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Quadrupedal rodent gait compensations in a low dose monoiodoacetate model of osteoarthritis

Emily H. Lakes[a,b], Kyle D. Allen[a,b,*]

[a] J Crayton Pruitt Family Department of Biomedical Engineering, University of Florida, Gainesville, FL, United States
[b] Institute for Cell & Tissue Science and Engineering, University of Florida, Gainesville, FL, United States

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ABSTRACT

Background: Rodent gait analysis provides robust, quantitative results for preclinical musculoskeletal and neurological models. In prior work, surgical models of osteoarthritis have been found to result in a hind limb shuffle-stepping gait compensation, while a high dose monoiodoacetate (MIA, 3 mg) model resulted in a hind limb antalgic gait. However, it is unknown whether the antalgic gait caused by MIA is associated with severity of degeneration from the high dosage or the whole-joint degeneration associated with glycolysis inhibition.
Research question: This study evaluates rodent gait changes resulting from a low dose, 1 mg unilateral intra-articular injection of MIA compared to saline injected and naïve rats.
Methods: Spatiotemporal and dynamic gait parameters were collected from a total of 42 male Lewis rats spread across 3 time points: 1, 2, and 4 weeks post-injection. To provide a detailed analysis of this low dose MIA model, gait analysis was used to uniquely quantify both fore and hind limb gait parameters.
Results: Our data indicate that 1 mg of MIA caused relatively minor degeneration and a shuffle-step gait compensation, similar to the compensation observed in prior surgical models.
Significance: These data from a 1 mg MIA model show a different gait compensation compared to a previously studied 3 mg model. This 1 mg MIA model resulted in gait compensations more similar to a previously studied surgical model of osteoarthritis. Additionally, this study provides detailed 4 limb analysis of rodent gait that includes spatiotemporal and dynamic data from the same gait trial. These data highlight the importance of measuring dynamic data in combination with spatiotemporal data, since compensatory gait patterns may not be captured by spatial, temporal, or dynamic characterizations alone.

1. Introduction

Gait analysis is a common method to quantify changes in orthopaedic diseases. While gait analysis is traditionally performed in humans, rodent gait analysis is becoming more popular as a behavioral assay. Rodent gait analysis provides a method for recording natural animal behavior, while providing robust, quantitative results for characterization of musculoskeletal models.

In our prior work, custom gait recording methods have been used to collect spatiotemporal gait parameters via high speed cameras, while simultaneously recording ground reaction forces [1–3]. This work introduced a custom rodent gait system, termed EDGAR (Experimental Dynamic Gait Arena for Rodents) [2], where EDGAR was used to evaluate gait in rats with either medial meniscus transection (surgical model) or intra-articular injection of monoiodoacetate (3 mg, chemical model). Here, meniscus transection resulted in a shuffle-step while injection of monoiodoacetate resulted in an antalgic gait [2]. These results confirm other prior work which found rats develop a shuffle-step compensation between 4 and 6 weeks after medial meniscus transection [3]. However, MIA is a glycolysis inhibitor which causes widespread joint damage, and 3 mg of MIA is the upper range traditionally used in joint degeneration models [4–11]. Thus, the varying gait compensations observed in the 3 mg MIA model may be associated with the severity of joint destruction or the widespread inhibition of glycolysis in the joint.

In the MIA model, the severity of joint damage and limb hypersensitivity can be titered with dose [12]. Thus, while previous work investigated a relatively high 3 mg dose of MIA, this study aims to evaluate gait changes resulting from 1 mg intra-articular injection of MIA. Again, EDGAR is used to evaluate rodent gait compensations, but since gait changes may be mild in a lower dose of MIA, gait analysis will be used to uniquely quantify both fore and hind limb gait parameters.

* Corresponding author at: J Crayton Pruitt Family Department of Biomedical Engineering, University of Florida, 1275 Center Drive, Biomedical Sciences Building, Gainesville, Florida 32610, United States.
E-mail address: kyle.allen@bme.ufl.edu (K.D. Allen).

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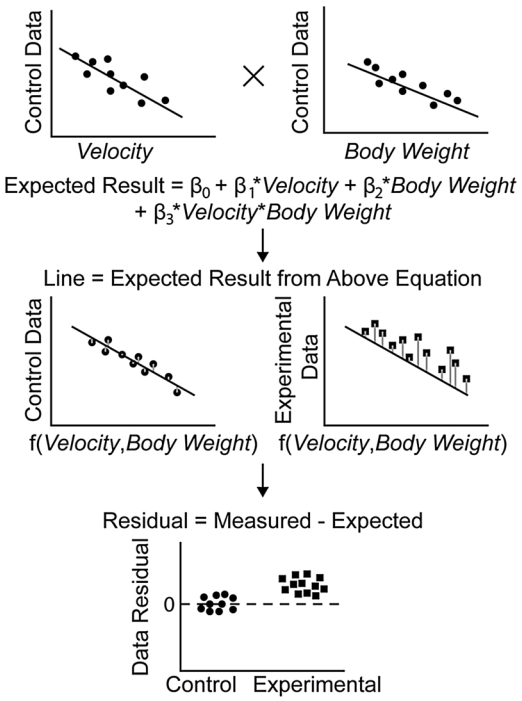

Fig. 1. Covariates for the data are determined by plotting the data against each predictor. For this study, both velocity and body weight were used as covariates to residualize experimental data.

