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5 **Ground reaction forces are more sensitive gait measures than temporal parameters in**
6 **rodents following rotator cuff injury**

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8 Running title: Kinetic parameters are more sensitive than temporal parameters in gait analysis
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Abstract

Gait analysis is a quantitative, non-invasive technique that can be used to investigate functional changes in animal models of musculoskeletal disease. Changes in ground reaction forces following injury have been observed that coincide with differences in tissue mechanical and histological properties during healing. However, measurement of these kinetic gait parameters can be laborious compared to the simpler and less time-consuming analysis of temporal gait parameters alone. We compared the sensitivity of temporal and kinetic gait parameters in detecting functional changes following rotator cuff injury in rats. Although these parameters were strongly correlated, temporal measures were unable to detect greater than 50% of the functional gait differences between injured and uninjured animals identified simultaneously by ground reaction forces. Regression analysis was used to predict ground reaction forces from temporal parameters. This model improved the ability of temporal parameters to identify known functional changes, but only when these differences were large in magnitude (i.e., between injured vs. uninjured animals, but not between different post-operative treatments). The results of this study suggest that ground reaction forces are more sensitive measures of limb/joint function than temporal parameters following rotator cuff injury in rats. Therefore, although gait analysis systems without force plates are typically efficient and easy to use, they may be most appropriate for use when major functional changes are expected.

INTRODUCTION

Animal studies provide valuable insight into the pathophysiology and treatment modalities of musculoskeletal injuries and diseases due to their ability to study tissue-level properties not possible with human studies. Interpretation of the clinical relevance of tissue-level animal studies can be aided with quantitative measures of limb/joint function (Fu et al., 2015; Reuther et al., 2014b). Gait analysis is a highly sensitive, non-invasive technique used to study the pathophysiology of various orthopaedic diseases (Clarke et al., 1997; Krizsan-Agbas et al., 2014; Mora-Macias et al., 2015). For example, abnormalities in kinetic gait parameters during locomotion have been observed in rat models of osteoarthritis, spinal cord injury recovery, and rotator cuff disease (Johnson et al., 2012; Reuther et al., 2015; Roemhildt et al., 2010). These disturbances in gait properties can be used to validate dysfunction in small animal disease models or to evaluate recovery of function following injury.

While previous systems used ink and paper methods, the primary types of rodent gait analysis systems currently utilize high-speed cameras that are coupled with or without force plate instrumentation. Coupled systems can simultaneously collect spatial (e.g., step width, length), temporal (e.g., duration of stance and swing phases), and kinetic (i.e., ground reaction forces) parameters to comprehensively quantify gait patterns. However, the use of such systems can be time consuming, as it requires isolation of the limb of interest on a force plate during locomotion and also involves laborious manual data processing (Muir and Whishaw, 1999). Small animal gait analysis systems without force plates are typically more time efficient as they are capable of continuous data collection during locomotion and often feature automated data processing, but lack the ability to calculate kinetic parameters.

Spatial parameters are less sensitive and consistent than both temporal and kinetic variables; however, it remains unknown whether temporal and kinetic parameters are equally sensitive measures compared to each other when analyzing gait compensations due to musculoskeletal injury (Allen et al., 2011; Reed et al., 2013). Previous human studies have reported the minimum detectable change (with 95% confidence) in temporal and kinetic gait parameters to be as low as 1% and 4%, respectively, compared to as high as 46% for spatial gait parameters (Owings and Grabiner, 2004; Paterson et al., 2008; Reed et al., 2013; Stolze et al., 1997). Importantly, accounting for velocity (which is strongly correlated to stride length and width) as covariate did not improve the sensitivity of these spatial properties when used to analyze rat gait (Allen et al., 2010; Allen et al., 2009; Allen et al., 2011; Shamji et al., 2009). Alternatively, temporal parameters are believed to correspond with force generation, and similar gait patterns have been obtained from both temporal records of paw placement and force plate analysis (Hampton et al., 2011; Kale et al., 2004). Indeed, decreases in temporal parameters (e.g., stance time) may coincide with decreases in kinetic gait parameters (e.g., vertical ground reaction force) observed following injury (Hsu et al., 2011; Sarver et al., 2010; Shih et al., 1993). Nevertheless, the relationship between temporal properties and ground reaction forces during locomotion has not been thoroughly investigated. This information is critical given the relative ease of measuring temporal parameters compared to the more complicated and challenging process of quantifying kinetic parameters during small animal locomotion.

