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Gait variability of patients with intermittent claudication is similar before and after the onset of claudication pain

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1 **GAIT VARIABILITY IS ALTERED IN PATIENTS WITH PERIPHERAL ARTERIAL**
2 **DISEASE**

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18 **Abstract**

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

25 *Design/Methods:* Nineteen symptomatic PAD patients (age: 63.6 ± 9.8 years, body mass: $82.1 \pm$
26 18.5 kg, body height: 1.71 ± 0.06 m) walked on a treadmill in the absence of pain or claudication
27 symptoms while joint flexion and extension kinematics were captured. Results were compared to
28 those obtained from 17 matched healthy controls (age: 65.2 ± 12.5 years, body mass: $82.0 \pm$
29 $25.9.5$ kg, body height: 1.73 ± 0.08 m). Relative joint angles were calculated for the ankle, knee
30 and hip flexion/extension and the stride to stride variability of joint flexion and extension was
31 calculated from at least 30 consecutive footfalls. Variability was expressed using the largest
32 Lyapunov Exponent, standard deviation and coefficient of variation. Independent t-tests were
33 used to compare gait variability between groups.

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

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

42 **Introduction**

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

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

65 makes the system more noisy and unstable (“drunken-like” walking). Study of variability in
66 different organ systems has demonstrated that alterations in heart rhythm variability can predict
67 arrhythmias ⁽¹⁰⁾ and sudden cardiac death syndrome ⁽¹¹⁾, while alterations in brain wave
68 variability are associated with ischemic brain syndromes ⁽¹²⁾ and epileptic seizures ⁽¹³⁾. Similarly,
69 analysis of the variability of the gait patterns of PAD patients may provide a window into the
70 status of the locomotor system of the patient. It can allow insight into the intricate strategies
71 PAD patients use to control movement and eventually help develop appropriate prognostic and
72 diagnostic tools. Gait variability can be measured using advanced biomechanical analysis and
73 can be described by using linear and nonlinear tools. Linear tools measure magnitude or amount
74 of variation and include the standard deviation and the coefficient of variation. Standard
75 deviation shows how much are a series of data spread around a central point (i.e. mean), while
76 coefficient of variation is a normalized measure of this dispersion to the mean. Nonlinear tools
77 measure how variability changes over time (from one stride to the next) and tell us about the
78 structure of variability. A commonly used nonlinear tool is the largest Lyapunov exponent ^(8,14)
79 ~~(16, 27, 28)~~. The purpose of this study was to determine the gait variability by evaluating the joint
80 kinematic variability of the lower extremities in claudicating patients as compared to age, height,
81 mass, and gender matched controls.

82

83 **Methods**

84 *Subjects*

85 Nineteen symptomatic PAD patients (age: 63.6 ± 9.8 years, body mass: 82.1 ± 18.4 kg, body
86 height: 1.71 ± 0.06 m) diagnosed with moderate arterial occlusive disease and bilateral
87 claudication were recruited from the vascular surgery clinics of the Veterans Affairs Medical
88 Center of Nebraska and Western Iowa and the University of Nebraska Medical Center, Omaha,
89 NE. In addition, seventeen height, mass, gender, and age matched healthy controls (age: $65.2 \pm$
90 12.5 years, body mass: 82.0 ± 25.9 kg, body height: 1.73 ± 0.08 m) were recruited from the
91 community and volunteered to participate. Informed consent was obtained from all subjects
92 prior to data collection according to the guidelines of the respective institutions' Institutional
93 Review Boards. Patients and controls were screened and evaluated by two board certified
94 vascular surgeons. Patient evaluation included detailed history, physical exam and direct
95 assessment/observation of the patient's walking impairment. A vascular surgeon observed the
96 patient walking to insure limitation was secondary to claudication pain. Those PAD patients with
97 ambulation limiting cardiac, pulmonary, neuromuscular or musculoskeletal disease or those who
98 experienced pain or discomfort during walking for any reason other than claudication (i.e.
99 arthritis, low back pain, musculoskeletal problems, neuropathy) were excluded.

