physiologia

Article

Assessing Asymmetry in Exercise Intensity Domains between Lower Limbs in Persons with Multiple Sclerosis: A Pilot Study

John W. Farrell III [1,*], Shelby Shipman [2], Christopher D. Black [2], Carl J. Ade [3] and Rebecca D. Larson [2]

[1] Department of Health and Human Performance, Texas State University, San Marcos, TX 78666, USA
[2] Department of Health and Exercise Science, University of Oklahoma, Norman, OK 73079, USA
[3] Department of Kinesiology, Kansas State University, Manhattan, KS 66506, USA
* Correspondence: jwf77@txstate.edu

Abstract: Persons with multiple sclerosis (PwMS) experience a variety of physical impairments that can present in an asymmetrical pattern, resulting in significant differences between contralateral limbs (i.e., >10%). Asymmetries in PwMS have been associated with walking impairment and postural instability. Exercise intensity has been shown to influence the degree of asymmetry outcomes in healthy populations, and may have an impact on appropriate exercise prescriptions. The purpose of the current pilot study was to investigate the potential presence of asymmetry in metabolic events demarcating exercise intensity domains during single-leg cycling in PwMS. Five PwMS (Expanded Disability Status Scale range 2.0 to 4.5) completed a single leg incremental cycling test (SLICT) and a series of single-leg constant power time-to-exhaustion trials to determine gas exchange threshold (GET), peak oxygen consumption (VO_2peak), peak power output (PPO), critical power (CP), and W′ (exercise tolerance above CP) for both lower limbs. Statistical analysis revealed no significant between-limb differences for VO_2peak, GET, CP, PPO, and W′. Only W′ asymmetry score was significantly (49.5 ± 28.7 vs. 10.0, $p = 0.04$) greater than 10%. No significant differences between asymmetry scores at the GET, CP, and PPO were observed. Results from the current pilot investigation suggest that exercise intensity may not influence asymmetry outcomes in PwMS. Future studies with larger sample sizes and those with higher disability levels are required to fully understand the influence of exercise intensity on asymmetry in PwMS.

Keywords: multiple sclerosis; critical power; asymmetry; cycling; exercise

check for updates

Citation: Farrell, J.W., III; Shipman, S.; D. Black, C.; Ade, C.J.; Larson, R.D. Assessing Asymmetry in Exercise Intensity Domains between Lower Limbs in Persons with Multiple Sclerosis: A Pilot Study. *Physiologia* **2023**, *3*, 1–10. https://doi.org/10.3390/physiologia3010001

Academic Editors: Anastassios Philippou and Philip J. Atherton

Received: 11 October 2022
Revised: 18 November 2022
Accepted: 14 December 2022
Published: 22 December 2022

1. Introduction

Due to the progressive neurodegenerative nature of multiple sclerosis (MS) and the resulting loss of myelin and axons, persons with MS (PwMS) can experience a variety of symptoms and physical impairments [1]. Reduced muscular strength, abnormal gait and balance, muscle spasticity, and fatigue are common amongst PwMS [1]. It has been observed that physical impairments can present in an asymmetrical pattern resulting in significant differences (i.e., >10% difference) in physiological fitness parameters and function between contralateral limbs [2].

Previous research investigating asymmetry in PwMS is still limited. However, investigations have identified asymmetry in upper and lower limb muscular strength, oxygen uptake and work performed during single-leg cycling, power produced by individual limbs during traditional (double leg) cycling at submaximal intensities, glucose uptake in the muscles of the lower limbs, and femoral neck bone mineral density [2–8]. Additionally, asymmetry in physiological fitness parameters in PwMS has been significantly associated with reduced walking speed and endurance and postural instability, and may contribute to the overall accumulation of disability impairing PwMS' ability to maintain employment and independence and reducing quality of life [2,3,6].

As previously mentioned, research investigating asymmetry in PwMS is limited. Most investigations have focused on asymmetry in muscular strength, via maximal voluntary isometric contractions, or asymmetry in peak oxygen uptake (VO_2peak) and power (watts (W)) produced during single-leg cycling at maximal intensities [4,6,8]. Previously, only one investigation has examined asymmetry in PwMS during submaximal cycling at 50%, 60%, and 70% of VO_2peak [7]. Asymmetry scores in W produced between contralateral limbs were observed to exceed 10% at all three exercise intensities [7]. The use of only a narrow range of submaximal intensities that are not anchored by metabolic events does not provide insight into the potential influence that exercise intensity could have on the manifestation of asymmetry in PwMS. Additional investigations incorporating both maximal and submaximal exercise intensities, as indicated by metabolic events rather than arbitrary intensities, are required.