Therefore, the objective of this study was to compare the sensitivity of temporal versus kinetic parameters in detecting functional changes in rodent models of rotator cuff injury using a validated gait analysis system (Sarver et al., 2010). We hypothesized that temporal and kinetic

parameters would correlate significantly, and that corresponding pairs of temporal and kinetic parameters would simultaneously denote changes in rodent gait following injury.

METHODS

Study Design

The data used in this study were obtained from our previous studies using rat rotator cuff injury models (Table 1). In study #1 (Reuther et al., 2014a), animals underwent unilateral detachment of the supraspinatus only (SO) or supraspinatus and infraspinatus (SI) rotator cuff tendons, and ambulatory measurements were collected up to 8 weeks post-operatively. To create a more general model, data from the SO and SI groups were combined and used for the correlation and regression analysis in the current study as significant differences between these groups were observed in shoulder function (as measured by kinetic gait parameters), as well as tendon and cartilage mechanical and histological properties. Data from two other studies were used to test the regression model created from the SO and SI data. In study #2 (Thomas et al., 2014), animals underwent unilateral detachment of the supraspinatus, infraspinatus, and biceps (SIB) tendons and ambulatory measures were collected identically to the SO and SI groups. In study #3 (Caro et al., 2014), animals underwent unilateral detachment and repair of the supraspinatus tendon and repair with (RW) or without (RWO) post-operative analgesics. Ambulatory measurements were collected up to 4 weeks following surgery.

Instrumented Walkway

Forelimb gait was quantified using a stationary walkway as described previously (Sarver et al., 2010). Briefly, the system used features a clear acrylic walkway with two 6-degree-of-

freedom miniature force/torque cells (nano17, ATI Industrial Automation, Apex North Carolina). Angled mirrors on both sides of the walkway capture ventral and sagittal views of the animal during locomotion using a 60 frames-per-second camera (A601fc, Basler Vision Technologies, Ahrensburg Germany). A darkened box was placed at the end of the walkway to encourage the animal to walk. Only trials where the animal isolated a single limb on the force plate were selected for analysis, and data were averaged from a minimum of two walks per animal at each time point.

Gait Parameters

Temporal and kinetic parameters were used to characterize rat locomotion (Figure 1). Braking and propulsion times were calculated by determining when the anterior-posterior ground reaction force curve crossed zero during a single stride. Stance time was calculated as the total time the foot remained in contact with the ground. Peak vertical (+z direction), braking (−y direction), and propulsion (+y direction) forces were determined for each stride, normalized to the animal's weight, and reported as a percentage of body weight (%BW).

Correlation Analysis

Pearson's correlation coefficients were calculated between temporal parameters and kinetic parameters from the SO and SI pooled data set. Average values for SI or SO at each time point were used rather than data from individual animals in order to reduce variability and allow for a more representative analysis.

Kinetic and Temporal Parameter Sensitivity

The total number of significant differences in kinetic parameters alone between SO & SI, SIB & baseline, and RW & RWO were compared to the subset of significant differences identified simultaneously in corresponding temporal-kinetic pairs. An illustration of this analysis is provided for example data where significant differences in vertical force between two groups were identified at 3, 7, and 14 days post-operatively (Figure 2, left panel), but stance time was only different at the 3 day time point (Figure 2, right panel). This analysis was repeated for each temporal-kinetic pair (i.e., vertical force and stance time, braking force and braking time, propulsion force and propulsion time) and totaled for each set of experimental groups. Similar comparisons between kinetic and temporal parameters were also performed for uninjured and injured (SO, SI, SIB pooled) animals after 3, 7, and 14 days of healing.

