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Gait analysis in a pre- and post-ischemic stroke biomedical pig model

Kylee Jo Duberstein [a,b], Simon R. Platt [a,e], Shannon P. Holmes [c], C. Robert Dove [a,b], Elizabeth W. Howerth [d], Marc Kent [e], Steven L. Stice [a,b], William D. Hill [f,g], David C. Hess [f], Franklin D. West [a,b,*]

[a] Regenerative Bioscience Center, University of Georgia, Athens, GA 30602, USA
[b] Department of Animal and Dairy Science, University of Georgia, Athens, GA 30602, USA
[c] Department of Veterinary Biosciences & Diagnostic Imaging, University of Georgia, Athens, GA 30602, USA
[d] Department of Pathology, University of Georgia, Athens, GA 30602, USA
[e] Department of Small Animal and Surgery, University of Georgia, Athens, GA 30602, USA
[f] Department of Neurology, Georgia Regents University, Augusta, GA 30912, USA
[g] Department of Cellular Biology & Anatomy, Georgia Regents University, Augusta, GA 30912, USA

HIGHLIGHTS

- Developed gait analysis system to study motor function in pig model.
- Determined key gait parameters for assessing normal pig movement.
- Demonstrated significant changes over time in 5 gait parameters in stroked pigs.

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ABSTRACT

Severity of neural injury including stroke in human patients, as well as recovery from injury, can be assessed through changes in gait patterns of affected individuals. Similar quantification of motor function deficits has been measured in rodent animal models of such injuries. However, due to differences in fundamental structure of human and rodent brains, there is a need to develop a large animal model to facilitate treatment development for neurological conditions. Porcine brain structure is similar to that of humans, and therefore the pig may make a more clinically relevant animal model. The current study was undertaken to determine key gait characteristics in normal biomedical miniature pigs and dynamic changes that occur post-neural injury in a porcine middle cerebral artery (MCA) occlusion ischemic stroke model. Yucatan miniature pigs were trained to walk through a semi-circular track and were recorded with high speed cameras to detect changes in key gait parameters. Analysis of normal pigs showed overall symmetry in hindlimb swing and stance times, forelimb stance time, along with step length, step velocity, and maximum hoof height on both fore and hindlimbs. A subset of pigs were again recorded at 7, 5 and 3 days prior to MCA occlusion and then at 1, 3, 5, 7, 14 and 30 days following surgery. MRI analysis showed that MCA occlusion resulted in significant infarction. Gait analysis indicated that stroke resulted in notable asymmetries in both temporal and spatial variables. Pigs exhibited lower maximum front hoof height on the paretic side, as well as shorter swing time and longer stance time on the paretic hindlimb. These results support that gait analysis of stroke injury is a highly sensitive detection method for changes in gait parameters in pig.

1. Introduction

Neurological injuries such as stroke and traumatic brain injury (TBI) or degenerative diseases including Parkinson's and amyotrophic lateral sclerosis (ALS) affect millions of patients worldwide from infants to the elderly [1–5]. Due to the loss of mobility, limb movement and other motor functions, patients with neurological disorders often need extensive long term care, experience a significant loss in productivity and an overall decrease in quality of life [1]. Helping patients gain lost motor function is a critical component of almost all treatment and rehabilitation programs with changes in gait often being an important parameter in measuring longitudinal changes and improvement [2–5]. Quantitative gait analysis approaches are used to characterize pathologies of

* Corresponding author at: Regenerative Bioscience Center, Department of Animal and Dairy Science, University of Georgia, Rhodes Center for Animal and Dairy Science, 425 River Road, Athens, GA 30602-2771, USA. Tel.: +1 706 542 0988; fax: +1 706 542 7925.
E-mail address: westf@uga.edu (F.D. West).

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motor control, injury and disease progression and to evaluate treatments. This approach enables quantitative measurements of changes in gait velocity, stride length, limb support and other key gait characteristics that are often affected by neurological disorders. Gait analysis is regularly performed in clinical settings, however its use in pre-clinical animal models may potentially serve as an additional tool to evaluate the efficacy and safety of treatments before testing in humans [6–8]. This is of particular importance in testing the efficacy of drug or cell therapy treatments that must undergo extensive testing in animal models before being utilized in patients.

Gait analysis has been performed in rodent animal models of stroke, ALS, Parkinson's and Huntington's diseases with encouraging results [6–9]. These studies found significant differences in multiple gait parameters that were similar to deficits observed in human patients. These studies showed high levels of repeatability and sensitivity for gait changes [6]. Rodent models of neurological conditions have led to significant advances, however they have proven to be limited in some respects because of physiological and anatomical differences between rodents and humans. The human brain is fundamentally different than the rodent brain being gyrencephalic, possessing significantly higher levels of white matter and being much larger in size [10,11]. These differences have been highlighted as a significant limitation in the development of therapies for a number of neurological conditions and have led to the development of large animal pig models of stroke, TBI, spinal cord injury (SCI) and Parkinson's disease to name a just a few [10,12–19]. However, quantitative gait analysis has not been assessed for its potential biomedical application in the pig, testing for clinically relevant gait parameter changes that would be pertinent in human neurological disorder patients.

In this study we utilize a computer based quantitative gait analysis system to determine gait symmetry and important baseline gait parameters in Yucatan miniature pigs including swing and stance time of the limb, velocity, step length, maximum step height and limb support phases. We then use the developed system to perform gait analysis on two animals with surgically induced neural injury. This study demonstrates that significant gait changes in pigs with ischemic stroke injuries can be detected with a high level of sensitivity and that this system is a viable option for studying pre-clinical pig injury and disease models.

2. Materials and methods

All work performed in this study was done in accordance with the University of Georgia Institutional Animal Care and Use Committee guidelines.

2.1. Gait analysis

2.1.1. Gait study

Eight Yucatan pigs were video recorded on three dates within a 10 day period (4 d between recording sessions). Pigs were individually walked to a separate climate controlled room to conduct gait data collection. Pigs were walked through a semi-circular track as described below. Pigs were familiarized and trained to walk through the chute three times per week for the two weeks prior to data collection.

2.1.2. Pre and post-stroke data collection

Each of two Yucatan pigs was video recorded on days 7, 5, and 3 prior to middle cerebral artery occlusion as described below. Pigs were evaluated following experimental stroke surgery again on days 1, 3, 7, 14, and 30 post surgery.