During exercise, the utilization of energy substrates and the accumulation of metabolic by-products leads to the transition between different exercise intensity domains [9]. The most commonly used exercise intensity domains are identified as moderate (below the gas exchange threshold (GET) (a non-invasive assessment of lactate threshold)), heavy (between GET and critical power (CP), and severe (above CP with the attainment of VO_2peak) which are anchored by metabolic events [9]. The metabolic response to exercise varies by the domain in which exercise is performed [9]. The moderate intensity domain is primarily characterized by blood lactate values and respiratory exchange ratios remaining at or near resting values during exercise, with VO_2 values rising but at a slower rate than the slow component of VO_2 and reaching a metabolic steady state within two to three minutes [9,10]. The physiological response to the heavy intensity domain includes an increase in blood lactate levels and the development of the VO_2 slow component, both of which stabilize within ten to twenty minutes [9]. Unlike the moderate intensity domain, exercise in the heavy intensity domain leads to the development of both global and peripheral fatigue that has been speculated to be due to the production of reactive oxygen species, K^+ accumulation, and glycogen depletion [9,11]. The defining physiological response to exercise in the severe intensity domain is the rapid increase in of VO_2, blood lactate levels, and metabolic by-products and their subsequent failure to achieve a steady state [9,12,13]. Specifically, the VO_2 slow component will rise until reaching VO_2peak [9,12,13]. An estimate of the energy stores, in kilojoules (KJ), available to allow individuals to exercise above CP can be quantified via W′ [9].

The benefits of participating in physical activity and exercise training are consistently and extensively supported for PwMS, with general guidelines available for both aerobic and resistance training exercise [14]. However, these do not take into consideration the presence of asymmetry between contralateral limbs. Examining the influence of exercise intensity, as demarcated by metabolic events such as GET, CP, and VO_2peak, on the manifestation of asymmetry in PwMS will provide valuable information for development of appropriate exercise prescription. Additionally, this would provide insight into potential asymmetry in metabolic processes between contralateral lower limbs in PwMS. Thus, the purpose of the current investigation was to assesses the presence of asymmetry in contralateral lower limbs in PwMS for GET, CP, peak power output (PPO), VO_2peak, and W′. The current investigators hypothesized that statistically significant lower limbs differences would be present for all variables. Additionally, it was hypothesized that all variables would have an asymmetry score statistically greater than 10%, indicating the presences of asymmetry, with levels decreasing as exercise intensity progressed from GET to CP and then to PPO.

2. Materials and Methods

2.1. Experimental Design

The current pilot study utilized a one group cross sectional design. PwMS completed a single leg incremental cycling test (SLICT) to determine GET, VO_2peak, and peak power output (PPO) for both lower limbs. Additionally, a series of single-leg constant power time-to-exhaustion trials were completed to determine CP and W′ for both lower limbs. The self-reporting version of the Kurtzke Expanded Disability Status Scale (EDSS) was used to determine disability [15]. PwMS were familiarized to all procedures prior to exercise testing, and a minimum of 48 h was required between all testing visits. All participants gave their informed consent for inclusion prior to participation. The current investigation was conducted in accordance with the Declaration of Helsinki, and the protocol was approved by the Institutional Review Board of the University of Oklahoma (IRB number 4423)

2.2. Participants

Inclusion criteria included between the ages of 18 and 65 years, physician's confirmed diagnosis of MS and clearance to participate in exercise testing, an EDSS of 1.0–6.0 (mild-to-moderate disability), and relapse-free 3 months prior to exercise testing. PwMS were excluded if there was a history of cardiovascular, metabolic, or respiratory disease, current or previous lower-limb orthopedic injury that could result in asymmetry, and previous or current use of prednisone medication [4,5,7]. Participants were recruited from Multiple Sclerosis Self-Help Groups located in the Norman and Oklahoma City, Oklahoma areas from August of 2013 to August 2014 with data collection occurring during the same time period.

2.3. Single Leg Incremental Cycling Test

Prior to testing, the cycle ergometer was adjusted to ensure the exercising leg was almost extended at the bottom of the pedal crank while the non-exercising leg was positioned with the knee bent, hips square, and leg resting and strapped to a stand to ensure it did not contribute to cycling action [3]. A counter weight of 20lbs was attached to the pedal arm of the non-exercising side [16,17]. This was done for both limbs, with positions recorded to ensure consistency across all visits.

PwMS performed a conventional (2-leg) 5 min warm-up at 0 watts (W) via a separate cycle ergometer from the one used for SLICTs. Following the warm-up, PwMS were immediately transferred and positioned on the SLICT cycle ergometer. SLICT consisted of a continuous ramp protocol beginning at 0 W and increasing 1 W/4s until participants' cadence dropped below 40 revolutions per minute (RPM), upon which the test was terminated. This protocol has previously been used with single-leg cycling in PwMS [3]. Metabolic measurements and heart rate (HR) were collected continuously during testing via a calibrated metabolic testing cart (True One 2400; Parvo Medics, Salt Lake City, UT, USA) and polar monitor (Polar T-31; Polar Electro Inc., Lake Success, NY, USA), respectively. The testing order of lower limbs was randomized, and participants were instructed to maintain the same pedaling cadence for each lower limb.

