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# Gait Variability Patterns are Altered in Healthy Young Individuals During the Acute Reperfusion Phase of Ischemia-Reperfusion

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1 **Gait variability pattern are altered in healthy young individuals during the acute**  
2 **reperfusion phase of ischemia-reperfusion.**

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14

15 Running Head: Gait variability changes with occlusion

16 Subject Category: Vascular

17 **Abstract**

18 *Background:* The role of ischemia reperfusion contributing to functional impairment in lower  
19 extremity peripheral arterial disease (PAD) patients has not previously been elucidated. The  
20 evaluation of gait variability patterns has proven useful in many pathological populations.  
21 Therefore, the purpose of this study is to isolate and determine the specific effect of the acute  
22 reperfusion phase of ischemia-reperfusion on gait variability in young individuals with no  
23 vascular disease.

24 *Materials and Methods:* Thirty healthy young individuals walked on a treadmill during baseline  
25 and acute reperfusion phase of ischemia-reperfusion conditions while lower extremity joint  
26 kinematics were captured. Stride to stride variability was assessed using the largest Lyapunov  
27 exponent, approximate entropy, standard deviation, and coefficient of variation. Differences in  
28 gait variability between conditions were assessed using dependent t-tests.

29 *Results:* The largest Lyapunov exponent values and approximate entropy values were  
30 significantly higher in the acute reperfusion phase of ischemia-reperfusion condition for the  
31 ankle, knee, and the hip. Coefficient of variation was significantly higher at the hip and standard  
32 deviation was higher at the knee and the hip during the acute reperfusion phase of ischemia-  
33 reperfusion condition.

34 *Conclusions:* The acute reperfusion phase of the ischemia-reperfusion cycle alters gait variability  
35 patterns at the ankle, knee and the hip in healthy young individuals. Our findings indicate  
36 increased noise and irregularity of gait variability patterns post ischemia. In young healthy  
37 individuals that do not have neuromuscular impairments, significant gait alterations are present  
38 during walking after a period of interruption of blood flow.

39 *Keywords:* Peripheral arterial disease, atherosclerosis, peripheral vascular disease

40

## 41 **Introduction**

42       The differences in gait parameters that occur across multiple steps are referred to as gait  
43 variability. The presence of a certain amount and an ordered structure of variability during  
44 movement are thought to be “healthy”, and these fluctuations allow individuals to adjust to  
45 changing stresses encountered during daily activities, including walking. Changes to this  
46 “optimal” amount or structure of variability are generally associated with disease and could be  
47 related with several physiological factors such as neural control, muscle function and posture<sup>(1)</sup>.  
48 Increased gait variability has been associated with unsteadiness during walking<sup>(2)</sup> and increased  
49 variability in elderly individuals has been linked to increased risk of falling<sup>(3-7)</sup>. Previous work in  
50 our laboratory determined that symptomatic peripheral arterial disease (PAD) patients have  
51 increased lower extremity gait variability as compared to healthy matched controls<sup>(8)</sup>. This is  
52 consistent with significant deterioration in the locomotor system of PAD patients. However, the  
53 specific mechanisms resulting in this deterioration and leading to mobility problems in patients  
54 with PAD remain unclear. Possible mechanisms resulting in functional impairment of PAD  
55 patients include insufficient blood flow, underlying neural and muscular abnormalities of the  
56 lower extremity, and systemic co-morbidities<sup>(9)</sup>. To attempt to isolate and determine the impact  
57 of reduced flow on gait parameters by evaluating joint kinematic variability during baseline and  
58 the acute reperfusion phase of ischemia reperfusion in healthy young individuals. We  
59 hypothesized that evaluation of the acute reperfusion phase of ischemia-reperfusion in the  
60 absence of underlying neuromuscular or systemic dysfunction would result in significant gait  
61 variability alteration in comparison to baseline gait.

62

## 63 **Methods**

### 64 *Participants*

65 Thirty healthy young participants (Age:  $22.8 \pm 4.16$  years, Mass:  $75.8 \pm 13.4$  kg, Height:  
66  $175.3 \pm 8.7$  cm, Gender: 26 males, 4 females) were recruited to participate in the study from the  
67 campus of the University of Nebraska at Omaha. The gender composition was recruited to reflect  
68 the composition of the PAD patients based on our previous studies <sup>(8, 10-12)</sup>. Informed consent was  
69 obtained from all participants before data collection according to the guidelines of the  
70 Institutional Review Board. Subjects were free from any significant health co-morbidities,  
71 including arthritis, history of lower extremity joint surgery, history of back or lower extremity  
72 injury or surgery that affects the subject's mobility or any other process limiting the ability to  
73 walk, including neurological disease or impairment (stroke, Parkinson's disease, multiple  
74 sclerosis). Additionally, all subjects had normal ankle brachial index values (ABI;  $>1.0$ ), and no  
75 subjective or objective ambulatory dysfunction. All subjects reported to our biomechanics  
76 facility for gait testing.