2.1.3. Video recording methods

Two high speed GigEye Ethernet Cameras (IDS Imaging Development Systems, Obersulm, Germany) set to capture footage (70 frames per second) of each side of the pig in profile view were synchronized through an IDS computer driver. Pigs were video recorded as they walked through a semi-circular chute measuring 4 m in diameter. Pigs exited the circular chute into a straight chute, 0.6 m in width, where they were video recorded as they moved perpendicular to two synchronized cameras recording each side of the pig. The straight portion of the chute consisted of a 2.4 m prerecording distance followed by a 2.4 m recording frame, and then a 1.7 m postrecording distance. Cameras were placed 3 m from the recording chute on either side of the pig with camera height set at 24 cm. The chute was constructed of commercial hog panel bolted to the floor, which tied into a 2.4 m recording frame constructed of the same hog panel, which was raised 26.5 cm off the ground to allow visibility of the hooves as the pig walked through the recording frame. The flooring was level and smooth with granulation to ensure a high level of traction.

Pigs were encouraged to walk by a handler walking behind them through the chute. During preliminary gait data collection, pigs were not timed as they walked through the chute. For pre- and post-stroke pig data, pigs were timed using electrical timers (Farmtek, Wylie, TX) as they walked through the recording frame. After 10 repetitions, the mean was calculated and any repetition that fell outside of 10% on either side of the mean was eliminated. Pigs were recorded until 10 usable repetitions were achieved (<20 min/pig).

Video data was captured into the program Equinetec (Monroe, GA, USA). Videos were calibrated using a known calibration video, and were then analyzed for swing time (frame where hoof first leaves the ground to frame where hoof first contacts ground), stance time (frame where hoof first contact ground to first frame where hoof is off ground), step length (distance that each hoof makes between sequential footfalls), step velocity, and maximum step height (peak height achieved by the toe of the hoof through the swing phase).

2.2. Middle cerebral artery occlusion (MCAO) ischemic stroke injury

Ischemic injury was surgically induced in 2 male Yucatan miniature pigs by performing a right sided rostrotentorial craniectomy. A curvilinear skin incision was made between the ear and eye. This exposed the branches of the superficial temporal artery and the associated vein. Vessels were occluded using high frequency bipolar forceps. Following resection of a portion of

Table 1
Comparison of left and right side data for temporal and spatial gait parameters measured on eight Yucatan pigs over three time points.[a]

Parameter	Limb	Left	Right	Std. error	p value
Step length (cm)	Front	76.28	76.05	0.373	0.662
	Hind	75.77	76.28	0.429	0.421
Step velocity (m/s)	Front	0.921	0.894	0.010	0.062
	Hind	0.885	0.863	0.010	0.125
Swing time (sec)	Front	0.248	0.259	0.0001	<0.0001
	Hind	0.328	0.328	0.003	0.801
Stance time (sec)	Front	0.536	0.527	0.0055	0.243
	Hind	0.485	0.492	0.007	0.527
Maximum hoof height (cm)	Front	6.71	6.65	0.061	0.441
	Hind	4.47	4.39	0.048	0.234

[a] Data reported as mean of 10 repetitions at each of three time points within a 10 day period.

overlying zygomatic arch, the temporalis muscle was identified and elevated dorsally off the parietal bone. A craniectomy window was generated in the exposed skull bone surface using a pneumatic drill and burr; the craniectomy was extended into the medial portion of the orbital bone following resection of the orbital ligament. The local underlying dura mater was incised, and the proximal MCA was then permanently occluded utilizing bipolar electrocautery forceps following its identification distal to the Circle of Willis. The exposed brain was then covered with a sterile biograft made of porcine small intestine submucosa; the temporalis muscle was replaced over the defect prior to routine closure of the subcutaneous tissues and the skin.