VO_2peak was defined as the highest 30 s average achieved during testing, while PPO was defined as the highest W achieved prior to test termination. GET was determined using the method described by Beaver, Wasserman, and Whipp [18]. By graphing VCO_2 as a function of VO_2, the factional concentration of end-tidal of O_2 and CO_2, the ventilatory equivalents for O_2 and CO_2, and respiratory exchange ratio (RER) the GET can be determined by the vertical alignment of these profiles. Criteria for identifying the corresponding work rate to GET include the identification of an increase in VCO_2 out of proportion to VO_2, an increase in the ventilatory equivalent of O2 with no increase in the ventilatory equivalent of CO2, (c) a rise in fractional concentration of end tidal CO_2 and O_2, and no inflection of the RER [18].

2.4. Critical Power Trials

To determine the CP of each participant's lower limb, three single-leg constant power time-to-exhaustion trials were performed with exercise intensity ranging between 40% and 110% of PPO for each lower limb [19]. PwMS began each trial with completion of the same warm-up protocol used prior to the SLICT. After completing the warm-up, the trial began with 30 s of unloaded single-leg cycling followed by an increase in resistance to the randomly predetermined percentage of PPO with the aim of the trial lasting 12–15 min [19]. Participants were instructed to maintain the same cadence as during the SLICTs, with the trial being terminated when the participant's cadence decreased to <40 RPM. PwMS were blinded to the exercise intensity and duration of the trial. Metabolic measurements and heart rate (HR) were collected continuously during testing via a calibrated metabolic testing cart and polar monitor, respectively. Time-to-exhaustion (TTE) was measured as the accumulated time from the completion of the warm-up to the termination of the trial, using the timer on the metabolic cart. Both lower limbs were assessed during each CP trial visit, with the lower limb testing order randomly assigned and with 30 min of rest between CP trials of contralateral limbs.

2.5. Asymmetry Scores

Asymmetry scores were calculated for GET, CP, PPO, W′, and VO_2peak using the following equation: $(1 - (\text{limb}_{\text{low performance}}/\text{limb}_{\text{high performance}})) \times 100$ [5,6]. Higher scores reflect greater asymmetry between contralateral limbs [6]. The higher performance limb was identified as the limb with the highest value for each measure. This method has previously been used in PwMS for determining asymmetry scores in contralateral limb muscular strength and oxygen uptake kinetics [3,6,7].

2.6. Disability

Disability was measured using the self-reported version of the Kurtzke EDSS [15]. Briefly, this questionnaire contains 17 items that reflect the certified rater-administered version of the EDSS. EDSS scores determined with the self-reported version have been strongly correlated with certified rater scores [15]. A minimal clinically important difference for the EDSS has been suggested to be a 1 point and 0.5 point change with a baseline EDSS of $\leq$5.5 and >5.5, respectively [20].

2.7. Statistical Analysis

Critical power analyses were performed using SigmaPlot software v. 12.5 (Systat Software, San Jose, CA, USA) while statistical analysis was performed using IBM SPSS Statistics (Version 26.0; IBM Corp. Armonk, NY, USA). Linear calculations using the 1/time model were used to determine CP and W′, with the y-intercept and slope representing CP and W′, respectively [19,21]. Independent samples *t*-test was used to assess statistically significant differences between the lower limbs for SLICT and CP trial measures. A one sample *t*-test was used to determine if asymmetry scores were statistically significantly different from 10%. This method of analysis and threshold for asymmetry between contralateral limbs has previously been used in PwMS [5,7,8]. Additionally, a one-way repeated measures analysis of variance (ANOVA) was used to determine if statistically significant differences were present between asymmetry scores for GET, CP, and PPO. Bonferroni corrections were conducted for post hoc analysis if statistically significant differences were found. Effect sizes were reported as Cohen's *d* when appropriate, with 0.2, 0.5, and 0.8 indicating a small, moderate, and large effect, respectively [22]. Effect sizes for ANOVA were analyzed when appropriate using eta-squared (η^2), with 0.02, 0.13, and 0.26 considered a small, moderate, and large effect, respectively [22,23]. Frequency statistics were used to describe the number of participants with asymmetry scores > 10%. Statistical significance was set at $p < 0.05$, with data expressed as means and standard deviation unless otherwise noted.

3. Results

3.1. Participants

Participant characteristics are presented in Table 1. Overall, five PwMS, (three females and two males) participated in the current investigation with the mean age of 43.2 (7.3) years and a median (interquartile range) EDSS score of 2.5 (2.0), indicating mild disability.

Table 1. Participant Characteristics (N = 5).

Participant	1	2	3	4	5	Mean (SD)
Sex	F	M	M	F	F	NA
Age (y)	34	54	45	40	43	43.2 (7.3)
Height (cm)	168.5	183.0	171.0	165.0	165.0	170.5 (7.4)
Weight (kg)	116.8	99.8	84.9	80.6	69	90.2 (18.5)
BMI (kg/m^2)	41.1	29.8	29.0	29.6	25.3	31.0 (6.0)
EDSS	2.5	2.5	2	3.5	4.5	2.5 (2.0–4.0)

Data are individual values with group data presented as mean (SD), EDSS presented as median (IQR). F = female; M = male; BMI = body mass index; EDSS = expanded disability status scale; SD = standard deviation; IQR = interquartile range; NA = not applicable.