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

104 *Experimental Procedure and Data Collection*

105 Prior to data collection, reflective markers were placed at specific anatomical locations of
106 each subject's lower limb utilizing the systems used by Vaughan⁽¹⁵⁾ and Nigg⁽¹⁶⁾. Subjects wore
107 a tightly fitting running suit to allow markers to be placed as close to the anatomical position as
108 possible. Following the marker placement, subjects were allowed to get accustomed to the
109 treadmill prior to recording data. During this familiarization period, subjects started walking at
110 0.45 m/sec and were free to increase or decrease the speed until a comfortable speed was found;
111 this speed was identified as the self-selected speed. Subjects were given up to 10 minutes to get
112 used to the treadmill, this time has previously been found to be adequate for subjects to achieve a
113 proficient treadmill walking pattern⁽¹⁷⁾. The patient was then allowed to rest to insure absence of
114 claudication pain before data collection began. Three dimensional kinematics were acquired at
115 60 Hz using EVART software (Motion Analysis Corp., Santa Rosa CA) while subjects walked
116 on a treadmill at their self-selected speed. Self-selected speed is the most comfortable and
117 natural walking speed and is the optimal speed to evaluate gait variability⁽¹⁸⁾. A predetermined
118 speed could put subjects into an uncomfortable situation, which may be manifested with
119 increased variability, as opposed to the more stable state that occurs with the self-selected speed
120⁽¹⁸⁾. Patients walked on the treadmill for three minutes or until the onset of claudication pain,
121 whichever came first. All kinematic measurements were taken prior to the onset of claudication
122 symptoms. For safety purposes, blood pressure was monitored before and after the treadmill test.