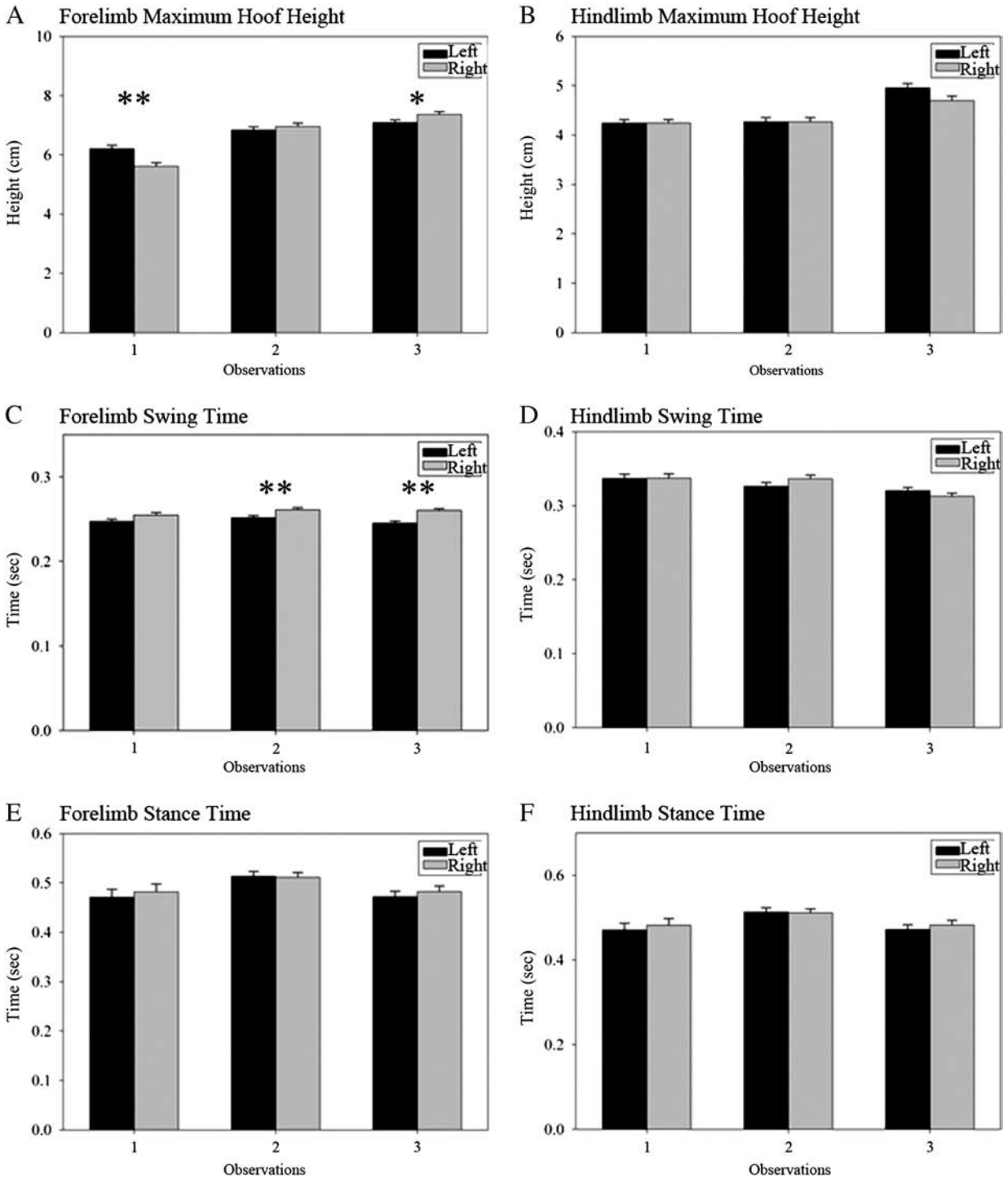

Fig. 1. Normal pigs demonstrate left and right side symmetry in maximum hoof height, swing time and stance time. Hindlimb maximum hoof height (B), swing (D) and stance time (F) and forelimb stance time (E) show now significant differences in symmetry in any of 3 observations. Forelimb maximum hoof height (A) and swing time (C) both showed significant (** = p-value < 0.01; * = p-value < 0.05) differences in symmetry at 2 observations.

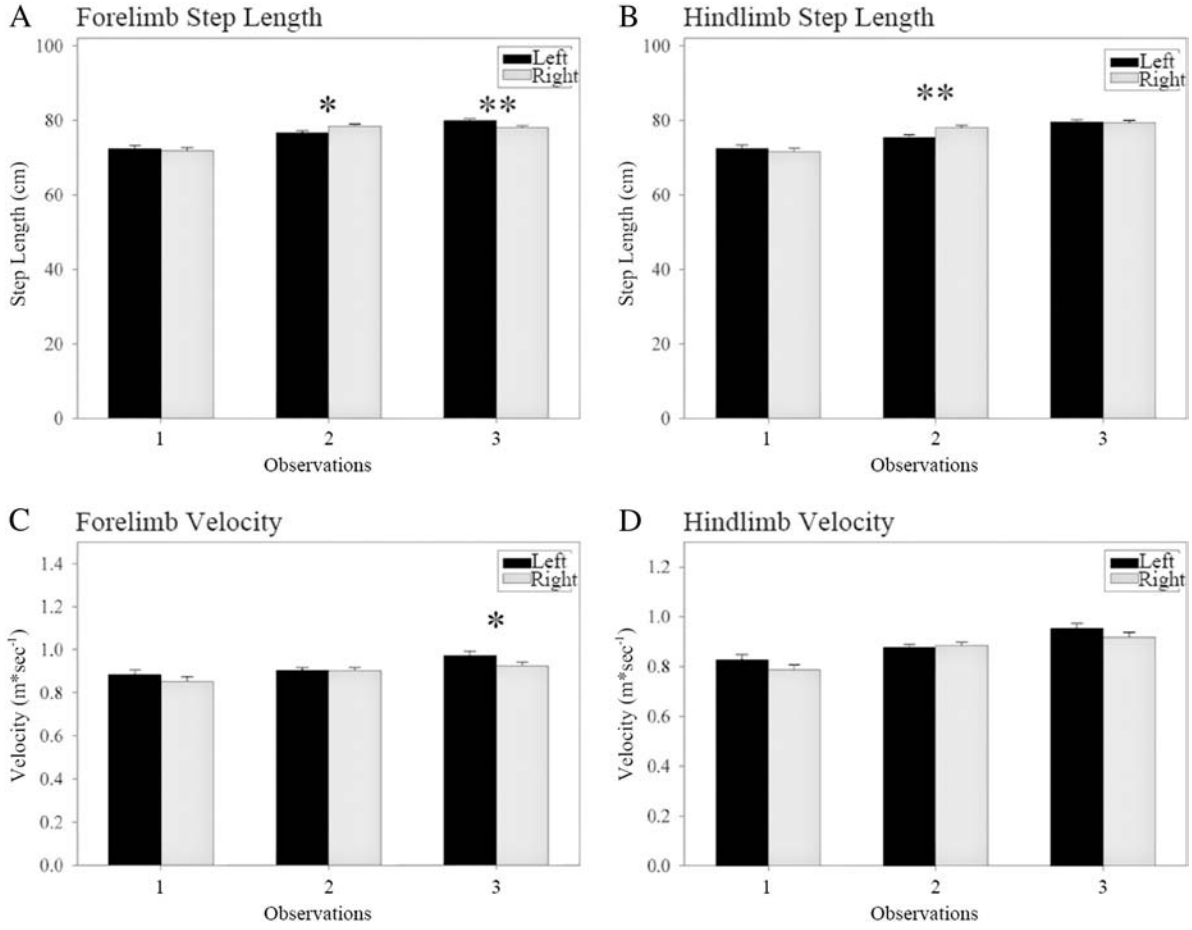

Fig. 2. Normal pigs demonstrate left and right side symmetry in step length and velocity. Forelimb step length showed significant (** = p-value < 0.01; * = p-value < 0.05) differences in symmetry at 2 observations (A). However, hindlimb step length (B) and forelimb velocity (C) were only significantly different at 1 observation and hindlimb velocity showed no significant difference in symmetry (D).

