forward n steps (we used $n = 3$). Then a new state vector replaces the evolved neighboring state vector if it meets the following two conditions:

- The distance of a replacing vector from the evolved state vector on the reference trajectory denoted as $L(t_j)$ is small.
- The angular separation between the evolved reference state vector and replacing vector is small.

New vectors are repeatedly generated $M = N - (d_E - 1)$ times where N is the length of the original time series. Then, the largest Lyapunov exponent is defined by Equation (4), where $k = 1, 2, \dots, M$ and $n = t_{k+1} - t_k$.