77

### 78 *Experimental procedure and data collection*

79 Upon arrival to the laboratory, lower extremity blood flow was measured by taking the  
80 systolic pressures at the brachial artery in the arm and the dorsal pedis and posterior tibial  
81 arteries at the ankle to confirm acceptable ABI values. Next, subjects' height, weight and  
82 anthropometric measures were taken. Before data collection reflective markers were placed as  
83 previously described <sup>(8)</sup>. After the markers were placed, participants were given ample time to get  
84 accustomed to walking on the treadmill (BodyGuard Fitness, St-Georges, QC (Canada)), during

85 which time they were asked to select a comfortable walking speed. This speed was identified as  
86 the self-selected walking speed.

87

88 Three-dimensional kinematics were acquired at 60 Hz using EVART software (Motion  
89 Analysis Corp, Santa Rosa, Calif) while participants walked on the treadmill. First the  
90 participants walked at their self-selected speed for three minutes. This was the baseline  
91 condition. Next, vascular occlusion was induced by placing thigh cuffs (Omron® Exactus  
92 Aneroid Sphygmomanometer Model 108MLNL) bilaterally on the upper thighs and occlusion  
93 tourniquets (CyberTech™ Mechanical Advantage Tourniquet MAT01) just above the knee while  
94 subjects stood on the treadmill. The cuffs were inflated to 200 mmHg and maintained for three  
95 minutes. The chosen level of pressure and time of occlusion are standard ranges used in the  
96 literature to induce ischemia in the legs <sup>(13-18)</sup>. After three minutes of occlusion, the thigh cuffs  
97 were removed and the subjects immediately began walking on the treadmill. Three minutes of  
98 treadmill walking was recorded during the acute reperfusion phase of ischemia reperfusion.

99

#### 100 *Data analysis*

101 Coordinate trajectories of each marker were exported and processed in custom software using  
102 MATLAB software (MathWorks Inc, Natick, Mass). This software was used to calculate relative  
103 joint angle time series from the kinematic data for the ankle, knee and hip for all trials. Joint  
104 kinematic variability was examined, because it has been shown that variability of stride  
105 characteristics (i.e. stride time, step time) offers a less sensitive measure of differences between  
106 groups than does variability of the joint kinematics <sup>(19)</sup>. All trials were cropped to 3300 data  
107 points, which corresponds to precisely 55 seconds and is long enough to allow 30 continuous

108 footfalls and is considered adequate for nonlinear analysis<sup>(20, 21)</sup>. The data were analyzed  
109 unfiltered to achieve the most accurate representation of the variability within the locomotor  
110 system. The same data collection system was used for all participants, and therefore we assumed  
111 the level of measurement noise was consistent between subjects. Thus, any differences between  
112 conditions can be recognized as differences in the locomotor system during the acute reperfusion  
113 phase of ischemia reperfusion.

114

#### 115 *Linear analysis*

116 The linear analysis provides information about the amount of variability present in the gait  
117 patterns and is used to complement the nonlinear analysis. Range of motion of the ankle, knee,  
118 and hip angles were calculated for each gait cycle and for every time series. Means, standard  
119 deviations, and coefficients of variation were then calculated for each variable and for each  
120 participant. MATLAB software was used for these calculations.

121

#### 122 *Nonlinear Analysis*

123 Nonlinear analysis methods included in the analysis were the largest Lyapunov exponent and  
124 approximate entropy. Unlike the linear statistics, both the largest Lyapunov exponent and  
125 approximate entropy take into account the entire time series of the joint angle, rather than  
126 looking at a few specific points in the series<sup>(20)</sup>. The largest Lyapunov exponent is a measure of  
127 the rate of divergence of neighbored state-space trajectories and it estimates the sensitivity of the  
128 locomotor system to perturbations. The largest Lyapunov exponent quantifies the exponential  
129 separation of nearby trajectories in the reconstructed state space of the joint angle time series. As  
130 nearby points of the state space separate, they diverge rapidly and can produce instability. The

131 largest Lyapunov exponent from a stable system with little to no divergence will be zero (eg,  
132 sine wave). Alternatively, the largest Lyapunov exponent for an unstable system that has a high  
133 amount of divergence will be positive with a larger value ( $>0.5$ ; Figure 1) <sup>(7, 20, 22)</sup>. The *Chaos*  
134 *Data Analyzer* professional version (American Institute of Physics <sup>(23)</sup>) was used to numerically  
135 calculate the largest Lyapunov exponent for each joint angle time series for each participant.  
136 Refer to the appendix for a detailed description of the actual calculation of this measure.