Regression Modeling

Step-wise backward elimination linear regression analysis was performed on the combined SO and SI pooled data set to select the best temporal variables for predicting kinetic gait parameters. Similar to the correlation analysis, average values for a given parameter and group at each time point were used to reduce variability. The resulting regression coefficients were then used to predict vertical, braking, and propulsion forces for all groups. In order to allow for statistical comparisons, the regression model was used to predict ground reaction forces for each animal at each time point such that a group average and standard deviation could be calculated. The total number of known significant differences in experimental ground reaction forces between groups was compared to the number of significant differences identified by predicted kinetic parameters for these groups.

Statistical Significance Evaluation

Correlation coefficients and two-tailed p-values were calculated using bivariate Pearson correlation. Comparisons between groups for temporal and kinetic parameters were made using two-tailed t-tests. Significance was set at $p < 0.05$ for all tests (SPSS, IBM SPSS, Inc., Version 20, Armon, NY).

RESULTS

Correlation Analysis

All temporal parameters were significantly correlated with ground reaction forces (Table 2). Corresponding temporal-kinetic pairs were among the highest correlations ($R \geq 0.76$, $p < 0.002$).

Kinetic and Temporal Parameter Sensitivity

Kinetic parameters were consistently more sensitive than temporal parameters in detecting functional changes in gait (Figure 3). This was especially true when distinctions between experimental groups were smaller (i.e., tendon repair with (RW) or without (RWO) post-operative analgesia) compared to when they are typically larger (i.e., animals with or without a multi-tendon (such as SIB) tear). This finding was also observed when comparing injured (SI, SO, SIB) and uninjured animals. Temporal parameters were best able to identify functional changes in gait at the first post-operative time point when these changes were greatest (Figure 4A). All of the individual temporal parameters investigated were similarly unsuccessful at consistently identifying differences between groups simultaneously observed in ground reaction forces at these time points (Figure 4B).

Regression Modeling

Stance and propulsion time satisfied the assumption of being independent variables ($R=0.10$, $p=0.745$) and were selected via step-wise backward elimination as the best variables for predicting vertical, braking, and propulsion force (Table 3). Predicted kinetic parameters were subsequently calculated using the formula: $\text{Force}_i = \beta_{0i} + \beta_{1i} * \text{StanceTime} + \beta_{2i} * \text{PropulsionTime}$.

When used to predict intra-model kinetic data (SO vs. SI), the regression coefficients were much more successful at identifying differences in gait between groups compared to temporal parameters alone (7/10 of known differences successfully identified compared to 2/10) (Figures 5A and 3). When applied to extra-model data in which differences in ground reaction forces were greatest in magnitude (SIB vs. uninjured), predictions of kinetic parameters using the regression model were less successful at identifying known functional differences but still more sensitive than temporal parameters alone (4/7 of known differences successfully identified compared to 2/7). However, use of the regression coefficients to predict kinetic parameters did not successfully identify any of the known functional differences between RW and RWO up to four weeks post-operatively (0/6 of known differences successfully identified). Differences in kinetic parameters between SI and SO were predicted with at least 50% success for each ground reaction force (Figure 5B). When extra-model data sets (not used to develop the model) were analyzed, the regression model was unable to predict greater than 50% of the known differences between groups in any of the kinetic properties evaluated (Figure 5C).

DISCUSSION

Longitudinal, non-invasive measures of joint/limb function are critical to support histological and mechanical results from animal studies, as well as to augment the clinical relevance of such studies. Gait analysis is a commonly used technique for studying musculoskeletal injuries and diseases, and has been demonstrated to be more sensitive to detecting changes in joint mechanics and tissue remodeling compared to other methods of assessing pain/function in rats (Allen et al., 2012). Despite this, not all gait analysis systems are coupled with force plate instrumentation to quantify ground reaction forces as the evaluation of temporal parameters alone is typically simpler and less time-intensive than the use of coupled systems.