123 *Data Analysis*

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

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

142 *Linear analysis*

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

148 *Largest Lyapunov Exponent*

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

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

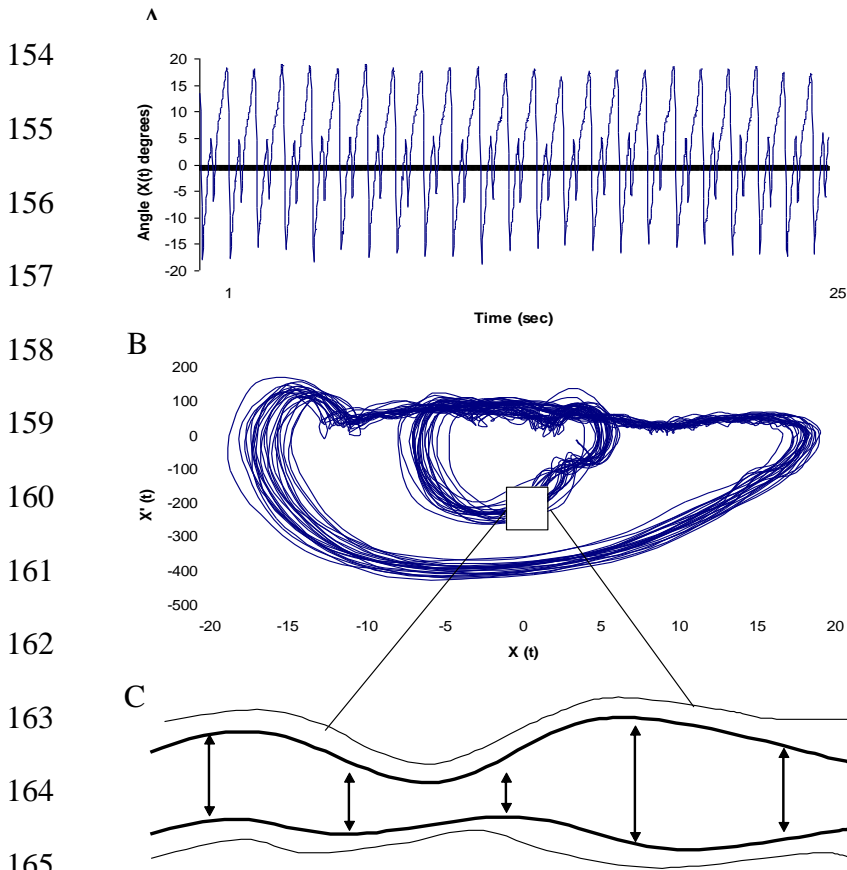


Figure 1. A graphical representation of the state space of an ankle joint angle time series and the calculation of the largest Lyapunov Exponent. (A) An original ankle plantarflexion-dorsiflexion time series from a control subject. (B) A two-dimensional state space created by the position and velocity 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⁾.

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

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

175 One of the assumptions made when calculating the largest Lyapunov Exponent is that the
176 source of the variation in a given time series is actually deterministic in nature ^(8-9,26). A
177 deterministic time series is one that has an ordered pattern (each point in the series is related to
178 its preceding points). Therefore, to ensure our time series met this assumption, we used the
179 method of surrogation. Surrogation compares the original time series data set to an equivalent
180 random data set with similar structure. Essentially, surrogation removes the deterministic
181 characteristics from the actual joint angle data set by shuffling the data to ~~and~~ produces a random
182 series with the same mean, variance and power spectra as the original data. The surrogated data
183 set includes the same values as the original time series, but the values are in a different order, so
184 that the points are no longer related with each other (random). Significant differences in largest
185 Lyapunov Exponent values between the original and surrogate counterparts reveal ~~show~~ that the
186 variations in the original time series are not randomly derived, but they are deterministic in
187 nature ⁽⁹⁾⁽⁴⁷⁾.

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

196 *Statistical Analysis*

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

202

203 **Results**

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

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

	<i>Patient</i> (<i>N= 19</i>)	<i>Control</i> (<i>N=17</i>)	<i>P values</i>
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

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

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

219

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 (*).

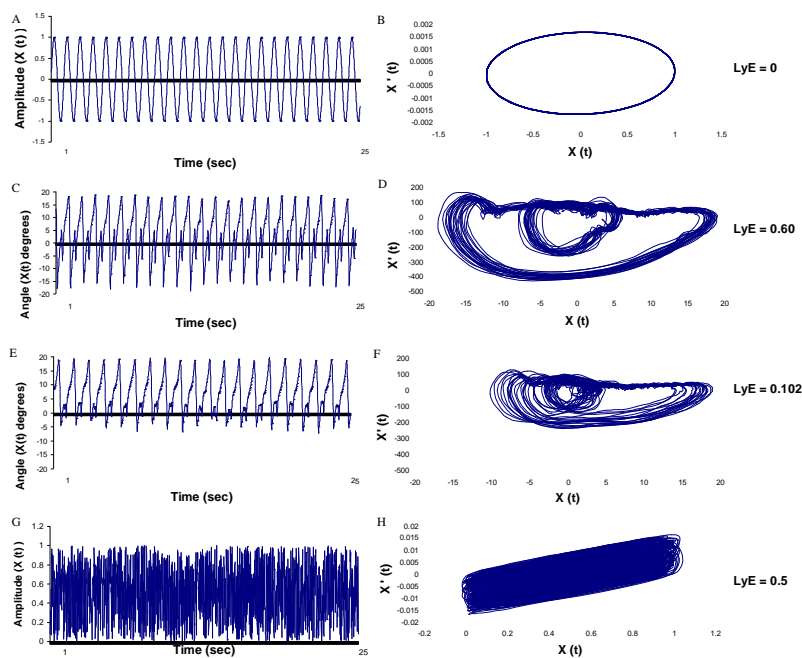


Figure 2. A graphical comparison of variability between a (A) periodic signal (sine wave), (C) Control subject ankle joint, (E) PAD ankle joint, and (G) a random signal (white noise). Graphs A, C, E, and G are the time series and graphs B, D, F, and H are two-dimensional state spaces created by plotting 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.

220 Discussion

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

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

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

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

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

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

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

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

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

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

313

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