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Review

Gait analysis methods for rodent models of arthritic disorders: reviews and recommendations

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SUMMARY

Gait analysis is a useful tool to understand behavioral changes in preclinical arthritis models. While observational scoring and spatiotemporal gait parameters are the most widely performed gait analyses in rodents, commercially available systems can now provide quantitative assessments of spatiotemporal patterns. However, inconsistencies remain between testing platforms, and laboratories often select different gait pattern descriptors to report in the literature. Rodent gait can also be described through kinetic and kinematic analyses, but systems to analyze rodent kinetics and kinematics are typically custom made and often require sensitive, custom equipment. While the use of rodent gait analysis rapidly expands, it is important to remember that, while *rodent* gait analysis is a relatively modern behavioral assay, the study of *quadrupedal* gait is not new. Nearly all gait parameters are correlated, and a collection of gait parameters is needed to understand a compensatory gait pattern used by the animal. As such, a change in a single gait parameter is unlikely to tell the full biomechanical story; and to effectively use gait analysis, one must consider how multiple different parameters contribute to an altered gait pattern. The goal of this article is to review rodent gait analysis techniques and provide recommendations on how to use these technologies in rodent arthritis models, including discussions on the strengths and limitations of observational scoring, spatiotemporal, kinetic, and kinematic measures. Recognizing rodent gait analysis is an evolving tool, we also provide technical recommendations we hope will improve the utility of these analyses in the future.

Introduction

Technological advances have made gait analysis a widely available tool for rodent models; however, gait analysis, itself, is not a new practice. Aristotle wrote on human motion, and scientists such as Boerhaave, Euler, and Carlet advanced the understanding of gait mechanics throughout the eighteenth and nineteenth centuries. In the late 1800s, human and quadrupedal gait patterns were famously recorded by Muybridge, and Hildebrand plots have been standard descriptors of the temporal gait sequence of quadrupeds since the 1960s[1,2]. In recent years, gait technologies have continued to improve, and with advances in high-speed videography and force plates, gait is now possible in smaller organisms, including preclinical arthritis models.

In the clinical assessment of arthritis, gait analysis can be effectively used to assess mobility and function, and while the quadrupedal gait patterns used by rodents clearly vary from bipedal human patterns, the conceptual basis for gait analysis remains analogous – an altered gait pattern can be used to protect an injured limb from loading and/or movement-evoked pain. As such, several compensatory patterns are shared between quadrupeds and bipeds, including shuffle-stepping and limping[3]. The frequent challenge in rodent gait analysis is that these compensatory patterns can be difficult to detect due to the ability to re-distribute load to three limbs rather than one and the rapidity of the gait sequence. Thus, although rodent gait varies significantly from human gait, it remains important to advance technologies for rodent and quadrupedal gait analysis.

In addition, bench to bedside translation in arthritis historically begins by testing new therapies in rodents before translating to larger organisms and clinical studies. However, gait analysis has

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followed the opposite trend, with sophisticated motion tracking and force measurements first being developed for humans and then scaled down to large animals and rodents. This trend is driven by scale advantages, with gait compensations being easier to detect in humans and large animals relative to rodents. In addition, rodents are prey animals, and evolution has likely conditioned rodents to mask signs of disability and pain[4–7], making rodent gait compensations relatively more difficult to detect. Only recently have sophisticated gait tracking systems been applied to rodent arthritis models[8–12], and even with these approaches, gait parameters are typically limited to the spatiotemporal pattern. Thus, even though quadrupedal gait has been studied for decades, sophisticated rodent gait analyses have only recently been applied to preclinical arthritis models. Nonetheless, use of gait analysis to study preclinical arthritis models will likely continue to expand.

In rodent models, gait is classified as a behavioral analysis. In her book, *What's Wrong With My Mouse? Behavioral Phenotyping of Transgenic and Knockout Mice*, Jacqueline N. Crawley, Ph.D. takes care to inform scientists of the complexity of rodent behavioral analyses, stating:

> "As in any field of science, behavioral research has evolved proper experimental designs and controls that must be correctly applied for the data to be interpretable. Little things, such as how to handle the mouse to reduce stress, can greatly affect the results of a behavioral experiment. Like microinjecting an oocyte or operating a DNA sequencer, the tricks of the trade are best learned from experts. You don't want to waste your time reinventing the wheel[13]."