2.3. Magnetic resonance imaging

Magnetic resonance imaging (MRI) was performed 24 h post-MCAO surgery on a GE 16-channel fixed-site Signa HDx 3.0 Tesla MRI system. Under anesthesia, MRI of the brain was performed using a multichannel phase array spine coil, with the patient in dorsal recumbency and the head positioned in the neck cradle portion of the coil. Diffusion weighted images (DWI) were acquire

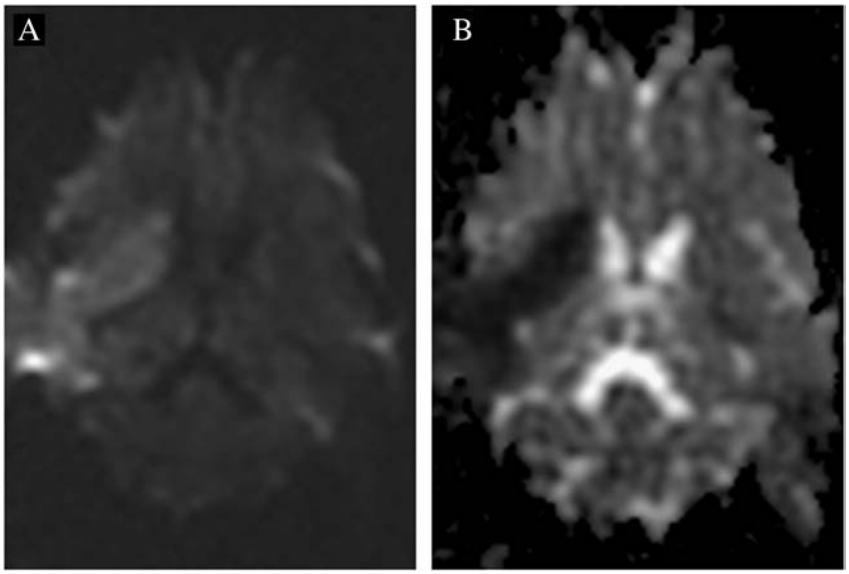

Fig. 3. MCAO ischemic stroke pigs show brain infarction. MRI analysis of stroked pigs showed lesioning of the brain in DWI (A; shown as hyperintense region) sequence and was confirmed in ADC map (B; shown as hypointense region).

with b = 0 and b = 1000. DWI and apparent diffusion coefficient (ADC) maps of the DW images were analyzed using Osirix (R) software for presence of cerebral infarction.

2.4. Statistical analysis

Data was analyzed with SAS version 9.3 (Cary, NC) using Proc GLM with side of pig and time being the variables of interest. A time * side interaction was run to determine significance at each time point. p values of $p < 0.05$ were considered significant.

3. Results

3.1. Normal pigs demonstrate gait symmetry

Overall effects for all time points averaged showed no statistical differences between the right and left limbs of the pig for step length, step velocity, maximum hoof heights, or stance time for the front and hindlimbs (Table 1). Differences were observed between the right and left forelimb swing time with an overall difference of approximately 0.01 s ($p < 0.01$). When each time point was examined individually, forelimb maximum hoof height for the eight pigs showed asymmetries at two of the three time points, measuring less than 0.5 cm difference between the left and right sides (Fig. 1). Hindlimb maximum hoof height did not show this asymmetry (Fig. 1). Hindlimb swing and stance times, as well as forelimb stance time, showed symmetry at all time points recorded (Fig. 1). Forelimb swing time, however, showed an approximate 0.02 s longer swing time on the right forelimb at two of the three time points recorded (Fig. 1). Forelimb step lengths showed alternating asymmetries of approximately 2 cm at two of the three recorded time points (Fig. 2), while hindlimb step lengths showed an asymmetry of approximately 2.5 cm at one of the three time points (Fig. 2). Hindlimb velocities showed close symmetry (Fig. 2), while forelimb velocities showed a difference of 0.05 m/s at one of the three time points (Fig. 2). These results indicate that most gait parameters are symmetrical or close to symmetrical in normal pigs and that gait analysis is highly sensitive and can detect subtle differences in gait.

3.2. Stroked pigs show significant loss of gait symmetry

Two animals were selected to undergo MCAO stroke surgery. After 24 h post-MCAO surgery, the changes on the DW and ADC images were consistent with a stroke. Specifically, a territorial area of abnormal

