ABSTRACT
SEX DIFFERENCES IN NEUROMUSCULAR FATIGABILITY POST STROKE

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The purpose of this dissertation was to determine sex differences in neuromuscular fatigability during dynamic exercise post stroke and identify potential mechanisms related to vascular dysfunction. Stroke outcomes are often less favorable for females compared to males. Female stroke survivors have worse functional recovery and lower qualify of life. Although multifactorial, one potential but overlooked contributor to sex differences post stroke is neuromuscular fatigability. Neuromuscular fatigability, hereafter referred to as fatigability, is defined as the acute, exercise-induced reduction in power. In addition to baseline weakness, stroke survivors have increased fatigability, which limits task endurance. Sex differences in fatigability and recovery from fatiguing tasks may in part explain the worse functional outcomes for female stroke survivors. Previous studies have shown that older estrogen-deficient females exhibit blunted vasodilatory responses during dynamic exercise compared to their younger counterparts, but this age-related difference is not observed in males. Take together, it is plausible that postmenopausal female stroke survivors have greater vascular dysfunction, resulting in greater fatigability compared to male stroke survivors. Understanding sex differences in fatigability could lead to the development of targeted rehabilitation interventions to improve functional recovery in females.

In Aim 1, we quantified differences in fatigability (reduction in power), exercise-induced hyperemia, and muscle oxygenation responses during dynamic knee extension exercise in stroke survivors as compared to age- and sex-matched neurotypical controls. Stroke survivors were more fatigable than neurotypical controls with greater declines in power. Female stroke survivors were more fatigable than male stroke survivors, but neurotypical males and females fatigued similarly. Fatigability in stroke survivors was negatively associated with muscle oxygenation responses, but not exercise-induce hyperemia, during exercise. Therefore, the mechanisms for sex differences in fatigability during dynamic exercise post stroke may be in part due to stroke-related micro-vascular versus large conduit dysfunction. In Aim 2, we further investigated sex differences in fatigability (total number of contractions) during ischemic dynamic knee extension exercise in stroke survivors. Female stroke survivors were more fatigable than male stroke survivors under whole leg ischemia with completion of fewer contractions. The total number of contractions was positively associated with the relative increase in neuromuscular activation measured via surface electromyography. Therefore, in conditions of ischemia, the inability to increase neuromuscular activation largely contributes to task endurance. In Aim 3, we explored the effects of ischemic conditioning (IC) on fatigability (reduction in power) during dynamic knee extension exercise in stroke survivors. IC is a non-invasive vascular stimulus which enhances vasodilation during exercise. After a single

session of IC treatment, stroke survivors were less fatigable compared to IC-sham treatment. Male and female stroke survivors had similar improvements in fatigability after IC versus IC-sham treatment. Improvements in fatigability were positively associated with self-selected and maximum walking speed. In summary, when there is full muscle perfusion/reperfusion during exercise, mechanisms involving micro-vascular dysfunction contributes more to the greater fatigability in female stroke survivors versus male stroke survivors; whereas in conditions where muscle perfusion/reperfusion is limited, mechanisms for sex differences in fatigability post stroke are likely neural in origin. Lastly, IC could serve as a potential intervention to reduce fatigability during dynamic exercise, especially for those with mild stroke-related walking impairments.