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

Sara A. Myers
University of Nebraska at Omaha, samyers@unomaha.edu

Nikolaos Stergiou
University of Nebraska at Omaha, nstergiou@unomaha.edu

Iraklis Pipinos
University of Nebraska Medical Center

Jason Johanning
University of Nebraska Medical Center

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

Sara A. Myers MS[1], Nick Stergiou PhD[1,4], Iraklis I. Pipinos MD[2,3], Jason M. Johanning MD[2,3]

[1] Nebraska Biomechanics Core Facility, University of Nebraska at Omaha, Omaha, NE

[2]Dept of Surgery, University of Nebraska Medical Center, Omaha, NE

[3]Dept of Surgery, Veterans Affairs Medical Center of Nebraska and Western Iowa, Omaha, NE

[4]College of Public Health, University of Nebraska Medical Center, Omaha, NE

Corresponding Author: Jason M. Johanning, MD

Address 983280 Nebraska Medical Center

Email: jjohanning@unmc.edu

Phone: (402) 559-4395

Fax: (402) 559-6479

Running Head: Gait variability changes with occlusion

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Abstract

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

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

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

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

Keywords: Peripheral arterial disease, atherosclerosis, peripheral vascular disease

Introduction

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

Methods

Participants

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

Experimental procedure and data collection

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

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

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

Data analysis

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

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

Linear analysis

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

Nonlinear Analysis

Nonlinear analysis methods included in the analysis were the largest Lyapunov exponent and approximate entropy. Unlike the linear statistics, both the largest Lyaponov exponent and approximate entropy take into account the entire time series of the joint angle, rather than looking at a few specific points in the series[20]. The largest Lyapunov exponent is a measure of the rate of divergence of neighbored state-space trajectories and it estimates the sensitivity of the locomotor system to perturbations. 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. 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; Figure 1) [7, 20, 22]. The *Chaos Data Analyzer* professional version (American Institute of Physics [23]) was used to numerically calculate the largest Lyapunov exponent for each joint angle time series for each participant. Refer to the appendix for a detailed description of the actual calculation of this measure.

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

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

Statistical analysis

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

Results

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

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

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

Discussion

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

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

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

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

In previous biomechanical studies of gait in PAD patients, changes have been consistently documented at the ankle, with differences in kinematics[12, 12, 36], kinematic variability[8], and peak plantarflexion torque at late stance[11] between PAD patients and healthy matched controls. The fact that gait variability changes in the acute reperfusion phase were pronounced at the ankle

in healthy young individuals demonstrates that the calf musculature appears to be the end organ of ischemia with regards to gait. This finding is consistent with the significant changes occuring in the lower extremities in patients with PAD [37-39]. The question remains however on how quickly the neuromuscular changes occur and over what time period these changes take place.

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

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

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

Conclusions

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

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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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