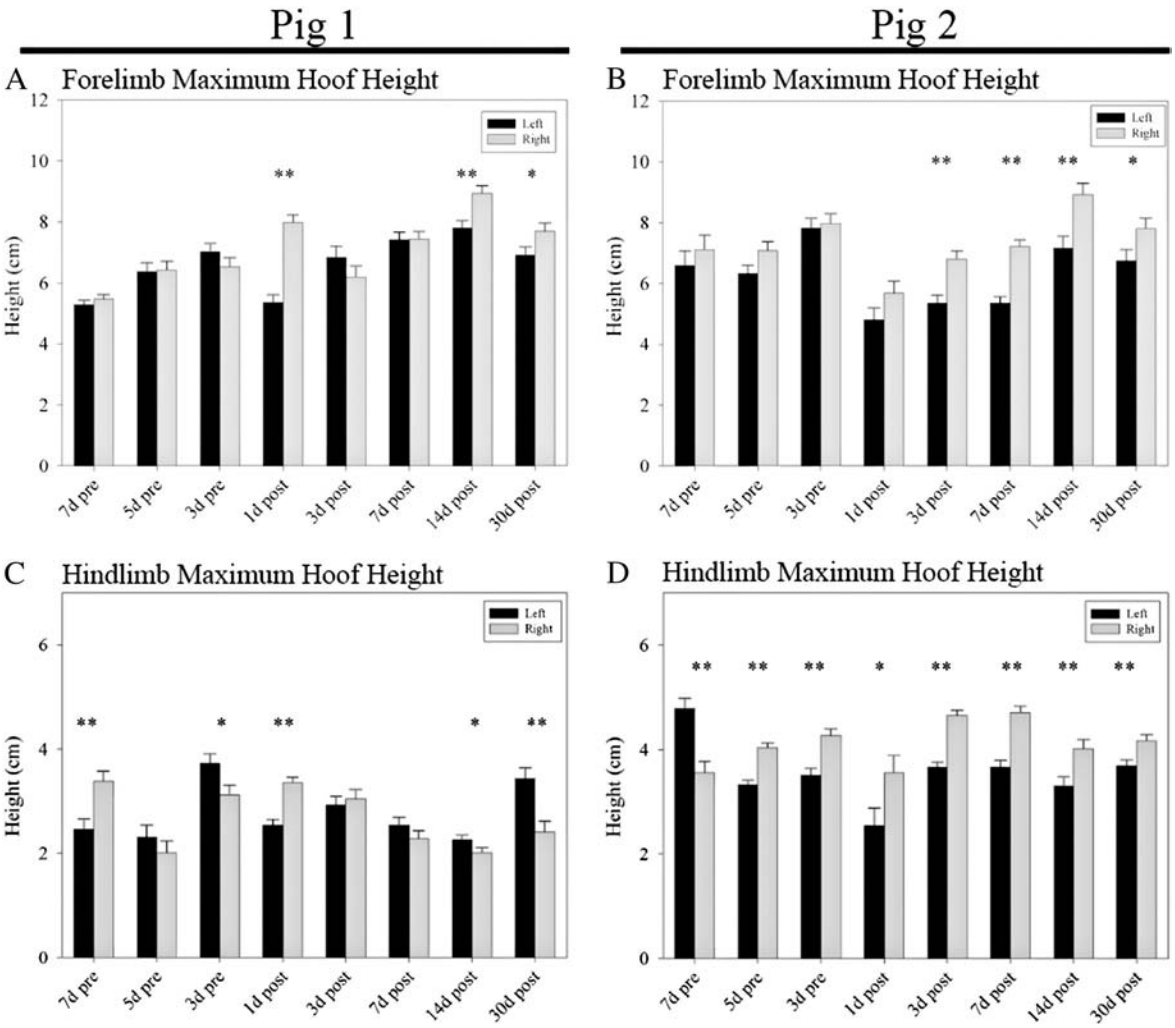

Fig. 4. Asymmetry in forelimb maximum hoof height in stroked pigs. Stroked Pigs 1 and 2 showed significant (** = p-value < 0.01; * = p-value < 0.05) asymmetry in maximum hoof height of forelimb post-stroke with the left leg (paretic limb) achieving lower height while showing no asymmetry pre-stroke (A, B). Hindlimb maximum hoof height Pig 1 was inconsistent (C) and Pig 2 showed consistently higher hoof height on the right side (D).

hyperintensity was present in the right cerebral hemisphere in the region of parenchyma supplied by the MCA. On the DWI and ADC maps, this territorial lesion was hyperintense and hypointense, respectively, consistent with restricted water diffusion and therefore an infarction (Fig. 3).

Gait analysis was performed pre-stroke at 7 d, 5 d, and 3 d and post-stroke at 1 d, 3 d, 7 d, 14 d, and 30 d. Gait analysis showed significant asymmetry in maximum hoof height of the front legs in both pigs post-stroke with the left leg (contralateral to occlusion of MCA) achieving a lower height at 1 d, 14 d, and 30 d post-stroke for the first stroked pig (Pig 1) and at 3 d, 7 d, 14 d, and 30 d post-stroke for the second stroked pig (Pig 2), while having shown no asymmetry pre-stroke (Fig. 4). Hindlimb hoof heights did not show the same consistent differences with Pig 1 showing inconsistent differences in hoof height symmetry throughout both pre and post-stroke data collection and Pig 2 showing a consistently higher right hindlimb hoof height at all but one time point pre and post-stroke (Fig. 4). Swing times of forelimbs showed no asymmetries (Fig. 5). However, swing time of the left hindlimb was shown to be shorter than the right at times 3 d, 7 d, and 14 d post-stroke for Pig 1 and at times 1 d, 3 d, 7 d, and 14 d post-stroke for Pig 2 (Fig. 5). Hindlimb stance time showed similar asymmetries with the left limb showing longer stance times at 3 d, 7 d, and 14 d post-stroke for Pig 1 and at 3 d and 14 d post-stroke for Pig 2 (Fig. 6). No difference in stance time between the right and left forelimbs was observed at any time point (Fig. 6). Additionally, hindlimb step length of the left limb was found to be shorter as compared to the contralateral limb at time points 7 d, 14 d, and 30 d post-stroke for Pig 1, but this difference was only observed at 30 d post-stroke for Pig 2 (Fig. 7). Front limb step length of the left limb showed a similar tendency in Pig 1 with shorter step lengths at times 1 d and 30 d post-stroke (Fig. 7) leading to slower step velocities (Fig. 8). However, a slightly longer front limb step length on the left side was noted for Pig 2 at times 14 d and 30 d post stroke with no accompanying change in stride velocity (Fig. 8). Hindlimb step velocity showed no asymmetry post-stroke for Pig 1 (Fig. 8), but Pig 2 was significantly faster on the left hindlimb at times 1 d, 3d, 7 d, and 14 d post-stroke. These data demonstrate that significant differences in gait characteristics occur after MCA stroke in the Yucatan pig and that such differences vary between individuals.

4. Discussion

In this study we demonstrate that gait analysis can be a highly sensitive approach with a high signal to noise ratio, detecting small, significant and consistent changes in movement in a pig MCAO ischemic stroke model. Major findings of this study are consistent asymmetries of a lower front hoof height, reduced hind swing