Professor Crawley's recommendation rings true for quadrupedal gait analysis as well. While the use of gait to assess rodent arthritis models is a relatively modern concept, the study of quadrupedal gait is not. Unfortunately, most commercial rodent gait analysis systems inundate users with large datasets – sometimes 50+ variables – to describe the rodent spatiotemporal gait pattern. Moreover, most of these variables are not independent and can be difficult to interpret without an understanding of quadrupedal gait[3]. The goal of this review is to describe the state of rodent gait analysis and highlight fundamental gait parameters needed to accurately evaluate preclinical arthritis models. Rodent gait parameters include observational scores or measurements of spatiotemporal, kinetic, and kinematic gait characteristics. We structured this review with these sections, describing research conducted in these areas and the strengths and limitations of current approaches (see Table I for introductory terminology).

Observational scoring

Terminology

Observational scoring uses rank-order scales to grade the severity of rodent gait abnormalities (Table II). Since these scales have been developed by individual labs, scoring systems are relatively inconsistent, with some defining 0 as normal while others define the maximum as normal. Thus, when comparing results across laboratories, it is important to first understand the scale.

Review of observational scoring techniques in rodents

Visually scoring an animal's gait may be the simplest form of gait analysis. Scoring systems often seek to identify "guarding gaits"[14,19], while others report a similar non-specific gait score that characterizes limping or failure to fully apply weight[15–18,20]. Advantages of scoring include individualized scales relevant to particular disease models, high throughput, and relatively simple data analysis. However, scoring systems are subject to observer bias and typically provide only semi-quantitative gait descriptions.

Recommendations for gait scoring in rodents

Observational scoring is typically performed by placing the animal in an open arena and directly scoring the animal or recording video to be scored later. Due to the rapidity of rodent gait, the human eye is often unable to detect subtle changes without assistance from videography, and these subtle gait compensations may be more likely to associate with diseases like osteoarthritis[3,5,9,21]. Hence, we recommend video be used for observational scoring whenever possible. In addition, since scoring is largely an assessment of self-selected behaviors, open arena testing is ideal to capture the animal's natural gait. Some laboratories have used treadmills and food incentive for these tests, but these factors could mask some gait characteristics[3]. Finally, as with any behavioral analysis, investigators should learn proper techniques to handle and acclimate their animals to the experiment.

For studies where gait is not a primary outcome measure, observational scores are a quick, though insensitive, measure of rodent behavior. In arthritis models, these measures could be improved by generating standard scales, similar to the BBB score in spinal cord injury[21]. But, this too is inhibited by the broad range of severities observed in arthritis models. As a general recommendation, observational scoring using videography should not use terms such as "mild" or "severe," as these terms are open to interpretation. Instead, scoring should be distinguished by tangible occurrences, such as the "guarding after noxious compression" definition used by Boettger *et al*[14,19]. Similarly, without videography, scoring should use a measurable system to categorize animal behavior, such as the ink prints used by Kumar *et al*[20]. Nonetheless, there is a need to refine these scales, but even with standardization, scientists should recognize observational methods will only

Table I
Terminology

Term	Definition
Spatial	Relating to positions in space
Temporal	Relating to time
Kinetic	Relating to the forces associated with motion
Kinematic	Relating to motion
Step length	Distance from foot strike to subsequent foot strike of the opposite foot
Stride length	Distance from foot strike to subsequent foot strike of the same foot
Step width	Distance between the limbs perpendicular to the direction of travel
Duty factor	Stance time divided by stride time
Temporal symmetry	Time between a right and left foot-strike divided by stride time
Limb phase	Time between same side forelimb and hindlimb foot-strikes divided by stride time
fps	Frames per second
GRF	Ground reaction force
Impulse	Area under the force-time curve
Braking/Propulsion forces	Forces that occur in the direction of travel (also anteroposterior). Typically associated with slowing of the center of mass immediately after foot-strike (braking) and push-off forces propelling the center of mass forward immediately prior to toe-off (propulsion)
Mediolateral forces	Forces that occur toward the animal's midline. Typically associated with the stability of the animal and the left-to-right/right-to-left sway of the center of mass during gait