3.2. Single Leg Incremental Cycling Test and Critical Power Trials

Analysis for between-lower-limb differences for the SLICT and critical power trials data are presented in Table 2. Independent samples *t*-test revealed that no statistically significant differences existed between HPL and LPL for VO_2peak, GET, CP, PPO, and W′, with small-to-moderate effect sizes observed. Individual and group asymmetry scores for SLICT and critical power trials are presented in Figure 1. One sample *t*-test revealed that the asymmetry scores of VO_2peak (5.0 ± 2.8 vs. 10.0, $p = 0.02$), GET (4.3 ± 3.8 vs. 10.0, $p = 0.03$), and W′ (49.5 ± 28.7 vs. 10.0, $p = 0.04$) were statistically significantly different from 10%, with only W′ being greater than 10%. No participants had an asymmetry score >10% for both VO_2peak and GET. However, 2 (40% of sample), 1 (20%) and 5 (100%) participants had an asymmetry score >10% for CP, PPO, and W′, respectively. Finally, a one-way repeated measures ANOVA found no statistically significant differences (F = 0.89, $p = 0.45$) between asymmetry scores at the GET, CP, and PPO.

Table 2. Physiological data from single leg incremental cycling test and critical power trials (N = 5).

Participant		1	2	3	4	5	Mean (SD)	*p*	*d*
GET (W)									
	HPL	63.0	67.0	70.0	43.0	55.0	59.6 (10.9)	0.67	0.28
	LPL	58.0	66.0	64.0	43.0	53.0	56.8 (9.2)		
CP (W)									
	HPL	55.0	88.0	80.0	52.0	37.0	62.4 (21.1)	0.63	0.32
	LPL	35.0	77.0	79.0	51.0	36.0	55.6 (21.4)		
PPO (W)									
	HPL	100.0	139.0	100.0	94.0	73.0	101.2 (23.9)	0.69	0.26
	LPL	96.0	123.0	96.0	94.0	69.0	95.6 (19.1)		
VO_2peak (mL/kg/min)									
	HPL	12.6	22.1	23.2	14.1	30.1	20.4 (7.1)	0.79	0.16
	LPL	12.1	21.2	21.3	13.9	27.9	19.3 (6.4)		
W′ (KJ)									
	HPL	111,112.9	15,489.9	10,140.9	5683.2	4149.5	29,315.3 (45,938.6)	0.28	0.73
	LPL	6455.8	9438.4	4235.4	4658.8	2569.9	5471.7 (2613.1)		

Data are individual values with group means presented as mean (SD). d = Cohen's d effect sizes; HPL = high performing limb; LPL = low performing limb; VO_2peak = peak oxygen consumption, GET = gas exchange threshold; W = watts; CP = critical power; PPO = peak power output, W′ = energy stores above critical power; KJ = kilojoules.