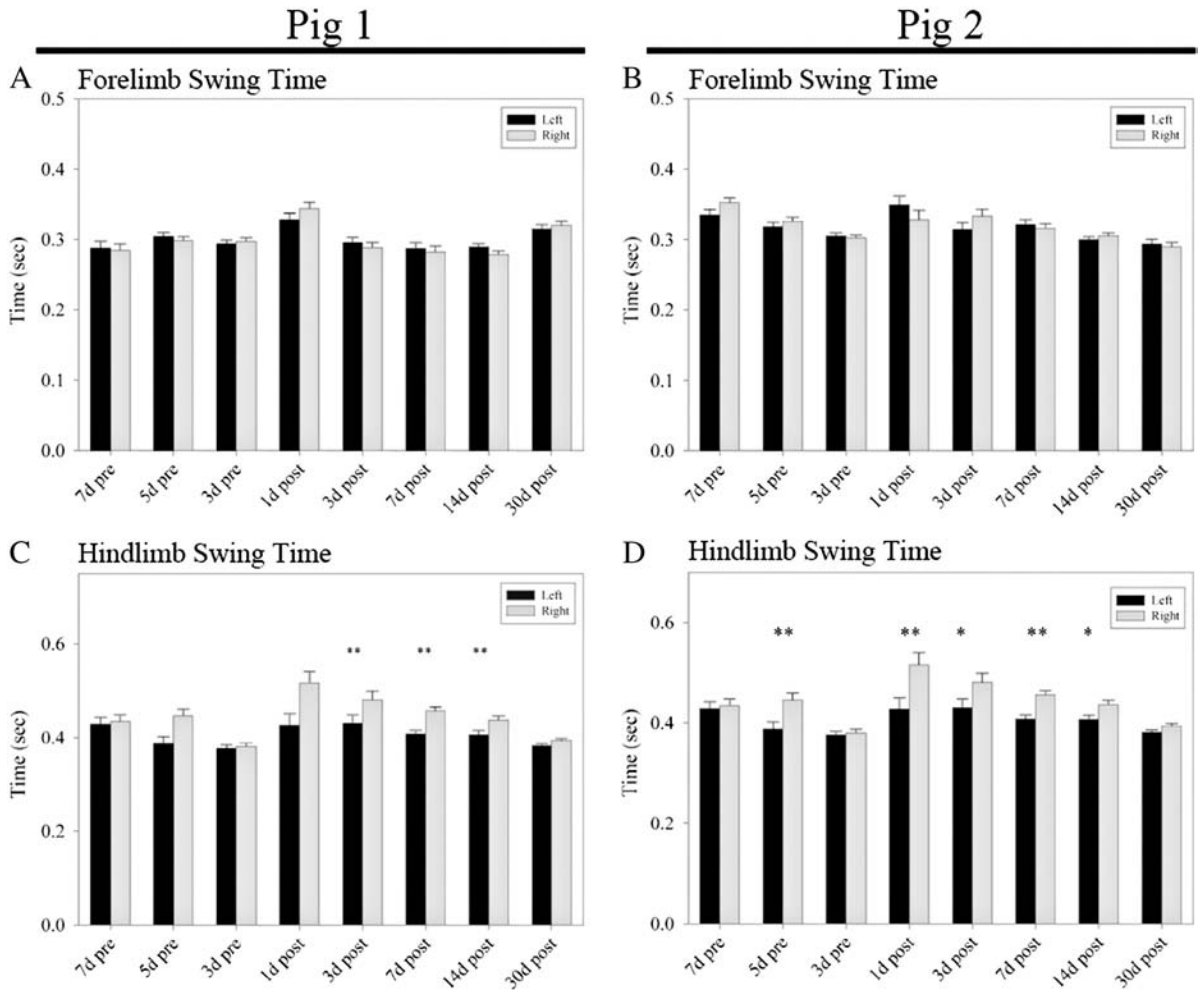

Fig. 5. Asymmetry in hindlimb swing time in stroked pigs. Swing time of the forelimb in stroked Pigs 1 and 2 was consistently symmetric (A, B). However, hindlimb swing times were asymmetric at 3 and 4 time points for Pigs 1 and 2 respectively post-stroke (C, D). (** = p-value < 0.01; * = p-value < 0.05).

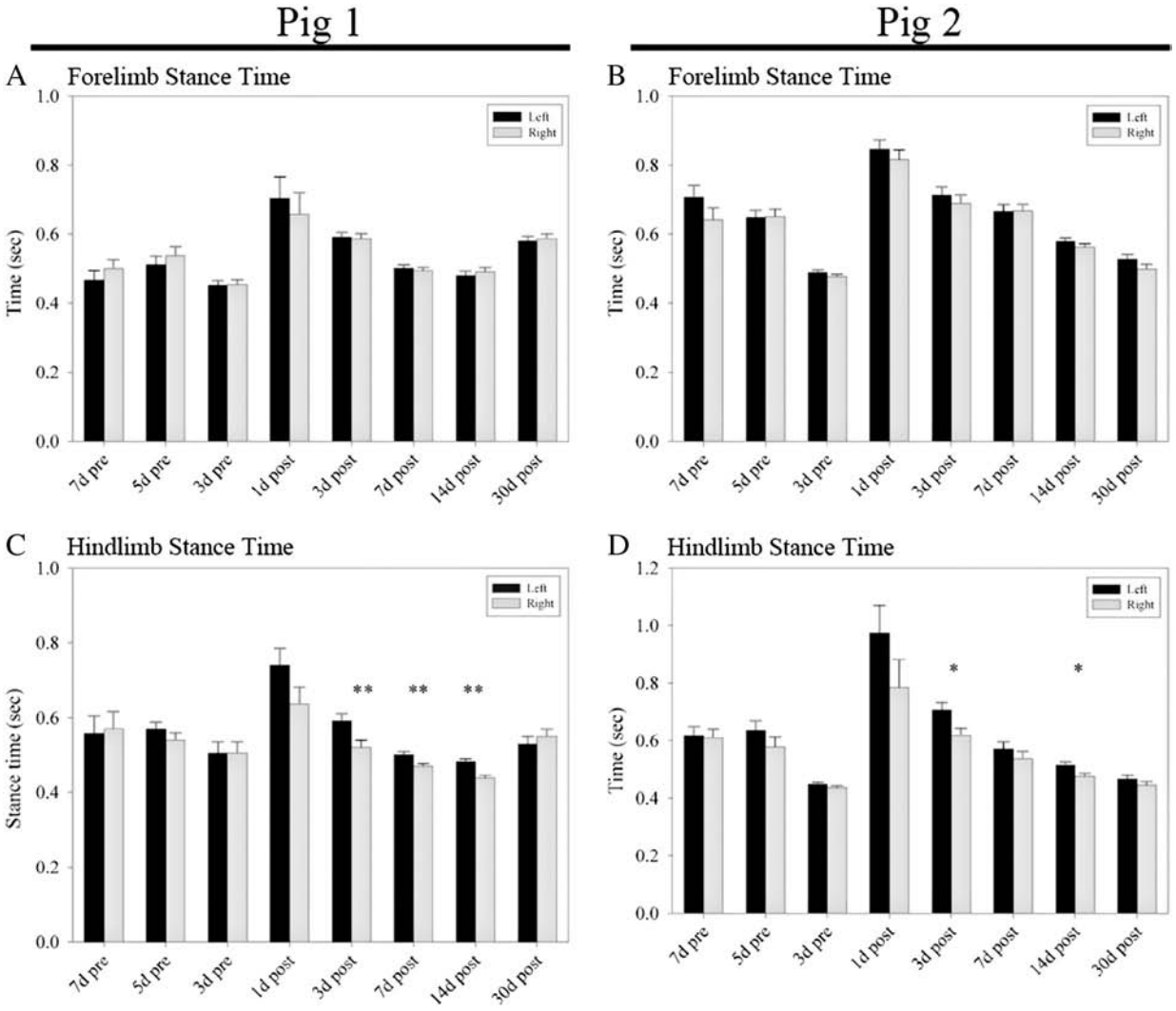

Fig. 6. Asymmetry in hindlimb stance time in stroked pigs. Stance time of the forelimb in both stroked Pigs 1 and 2 was consistently symmetric (A, B). However, hindlimb swing times showed significant (** = p-value < 0.01; * = p-value < 0.05) asymmetries at 3 and 2 time points for Pigs 1 and 2 respectively post-stroke (C, D).