Previous studies have suggested that braking and propulsion duration may relate to braking and propulsion ground reaction forces (Hampton et al., 2011; Kale et al., 2004). Similarly, Vrinten and colleagues reported a significant correlation between stance time and von Frey thresholds ($R=0.67$, $p<0.001$), the latter of which was strongly correlated with an indirect measure of pressure applied during locomotion using light intensity ($R=0.63$, $p<0.001$) (Vrinten and Hamers, 2003). Our results quantitatively demonstrate that temporal parameters and ground reaction forces have a strong positive linear correlation, especially for temporal-kinetic pairs ($R\approx 1.00$). A simple possible mechanism for this observation is that the longer a limb remains in contact with the ground, the greater potential there is to generate more force during this interval. However, our results also reveal that such correlations do not imply equivalent sensitivity of temporal and kinetic measures in detecting functional changes in rats following rotator cuff injury.

Analysis of kinetic parameters identified distinctions between varying degrees of injury (i.e., one or two tendon tear) and treatment regimens (i.e., tendon repair with or without pain

relief). However, even when comparing uninjured and injured animals three days post-operatively, temporal parameters were unable to identify known functional differences between groups with greater than 50% success. These results agree with a previous study that did not find significant differences in stance time between rats with or without medial meniscus transection, but did report significant differences in peak vertical and propulsion forces (Allen et al., 2012). Several studies that report changes in temporal parameters following injury only compare to a pre-surgical baseline or uninjured control group, suggesting that these measures are sensitive enough to detect differences above a given functional threshold (Giszter et al., 2008; Hampton et al., 2011; Vrinten and Hamers, 2003). The decreased sensitivity of temporal gait parameters may lead investigators to conclude that there is no effect of a treatment when a difference does indeed exist but cannot be detected (type-II statistical error) (Webb et al., 2011). Interestingly, Kale et al. demonstrated a dose-dependent functional response to ethanol in mice with respect to stance, propulsion, and braking times, indicating that analysis of temporal parameters alone may be adequately sensitive for some applications (Kale et al., 2004). Similarly, Angeby-Möller and colleagues found that morphine and rofecoxib both reduced pain behavior (according to stance time and a surrogate measure for weight-bearing) in monoarthritic rats compared to a saline-injected control (Angeby-Moller et al., 2008). Nevertheless, the results of the current study suggest that direct measurement of kinetic parameters using a coupled gait analysis system increases the sensitivity of gait analysis.

Compared to individual temporal parameter analysis, the regression model we developed greatly improved the likelihood of successfully identifying functional differences between groups without direct ground reaction force measurements. However, this was not true in the case of RW vs. RWO, suggesting that while use of the regression model effectively lowered the

threshold of detection, kinetic parameters remain more sensitive to more subtle and important functional differences in rats following rotator cuff injury. Nevertheless, our results indicate that use of a regression model with non-force coupled gait analysis systems can be used to quantitatively predict ground reaction forces and may improve the sensitivity of such analyses, especially when considerably large differences between groups are expected.

This study has several limitations. First, the data sets used for correlation and regression analysis all consider forelimb gait disruption as a result of shoulder injury to provide consistency and reduce potential variability in the current work. Thus, while gait analysis is widely used to study a diverse range of injuries and diseases, future examination of other injury models/hindlimb gait may be useful to fully establish the broad applicability of our results. Second, it is noted that non-force couple gait analysis systems can calculate temporal metrics other than stance, propulsion, and braking duration. However, these parameters were selected for the current study as they are commonly reported, easy to interpret, and have been previously associated with the interval available for force generation (Allen et al., 2009; Angeby-Moller et al., 2008; Hampton et al., 2011; Krizsan-Agbas et al., 2014). Despite these limitations, our results clearly demonstrate that ground reaction forces are more sensitive than kinetic parameters to differences in gait in a rat model of rotator cuff injury.

In conclusion, our results confirmed that temporal and kinetic parameters are strongly correlated, but that temporal properties are less sensitive to functional changes in rat gait. This information is important as measuring temporal parameters is much easier and more efficient than recording ground reaction forces. Non-force coupled gait analysis systems may be most appropriate for confirming the presence of functional deficits as a result of injury or disease if large changes are expected (e.g., injured compared to baseline), whereas force-coupled systems

may be more appropriate when high sensitivity is required to evaluate potentially subtle differences between groups (e.g., investigation of various treatment regimens).