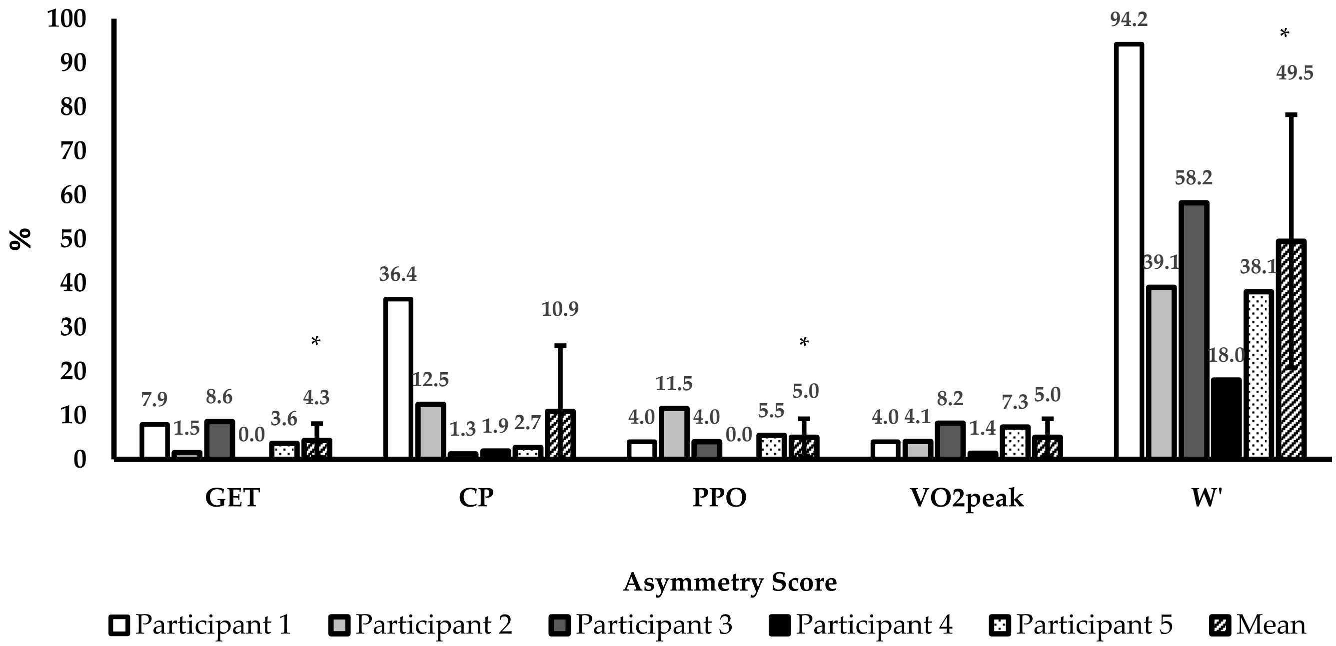

Figure 1. Individual and mean asymmetry scores at gas exchange threshold, critical power, and peak power output. Mean asymmetry scores presented as mean and standard deviation. * = statistically significantly different from 10%.

4. Discussion

The purpose of the current investigation was to assess the presence of asymmetry in contralateral lower limbs in PwMS for GET, CP, peak power output (PPO), VO_2peak, and W′. The current investigators hypothesized that significant lower-limb differences would be present for all variables. Additionally, it was hypothesized that all variables would have an asymmetry score significantly greater than 10%, indicating the presence of asymmetry, with levels decreasing as exercise intensity progressed from GET to CP and then to PPO. The results of the current investigation indicated no significant differences between lower limbs for all variables, thus the hypothesis was rejected. No significant differences were observed between asymmetry scores at GET, CP, and PPO, thus again our hypothesis was rejected. Additionally, only W′ had a significantly greater asymmetry score than 10%.

A previous investigation utilizing single-leg cycling in PwMS reported differences of 3.1 ± 1.9 mL/kg/min and 18.1 ± 14.0 W for VO_2peak and PPO between lower limbs, respectively [3]. These differences were also significantly greater than those differences observed in healthy controls [3]. The differences observed in the current investigation are much lower than those previously reported, despite both investigations using similar methodologies. However, differences may be contributed to differences in EDSS of participants, differences in sample size (5 PwMS vs. 8 PwMS), and the use of a counterweight during single-leg cycling. Although both investigations have similar median EDSS, within the current sample only two out of five participants had an EDSS > 3.0 compared to five out of eight in the previous investigation [3]. A higher concentration of individuals with greater disability may explain the difference in results. Other previous investigations have observed greater amounts of asymmetry in muscular strength between contralateral limbs in PwMS with higher disability compared to those with lower disability [8,24]. It has been suggested that asymmetry may not fully manifest until greater degrees of disability are reached due to the progressive loss of both central (e.g., neural drive) and peripheral (e.g., muscle cross sectional area and mitochondrial density) factors [7,25,26]. Thus, future investigations are required in order to better understand the association between asymmetry and disability in PwMS. Additionally, previous investigations did not utilize a counterweight during single-leg cycling with PwMS [3,4]. The biomechanics and muscle recruitment patterns are quite different between single-leg cycling with and without a counter weight [17].

The hip flexors of the active limb are recruited to a greater degree in order to lift the limb and return the pedal to top dead center during single-leg cycling without a counter weight [17]. Due to the lower force production capabilities and greater fatiguability of the hip flexors, it can be speculated that single-leg cycling without a counter weight places a greater physiological demand on the active limb than if a counter weight were used [27]. The biomechanical limitations of single-leg cycling without a counter weight may have contributed to a reduced exercise tolerance in the impaired limb, thus resulting in larger differences and asymmetry scores between limbs compared to the current results [3].

It has previously been reported that asymmetry in power production between the lower limbs decreases as exercise intensity increases in trained cyclist [28]. This pattern has also been observed in PwMS during conventional cycling [7]. A previous investigation in PwMS reported the highest asymmetry score, 20.1% ± 18.6%, at 50% of PPO with scores decreasing to 15.5% ± 14.8% and 13.9% ± 12.1% at 60% and 70% of PPO, respectively [7]. The authors noted that although the asymmetry scores were decreasing, they still exceeded the 10% threshold at all three exercise intensities [7]. However, the current investigation did not observe the same relationship between asymmetry scores and exercise intensity. The mean asymmetry score was 4.3% ± 3.8% at GET, rose to 10.9% ± 14.9% at CP, and then decreased to 5.0% ± 4.2% at PPO. It must be noted that although the asymmetry score at CP exceeded the 10% threshold, it was not significantly greater than 10%. It is unclear why the asymmetry scores did not follow a similar pattern as previously reported [7,28]. However, it can be speculated that this may be due to difference in methodology. Previous investigations into asymmetry in power production in both PwMS and trained cyclist had participants progress continuously through the various exercise intensities via an incremental cycling test. Both GET and PPO of the current investigation were derived through the same SLICT, but CP was derived from a series of trials. Participants never completed a continuous incremental cycling test starting at GET and progressing to CP and PPO. The reductions in power production asymmetry have been speculated to be due to the influence of fatigue on motor unit recruitment [29]. The accumulation of fatigue during incremental exercise has been shown to lead to an increase in common bilateral input through inter-hemispheric cortical communication, which is reportedly among the main factors for reducing lateral differences [29–32]. Perhaps the lack of accumulation of fatigue due to the assessments being conducted over separate trials in a discontinuous manner altered the nature of the accumulation of fatigue. Additionally, with the lower limbs being tested independently the need for the minimization of lateral differences through inter-hemispheric input may have been attenuated. It is unclear how differences in exercise testing modalities (i.e., single leg vs. double leg) affect the manifestation of asymmetry in PwMS.