137

138 A method to determine the complexity in the gait time series is to compute the approximate  
139 entropy<sup>(20, 24, 25)</sup>. Approximate entropy is a measure that can quantify the regularity or  
140 predictability of a time series<sup>(26)</sup>. A more predictable and regular time series is also less  
141 complex. A change in complexity may be indicative of learning and a reorganization of the  
142 available degrees of freedom<sup>(26, 27)</sup>. The approximate entropy measures the logarithmic  
143 probability that a series of data points a certain distance apart will exhibit similar relative  
144 characteristics on the next incremental comparison with the state space<sup>(27-29)</sup>. Time series with a  
145 greater likelihood of remaining the same distance apart upon comparison will result in lower  
146 approximate entropy values, while data points that exhibit large differences in distances between  
147 data points will result in higher values. Values typically range from zero to two. Values closer to  
148 zero are consistent with greater periodicity (less complexity). Conversely, values nearing two  
149 represent greater irregularity (higher complexity). The approximate entropy value for a periodic  
150 time series such as the sine wave will be close to zero, for a random signal such as white noise  
151 will be close to two, while a deterministic signal like the joint angle time series will be  
152 somewhere in between (Figure 1). A detailed description of the calculation of the approximate  
153 entropy can be found in the appendix.



154

155       When using nonlinear analysis techniques, it is important to validate results against surrogate  
156 data to distinguish a deterministic origin from randomness. Surrogation is also an important  
157 measure used to determine if the source of the variation is deterministic in nature<sup>(7, 20, 30)</sup>. This  
158 method compares the original time series data set and an equivalent random data set with similar  
159 structure. Surrogation removes the deterministic characteristics from the actual data set, leaving a  
160 random series with the same mean, variance and power spectra as the original data. Significant  
161 differences between LyE values for the original and surrogate time series indicate that the  
162 variations observed in the actual data series are not random in nature and have deterministic  
163 properties<sup>(20)</sup>. Surrogation analysis was performed on every continuous joint angle using the  
164 method described by Small et al.<sup>(30, 31)</sup> for periodic time series.

165

#### 166 *Statistical analysis*

167       Means for the standard deviation and the coefficient of variation of the range of motion,  
168 largest Lyapunov exponent values, and approximate entropy values were calculated for the  
169 ankle, knee, and hip joints for the baseline and acute reperfusion phase of ischemia-reperfusion  
170 conditions. Differences between conditions were determined using dependent t-tests. To ensure  
171 that the sample of differences are normally distributed and confirm the applicability of the  
172 dependent t-tests, the Shapiro-Wilk test for normality was calculated for each dependent  
173 variable. The average W values suggest that our data is from a normal distribution (Table 1).  
174 Statistical comparisons were performed using SPSS 12.0 software (SPSS Inc, Chicago, Ill) with  
175 a level of significance set at  $\alpha = 0.05$ .

176

177 **Results**

178       There was a significant increase in standard deviation of the knee and hip joint range of  
179 motion in the post vascular occlusion condition (Table 1). Additionally, there was a significant  
180 increase in the coefficient of variation of the hip joint range of motion during the acute  
181 reperfusion phase of ischemia reperfusion condition as compared with the baseline condition.  
182 These differences indicate an increase in the amount of variability at the hip and the knee during  
183 the acute reperfusion phase of ischemia reperfusion.

184  
185       Regarding structure of variability, there were significant differences between baseline and  
186 acute reperfusion phase of ischemia reperfusion conditions for the ankle, knee, and hip joints  
187 time series (Table 1). Specifically, the largest Lyapunov exponent and approximate entropy  
188 values increased post vascular occlusion. These increases indicate a change in the structure of  
189 variability while walking in the acute reperfusion phase of ischemia reperfusion. Increases in the  
190 largest Lyapunov exponent show that joint movement patterns were farther apart in consecutive  
191 strides. For the approximate entropy, larger values represent greater irregularity of the joint angle  
192 time series. For the largest Lyapunov exponent and the approximate entropy, the mean difference  
193 between conditions progressively increased in the more distal joints.