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Table 1 – Summary of Data Sets Used for Correlation and Regression Analysis of Gait Parameters					
Group (sample size)	Study #1 (Reuther et al., 2014a)		Study #2 (Thomas et al., 2014)	Study #3 (Caro et al., 2014)	
	SO (n=14)	SI (n=14)	SIB (n=18)	RW (n=10)	RWO (n=10)
Injury	Supraspinatus tendon tear	Supraspinatus and infraspinatus tendon tears	Supraspinatus, infraspinatus, and biceps tendon tears	Supraspinatus tendon tear and repair <i>with</i> post-op analgesia	Supraspinatus tendon tear and repair <i>without</i> post-op analgesia
Gait Analysis Time Points (days post-op)	-1, 3, 7, 14, 28, 42, 56	-1, 3, 7, 14, 28, 42, 56	-1, 3, 7, 14, 28, 42, 56	2, 4, 6, 14, 28	2, 4, 6, 14, 28

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Table 2 – Kinetic & Temporal Parameter Correlation Coefficients			
Significance Key: * (p<0.05), ** (p<0.01), *** (p<0.001)			
	Stance Time	Braking Time	Propulsion Time
Vertical Force	0.85***	0.91***	0.53*
Braking Force	0.55*	0.84***	0.84***
Propulsion Force	0.41*	0.77**	0.76**

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Table 3 – Multivariable Linear Regression Results						
Significance Key: # (p<0.10), * (p<0.05), ** (p<0.01), *** (p<0.001)						
Force	R ²	Std. Error of the Estimate (%BW)	F-Statistic	Constant β_0	Stance Time Coefficient β_1	Propulsion Time Coefficient β_2
Vertical	0.92	2.50%	62.5***	0.10	1.33***	-1.00***
Braking	0.92	0.66%	61.4***	0.06	0.21***	-0.46***
Propulsion	0.70	0.68%	12.5**	0.03	-0.08 [#]	0.23**

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FIGURE CAPTIONS

Figure 1 – Model Gait Signals During Stance Phase. Typical vertical and anterior-posterior (braking/propulsion) ground reaction forces are shown for a single step. Peak forces in each direction are highlighted. Braking and propulsion phases are separated by when $F_y = 0$ in order to calculate their respective durations, whereas stance time is defined as the entire interval in which the foot remains in contact with the ground.

Figure 2 – Example Data Demonstrating Kinetic vs. Temporal Parameter Sensitivity. Kinetic alone differences are the total differences between groups for all ground reaction forces and kinetic-temporal pair differences are the subset of differences identified simultaneously by corresponding parameters (vertical force and stance time, braking force and braking time, propulsion force and propulsion time). In this generic example, there were three significant differences identified in vertical force alone and only one of these differences was simultaneously identified in the corresponding temporal parameter (stance time, 3 days post-op). Error bars represent standard deviation and asterisks represent significant differences between groups ($p < 0.05$).

Figure 3 – Sensitivity of Kinetic vs. Temporal Gait Parameters. The total number of significant differences between experimental groups in kinetic parameters (ground reaction forces) (black bars) was compared to the subset of differences identified simultaneously in corresponding kinetic-temporal pairs (e.g., braking force and time) (white bars).

Figure 4 – Sensitivity of Kinetic vs. Temporal Gait Parameters for Injured Compared to Uninjured Animals. (A) The total number of significant differences between experimental groups in kinetic parameters (ground reactions forces) (black bars) was compared to the subset of differences identified simultaneously in corresponding kinetic-temporal pairs (e.g., braking force and time) (white bars) between injured (SI, SO, SIB) and uninjured animals at 3, 7, and 14 days post-operatively. (B) Breakdown of analysis by each kinetic-temporal pair.

Figure 5 – Kinetic Parameter Predictability Using Multivariable Linear Regression. (A) Stance and propulsion times were used to predict ground reaction forces for intra-model (SO vs. SI; used to create the regression model) and extra-model (SIB vs. Uninjured, RW vs. RWO; not used to develop the regression model) data sets. Significant differences between groups in predicted kinetic parameters (white bars) were compared to known significant differences in true kinetic parameters (black bars). (B) Breakdown of analysis by each ground reaction force for intra-model and (C) extra-model data.

Figure 1

Figure 2

Figure 3

Figure 4

Figure 5