W′ was the only parameter in the current study with an asymmetry score, 49.5% ± 28.7%, that was significantly greater than the 10% threshold for asymmetry. W′ represents the finite amount of work that can be done when exercise is performed above CP in the severe intensity domain [9,19]. The mechanisms by which fatigue accumulates and task failure is reached in this domain is complex and not fully understood. However, it has been suggested that the decrease in muscle phosphocreatine, blood pH, and the increase in inorganic phosphates and hydrogen ion accumulation contribute to reduced muscle fiber force production, shortening velocity, handling of Ca^{2+}, and thus muscular power [9]. Additionally, the progressive reductions in contractile function of muscle fibers requires the recruitment of additional motor units to maintain power production demands and to sustain exercise [9,33]. The recruitment of these additional motor units further increases energy demand, thus contributing to the manifestation of the VO_2 slow component, which will rise until reaching VO_2peak and task failure [9,34]. The large amount of asymmetry for W′ in this sample is an interesting observation, and perhaps suggests differences between contralateral lower limbs for substrate utilization, regulation of blood pH, and muscle activation and recruitment during exercise. However, it is unclear if asymmetry in W′ is present within a healthy population and warrants investigation to provide additional context for the results of the current investigation. Although asymmetry in these parameters in response to exercise has not been directly investigated, there is evidence of asymmetry in similar parameters such as glucose uptake and the Hoffman reflex, an assessment of motor neuron excitability, in the lower limbs of PwMS [35]. Future investigations are required to explore potential biological mechanisms that contribute to the manifestation of asymmetry in response to exercise.

Although asymmetry in various muscular fitness parameters and physical function outcomes has been observed in PwMS, the physiological reasoning for the development of asymmetry in PwMS is still unclear [2]. It should be noted that asymmetrical muscular adaptations have been observed in healthy individuals as a necessity to perform physical tasks and do not always reflect a pathological origin [2]. However, for PwMS, the presence of asymmetry has been speculated to be due to the progressive loss of both central (e.g., neural drive) and peripheral (e.g., muscle cross sectional area and mitochondrial density) factors that contribute to muscular fitness components and physical function [2,7,8,27]. These reductions in both central and peripheral factors are thought to be the result of impaired nerve signal conduction that can result in the complete blockage of action potentials from the central nervous system to the peripheral tissue, and have been observed to worsen with disease progression [1]. The asymmetrical pattern of loss of muscular fitness and physical function may reflect a potential localization of neurodegeneration though this has yet to be investigated.

Although the current investigation contributes to the body of literature pertaining to asymmetry in PwMS, it must be acknowledged that it is not without limitations. First, this is a pilot investigation with only five PwMS, with mild disability, and no controls and the results must be interpreted with caution. Although a value of 10% has been used as a threshold for asymmetry in PwMS and non-clinical populations, it may not provide a meaningful and specific threshold for PwMS [7,8,28,29]. No functional assessments were included in the current investigation, and thus no inferences on the association between measures of asymmetry and functional capacity can be made from the current analysis. Additionally, parameters were determined over a series of trials and participants did not perform a SLICT that began at GET and progressed to the CP and PPO intensities specifically. This may have altered the mechanisms of fatigue development and the manifestation of asymmetry.

5. Conclusions

The current investigation explored the potential influence of exercise intensities, anchored by metabolic events, on the manifestation of asymmetry during single-leg cycling in PwMS. It was observed that that no statistically significant differences were observed between contralateral lower limbs for all parameters. Additionally, asymmetry in power production between lower limbs did not statistically change between exercise intensities, which is in disagreement with previous investigations in PwMS and trained cyclists [7,28]. Only the asymmetry score for W′ was significantly greater than the 10% threshold for asymmetry, suggesting potential asymmetries in substrate utilization, regulation of blood pH, and muscle activation and recruitment. Based on these findings, future investigations with large sample sizes are needed to further explore the potential asymmetries in the metabolic response to exercise in different exercise intensity domains.

Author Contributions: Conceptualization—R.D.L., S.S., C.D.B. and C.J.A.; Methodology—R.D.L., S.S., C.D.B. and C.J.A.; Analysis—J.W.F.III and R.D.L.; Original draft preparation—J.W.F.III and R.D.L.; Reviewing and Editing—J.W.F.III, R.D.L., C.D.B. and C.J.A. All authors have read and agreed to the published version of the manuscript.

Funding: This research received no external funding.

Institutional Review Board Statement: The study was conducted according to the guidelines of the Declaration of Helsinki, and approved by the Institutional Review Board (or Ethics Committee) of The University of Oklahoma (protocol code: 4423 approved on 8/25/2014).