Our data shows that gait compensations subsequent to 1 mg of MIA are relatively minor and tend to follow the shuffle-step compensations; this type of compensation is similar to those observed in prior surgical models, rather than a 3 mg dose of MIA [2].

2. Experimental design and methods

Animal use was approved by the University of Florida's Institutional Animal Care and Use Committee. Male Lewis rats (n = 42, 250–400 g, Charles Rivers Laboratories, Wilmington, MA) were divided into three groups: monoiodoacetate (MIA) injection (n = 6 per time point), saline injection (n = 6 per time point), or naïve (n = 6 total). Six animals from each group underwent gait testing at 1, 2, and 4 weeks post-injection. After gait testing at each time point, 6 MIA and 6 saline animals were euthanized, while the 6 naïve animals (300–450 g) were tested at each time point and euthanized at the end. Following euthanasia, knee joints were dissected and processed for histology.

2.1. MIA intra-articular injection procedure

Animals were placed in an induction chamber with 4% isoflurane and maintained via mask inhalation. The right hind limb was shaven and aseptically prepared using povidone-iodine and alcohol in triplicate, with a final application of povidone-iodine left on the skin. Then, an intra-articular injection of MIA or sterile saline was given. For MIA and saline injections, a 29 gauge syringe was inserted through the superior portion of the patellar ligament and followed the femoral groove behind the patella until the needle was in the joint space. Then, either 1 mg of MIA suspended in 25 µL of sterile saline (n = 18 total) or 25 µL of sterile saline alone (n = 18 total) was delivered. Animals recovered in a warming box until weight bearing.

2.2. Gait analysis

The Experimental Dynamic Gait Arena for Rodents (EDGAR) is designed to simultaneously collect spatiotemporal and dynamic ground reaction gait data from freely walking rodents [2]. Specifications for EDGAR are provided at www.GAITOR.org. Briefly, EDGAR requires an unobstructed view of the lateral and ventral planes of the animal, achieved by placing a mirror 45° below the arena floor (see

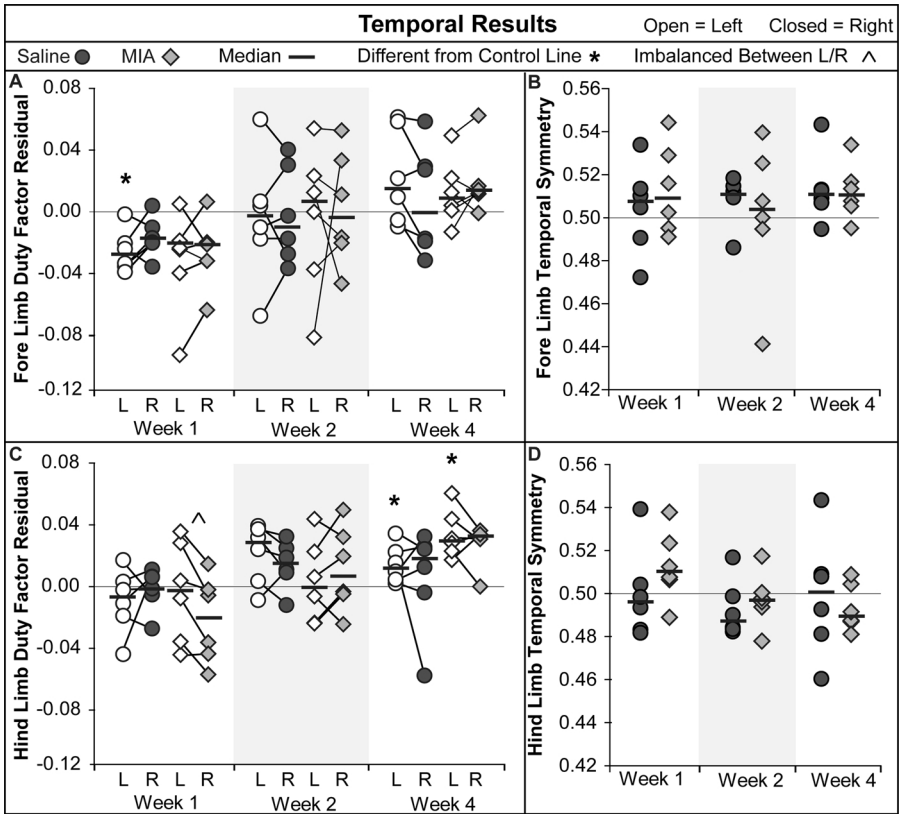

Fig. 2. Temporal results are shown as scatterplots, where the left and right duty factors are shown paired for the same animal, (connecting lines on duty factor plots). These lines represent the duty factor imbalance. Solid lines for each scatterplot set represent the median for each group and foot. * indicates a significant difference from the control line, while ∧ represents a significant imbalance between right and left (sign test, $p < 0.05$). Duty factor describes the ratio of limb stance time over stride time. Temporal symmetry describes the time between a right and left foot strike divided by the stride time. These definitions are from the classic description of the temporal gait sequence, largely attributed to the work of Milton Hildebrand [21].