time and increased hind stance time post stroke on the side contralateral to MCA occlusion. Human stroke patients have been shown to display alterations in gait, often times manifested as both a decreased walking velocity as well as asymmetry of the lower limbs, and that improvements in these parameters may be used to gauge recovery from stroke [20,21]. Specifically, stroke patients have been shown to have a greater degree of temporal gait asymmetry as the severity of stroke increases, with severe stroke patients tending to exhibit longer swing times and shorter stance times on the paretic limb (contralateral to stroke) [20]. Pigs in this study displayed the opposite finding, showing an increased stance time and reduced swing time on the contralateral hindlimb. However, an important consideration is that in humans the swing phase of the paretic limb coincides with the stance phase of the non-paretic limb, and therefore the forward movement of the paretic limb comes from balance and propulsion of the non-paretic limb, and vice versa [22]. Pigs are quadrupeds as opposed to bipeds, and therefore their gait must be examined differently. The two animals examined post-stroke demonstrate the same main asymmetries of a lower front hoof height as well as a reduced hind swing time and increased hind stance time on the side contralateral to MCA occlusion. Argument for the contralateral side being the side affected by paresis post-stroke can be derived from the function of each limb. Front limbs exhibit higher vertical ground reaction forces [23]; therefore, if the left side is affected by paresis post-stroke and thereby less able to exert force, this would be manifested as a decrease in maximum hoof height achieved through the swing phase of the front hoof of the affected limb. Likewise, the hindlimb may be compensating by decreasing the swing time and increasing the stance time for multiple reasons. First, in a lateral sequence walk, as the left hindlimb leaves the ground, the weight of the left (paretic) side of the pig is now borne more over the affected forelimb, and thus the swing time of the hindlimb may be shortened in an effort to hasten ground contact and help stabilize weight distribution on the affected side. Another plausible explanation may be that the affected hindlimb does not exert the same propulsive forces as the unaffected side and thereby has a reduction in time spent off the ground. Increased stance time of the affected hindlimb may help to distribute weight of the pig on the affected side as well as stabilize the mediolateral balance of the pig.

Previous studies have examined locomotor patterns in pigs as related to flooring surfaces [24,25] and flooring cleanliness [26] providing basic stride characteristics (stride length and velocity, swing and stance time). However, no research has been conducted on miniature pig

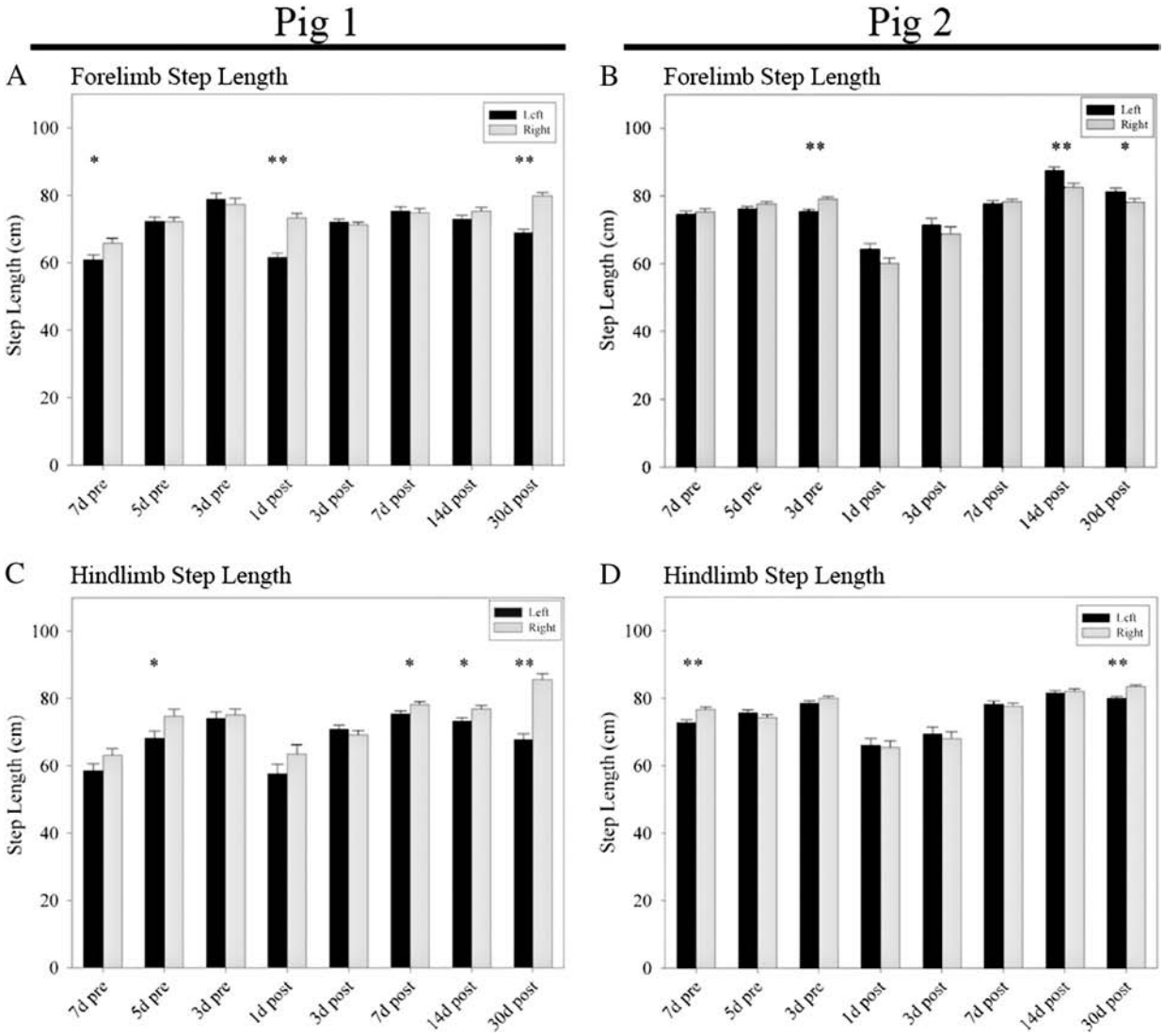

Fig. 7. Asymmetry in step length in stroked pigs. Stroked Pigs 1 and 2 both showed significant (** = p-value < 0.01; * = p-value < 0.05) asymmetry at 2 time points in forelimb step length post-stroke (A, B). Pig 1 also demonstrated asymmetry in hindlimb at 3 time points post-stroke (C), while Pig 2 only showed asymmetry at 30 d (D).