194  
195       For the surrogation analysis, the surrogate data series had significantly higher largest  
196 Lyapunov exponent values than the original data for the ankle, knee, and the hip during walking  
197 in both the baseline and acute reperfusion phase of ischemia reperfusion conditions (Table 1).

198

199

## 200 Discussion

201 The purpose of this study was to isolate and determine the specific effect of the acute reperfusion  
202 phase of ischemia-reperfusion on gait variability in individuals without the neuromuscular and  
203 systemic impairments that exist in patients with PAD. We assessed this by inducing lower  
204 extremity vascular occlusion and examining gait variability by evaluating the joint kinematics of  
205 the lower extremities in healthy young individuals. Gait variability was chosen because it is  
206 associated with risk of falling and previously found in our laboratory to be altered in patients  
207 with PAD<sup>(8)</sup>. We hypothesized that the gait of healthy young individuals would be altered during  
208 the acute reperfusion phase of ischemia reperfusion.

209  
210 Nonlinear analysis demonstrated significant gait variability changes for all lower extremity  
211 joints based on the largest Lyapunov exponent and approximate entropy. For the linear measures,  
212 differences were seen only for the knee and the hip. Therefore, our hypothesis of altered  
213 variability was supported and more specifically, the differences indicated an increase in the  
214 noise, randomness, and instability of the locomotor system and an increase in the amount of  
215 variability while walking during the acute reperfusion phase of ischemia reperfusion.

216  
217 In the current study, the healthy young subjects' baseline condition is considered to have the  
218 "optimal" amount of variability. The changes to gait variability between baseline and the acute  
219 reperfusion phase of ischemia reperfusion conditions in healthy individuals are similar to those  
220 found in a previous study between healthy matched controls and patients with PAD<sup>(8)</sup>. Utilizing  
221 data from our previous studies, we can make direct comparisons between the response of young  
222 healthy subjects and PAD patients<sup>(8)</sup>. For this comparison we consider the average differences

223 from the young baseline condition expressed as percentage change averaged across the ankle,  
224 knee, and the hip for the acute reperfusion phase of ischemia reperfusion condition and for PAD  
225 patients as compared to the young baseline condition. The acute reperfusion phase of ischemia  
226 reperfusion condition had average increases of 21% for the largest Lyapunov Exponent, 26% for  
227 the standard deviation, and of 22% for the coefficient of variation as compared to the baseline  
228 condition. When comparing variability values from a previous investigation of PAD patients<sup>(8)</sup>,  
229 PAD patients on average had increases of 48% for largest Lyapunov Exponent values, 62% for  
230 the standard deviation and 99% for the coefficient of variation. The acute reperfusion phase of  
231 ischemia-reperfusion condition did lead to increases in the largest Lyapunov Exponent, standard  
232 deviation, and coefficient of variation, but the presence of PAD led to even greater increases.  
233 The difference in gait variability from baseline to the acute reperfusion phase of ischemia  
234 reperfusion condition in healthy young is clearly the result of ischemia-reperfusion that resulted  
235 from the induced vascular occlusion procedure in this study. However, the ischemia-reperfusion  
236 condition does not alter gait variability to the same magnitude as PAD, which suggests that other  
237 manifestations of the pathophysiology of PAD are leading to additional differences. These  
238 additional increases in variability seen in PAD patients are likely due to underlying cellular  
239 abnormalities in the lower extremity muscles and nerves that has been demonstrated in these  
240 patients<sup>(32-35)</sup>.

241  
242 In previous biomechanical studies of gait in PAD patients, changes have been consistently  
243 documented at the ankle, with differences in kinematics<sup>(12, 12, 36)</sup>, kinematic variability<sup>(8)</sup>, and  
244 peak plantarflexion torque at late stance<sup>(11)</sup> between PAD patients and healthy matched controls.  
245 The fact that gait variability changes in the acute reperfusion phase were pronounced at the ankle

246 in healthy young individuals demonstrates that the calf musculature appears to be the end organ  
247 of ischemia with regards to gait. This finding is consistent with the significant changes occurring  
248 in the lower extremities in patients with PAD <sup>(37-39)</sup>. The question remains however on how  
249 quickly the neuromuscular changes occur and over what time period these changes take place.