Informed Consent Statement: Informed consent was obtained from all subjects involved in the study.

Data Availability Statement: The data presented in this study are available on request from the corresponding author. The data are not publicly available due to privacy and ethical concerns.

Conflicts of Interest: The authors declare no conflict of interest.

References

1. Lassmann, H. Multiple sclerosis pathology. *Cold Spring Harb. Perspect. Med.* **2018**, *8*, a028936. [CrossRef] [PubMed]
2. Rudroff, T.; Proessl, F. Effects of Muscle Function and Limb Loading Asymmetries on Gait and Balance in People With Multiple Sclerosis. *Front. Physiol.* **2018**, *9*, 531. [CrossRef] [PubMed]
3. Larson, R.D.; McCully, K.K.; Larson, D.J.; Pryor, W.M.; White, L.J. Bilateral differences in lower-limb performance in individuals with multiple sclerosis. *J. Rehabil. Res. Dev.* **2013**, *50*, 215–222. [CrossRef] [PubMed]
4. Larson, R.D.; McCully, K.K.; Larson, D.J.; Pryor, W.M.; White, L.J. Lower-limb performance disparities: Implications for exercise prescription in multiple sclerosis. *J. Rehabilitation Res. Dev.* **2014**, *51*, 1537–1544. [CrossRef] [PubMed]
5. Larson, R.D.; Barton, M.; Farrell, J.W., III; Cantrell, G.S.; Lantis, D.J.; Black, C.D.; Ade, C.J. Evaluation of Oxygen Uptake Kinetic Asymmetries in Patients with Multiple Sclerosis: A Pilot Study. *Int. J. Kinesiol. Sports Sci.* **2018**, *6*, 21–24. [CrossRef]
6. Chung, L.H.; Remelius, J.G.; Van Emmerik, R.E.; Kent-Braun, J.A. Leg power asymmetry and postural control in women with multiple sclerosis. *Med. Sci. Sports Exerc.* **2008**, *40*, 1717–1724. [CrossRef]
7. Farrell, J.W.; Bemben, D.A.; Black, C.D.; Larson, D.J.; Pardo, G.; Fjeldstad-Pardo, C.; Larson, R.D. Evaluation of Power Production Asymmetry during Cycling in Persons with Multiple Sclerosis. *Int. J. Environ. Res. Public Heal.* **2019**, *16*, 3445. [CrossRef]
8. Farrell, J.W.; Motl, R.W.; Learmonth, Y.C.; Pilutti, L.A. Persons with Multiple Sclerosis Exhibit Strength Asymmetries in both Upper and Lower Extremities. *Physiotherapy* **2020**, *111*, 83–91. [CrossRef]
9. Burnley, M.; Jones, A.M. Power–duration relationship: Physiology, fatigue, and the limits of human performance. *Eur. J. Sport Sci.* **2016**, *18*, 1–12. [CrossRef]
10. Davies, C.T.; Thompson, M.W. Physiological responses to prolonged exercise in ultramarathon athletes. *J. Appl. Physiol.* **1986**, *61*, 611–617. [CrossRef]
11. Allen, D.G.; Lamb, G.D.; Westerblad, H. Skeletal Muscle Fatigue: Cellular Mechanisms. *Physiol. Rev.* **2008**, *88*, 287–332. [CrossRef] [PubMed]
12. Jones, A.M.; Wilkerson, D.P.; DiMenna, F.; Fulford, J.; Poole, D.C. Muscle metabolic responses to exercise above and below the "critical power" assessed using ^{31}P-MRS. *Am. J. Physiol. Integr. Comp. Physiol.* **2008**, *294*, R585–R593. [CrossRef] [PubMed]
13. Poole, D.C.; Ward, S.A.; Gardner, G.W.; Whipp, B.J. Metabolic and respiratory profile of the upper limit for prolonged exercise in man. *Ergonomics* **1988**, *31*, 1265–1279. [CrossRef] [PubMed]
14. Kalb, R.; Brown, T.R.; Coote, S.; Costello, K.; Dalgas, U.; Garmon, E.; Giesser, B.; Halper, J.; Karpatkin, H.; Keller, J.; et al. Exercise and lifestyle physical activity recommendations for people with multiple sclerosis throughout the disease course. *Mult. Scler. J.* **2020**, *26*, 1459–1469. [CrossRef]
15. Godin, G. Godin leisure-time exercise questionnaire and science in sports and exercise. 29 June Supplement: S36-S38. Godin leisure-time exercise questionnaire. *Med. Sci. Sports Exerc.* **1997**, *29*, S36–S38.
16. Bundle, M.W.; Ernst, C.L.; Bellizzi, M.J.; Wright, S.; Weyand, P.G. A metabolic basis for impaired muscle force production and neuromuscular compensation during sprint cycling. *Am. J. Physiol. Integr. Comp. Physiol.* **2006**, *291*, R1457–R1464. [CrossRef]
17. Burns, K.J.; Pollock, B.S.; Lascola, P.; McDaniel, J. Cardiovascular responses to counterweighted single-leg cycling: Implications for rehabilitation. *Eur. J. Appl. Physiol.* **2014**, *114*, 961–968. [CrossRef]
18. Beaver, W.L.; Wasserman, K.; Whipp, B.J. A new method for detecting anaerobic threshold by gas exchange. *J. Appl. Physiol.* **1986**, *60*, 2020–2027. [CrossRef]
19. Jones, A.M.; Vanhatalo, A.; Burnley, M.; Morton, R.H.; Poole, D.C. Critical Power: Implications for Determination of $\dot{V}$O2max and Exercise Tolerance. *Med. Sci. Sports Exerc.* **2010**, *42*, 1876–1890. [CrossRef]
20. Fukuba, Y.; Miura, A.; Endo, M.; Kan, A.; Yanagawa, K.; Whipp, B.J. The Curvature Constant Parameter of the Power-Duration Curve for Varied-Power Exercise. *Med. Sci. Sports Exerc.* **2003**, *35*, 1413–1418. [CrossRef]
21. Cohen, J. *Statistical Power Analysis for the Behavioral Sciences*, 2nd ed.; Routledge: London, UK, 1988.
22. Olejnik, S.; Algina, J. Generalized Eta and Omega Squared Statistics: Measures of Effect Size for Some Common Research Designs. *Psychol. Methods* **2003**, *8*, 434–447. [CrossRef] [PubMed]
23. Sandroff, B.; Pilutti, L.A.; Benedict, R.H.B.; Motl, R.W. Association Between Physical Fitness and Cognitive Function in Multiple Sclerosis. *Neurorehabilit. Neural Repair* **2014**, *29*, 214–223. [CrossRef] [PubMed]
24. Scott, S.M.; Hughes, A.R.; Galloway, S.D.R.; Hunter, A.M. Surface EMG characteristics of people with multiple sclerosis during static contractions of the knee extensors: Faster MFCV in people with MS during isometric contraction. *Clin. Physiol. Funct. Imaging* **2010**, *31*, 11–17. [CrossRef] [PubMed]
25. Wens, I.; Dalgas, U.; Vandenabeele, F.; Krekels, M.; Grevendonk, L.; Eijnde, B.O. Multiple Sclerosis Affects Skeletal Muscle Characteristics. *PLoS ONE* **2014**, *9*, e108158. [CrossRef]
26. Wezenberg, D.; De Haan, A.; van der Woude, L.; Houdijk, H. Feasibility and Validity of a Graded One-Legged Cycle Exercise Test to Determine Peak Aerobic Capacity in Older People With a Lower-Limb Amputation. *Phys. Ther.* **2012**, *92*, 329–338. [CrossRef]