breeds to establish parameters of relevance for future biomedical testing. This is the first study that describes gait parameter symmetry between the right and left sides in pigs. This information is critical if gait analysis is to be used in future studies to establish the pig as a large animal stroke model to test responses to potential treatments given that gait symmetry is a commonly affected parameter in stroke patients. Results of this study indicate that overall, non-stroked pigs have a symmetrical gait in the parameters of step length and velocity, maximum hoof height, stance time on both the front and hindlimbs, and swing time of the hindlimb. Swing and stance time of the hindlimb showed the most consistent symmetry, with no time points showing differences between sides of the pig. Hoof height, step length, and stride velocity showed some asymmetry at individual time points, but differences were small and of questionable biological significance. Of particular interest, maximum hoof height of the front limbs showed consistent changes post-stroke in both pigs, while there were no asymmetries noted in these pigs at the pre-stroke time points. Non-stroked pigs did show asymmetries in maximum hoof height, however differences of symmetry were $\leq$0.5 cm whereas post-stroke differences were of much higher magnitude (up to 2.5 cm). These findings suggest that the pig gait is symmetrical and may be used as an assessment tool in stroke model testing.

5. Conclusion

Results of this study indicate that Yucatan miniature pigs exhibit overall gait symmetry in both temporal and spatial parameters that may be readily analyzed in the pig at walking speeds. Stroke induced by MCA occlusion resulted in asymmetries in temporal parameters of the hindlimb as well as maximum front hoof height. These changes can be compared to asymmetries exhibited by human stroke patients when results are put in context of quadruped walking patterns.

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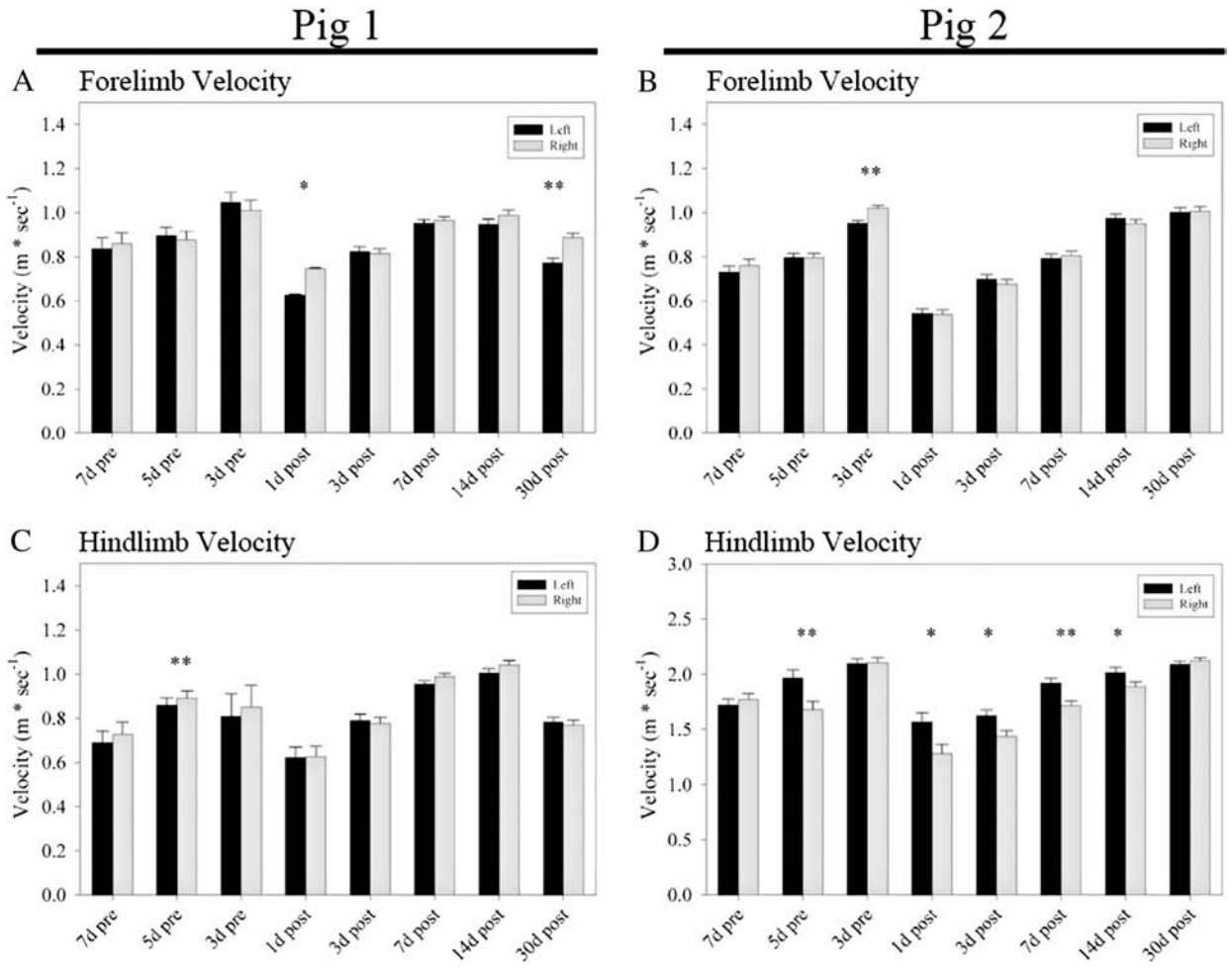

Fig. 8. Asymmetry in velocity in stroked pigs. Stroked Pig 1 demonstrated asymmetry in forelimb velocity at 2 time points post-stroke, while velocity asymmetry was not observed for Pig 2 forelimb and Pig 1 hindlimb. Pig 2 hindlimb showed significant (** = p-value < 0.01; * = p-value < 0.05) asymmetry at 4 time points post-stroke.

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