250 Results from the surrogation analysis established that the largest Lyapunov exponent values  
251 of the original time series were significantly different from their surrogate counterparts for the  
252 ankle, knee, and the hip during both conditions (baseline and post occlusion). Surrogation  
253 analysis was performed to confirm that our data has a deterministic origin (the time series is not  
254 random). Our findings demonstrate that the variability present in the subjects is deterministic,  
255 even in the acute reperfusion phase of ischemia reperfusion. Significant differences between  
256 original and surrogate time series were previously found in healthy young and elderly  
257 populations during normal walking conditions<sup>(7, 30)</sup>. The presence of determinism in the  
258 variability of gait patterns provides individuals with the ability to respond to challenging  
259 circumstances that may affect walking conditions (i.e. icy sidewalks, walking in crowds). Even  
260 though the gait variability had increased noise in the acute reperfusion phase of ischemia  
261 reperfusion, the deterministic structure of variability was maintained. This finding is in contrast  
262 to results of surrogation analysis in PAD patients that showed a degradation of the variability  
263 structure during pain free walking<sup>(8)</sup>. Therefore, while the deterministic structure was degraded  
264 with PAD, acute perturbations such as the acute reperfusion phase of ischemia reperfusion used  
265 in the current study, does not impact the neuromuscular system of healthy young individuals to  
266 the same extent.

267

268        Although the ischemia was produced by occlusion in the proximal thigh distal to the hip  
269 joint, significant differences in gait function were noted for the hip joint. Gait differences at the  
270 hip could be an attempt to compensate for ankle and knee alterations. Conversely, ischemia  
271 within the quadriceps and hamstrings may have contributed to the alterations of the hip joint.  
272 Regardless, our data would suggest that the level of disease and distribution of ischemia may  
273 play a significant role in the gait patterns in PAD patients. Based on the results of this  
274 investigation, muscles proximal to the atherosclerotic blockage may also be affected. Future  
275 research is needed to examine the effect of level of disease on functional impairments in patients  
276 with PAD.

277  
278        A limitation of the study is that it is difficult to specifically isolate the effect of reduced blood  
279 flow, especially because using a tourniquet creates obstruction to venous outflow in addition to  
280 reduced arterial inflow. While it is not possible to continuously monitor the ankle-brachial index  
281 of subjects, the current study created an acute period of clinical ischemia consistent with reduced  
282 arterial inflow. The experimental design is similar to the vascular laboratory technique of  
283 ischemia reperfusion which creates a supply-demand imbalance and creates a low grade ischemia  
284 of the distal muscle beds. In contrast to the PAD patients, reperfusion in healthy young  
285 individuals likely occurs quickly. Despite these factors, ambulatory functions during the acute  
286 reperfusion phase of ischemia reperfusion were significantly changed. Obviously the ideal  
287 experiment would be temporary occlusion of the arterial circulation in an invasive manner which  
288 for obvious reasons is not feasible in normal healthy subjects.

289

290    **Conclusions**

291 Results of our study indicate that ischemia-reperfusion, in the absence of neuromuscular and  
292 systemic pathology and comorbidities, significantly alters gait variability patterns. This study  
293 demonstrates that ischemia-reperfusion significantly alters gait in healthy young individuals.  
294 However, the change in the gait variability patterns was not as severe as previously documented  
295 in symptomatic PAD patients during pain free ambulation. Therefore, the current study  
296 demonstrates that gait variability differences are present during the acute reperfusion phase of  
297 ischemia reperfusion, however our results also support the hypothesis promoted by our group  
298 that damaged muscles and nerves in the lower extremities further contribute to altered gait  
299 variability patterns in patients with PAD.

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304 Dance, and the NASA Nebraska Space Grant Fellowship to [SM].

305

306 **Figure Captions**

307 Figure1. A visual comparison of variability between a (A) known periodic signal (sine wave),  
308 (B) ankle joint flexion-extension from a representative subject during baseline walking, (C)  
309 ankle joint flexion-extension from the same representative subject during walking post vascular  
310 occlusion, and (D) known random signal (white noise). The two-dimensional state spaces in  
311 graphs E, F, G, and H were created by plotting the position ( $X(t)$ ) versus the velocity ( $X'(t)$ )  
312 from the corresponding signals. The calculated largest Lyapunov exponent (LyE) and  
313 approximate entropy (ApEn) values are shown for each signal.

314



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