27. Carpes, F.P.; Rossato, M.; Faria, I.E.; Mota, C.B. During an incremental exercise cyclists improve bilateral pedaling symmetry. *Braz. J. Biomotricity* **2008**, *2*, 155–159.
28. Carpes, F.P.; Mota, C.B.; Faria, I.E. On the bilateral asymmetry during running and cycling—A review considering leg preference. *Phys. Ther. Sport* **2010**, *11*, 136–142. [CrossRef]
29. Boonstra, T.; Daffertshofer, A.; van Ditshuizen, J.; Heuvel, M.V.D.; Hofman, C.; Willigenburg, N.; Beek, P. Fatigue-related changes in motor-unit synchronization of quadriceps muscles within and across legs. *J. Electromyogr. Kinesiol.* **2008**, *18*, 717–731. [CrossRef]
30. Anguera, J.A.; Russell, C.A.; Noll, D.C.; Seidler, R.D. Neural correlates associated with intermanual transfer of sensorimotor adaptation. *Brain Res.* **2007**, *1185*, 136–151. [CrossRef]
31. Seidler, R.D.; Noll, D.C. Neuroanatomical Correlates of Motor Acquisition and Motor Transfer. *J. Neurophysiol.* **2008**, *99*, 1836–1845. [CrossRef]
32. Burnley, M.; Vanhatalo, A.; Jones, A.M. Distinct profiles of neuromuscular fatigue during muscle contractions below and above the critical torque in humans. *J. Appl. Physiol.* **2012**, *113*, 215–223. [CrossRef] [PubMed]
33. Burnley, M.; Jones, A.M. Oxygen uptake kinetics as a determinant of sports performance. *Eur. J. Sport Sci.* **2007**, *7*, 63–79. [CrossRef]
34. Rudroff, T.; Kindred, J.; Koo, P.; Karki, R.; Hebert, J. Asymmetric glucose uptake in leg muscles of patients with Multiple Sclerosis during walking detected by [18F]-FDG PET/CT. *NeuroRehabilitation* **2014**, *35*, 813–823. [CrossRef] [PubMed]
35. Cantrell, G.S.; Lantis, D.J.; Bemben, M.G.; Black, C.D.; Larson, D.J.; Pardo, G.; Fjeldstad-Pardo, C.; Larson, R.D. Relationship between soleus H-reflex asymmetry and postural control in multiple sclerosis. *Disabil. Rehabilitation* **2020**, *44*, 542–548. [CrossRef] [PubMed]