FUTURE PLANS

Michael will pursue a post-doctoral fellowship in spinal cord injury research. His career goal is to direct is own research laboratory.

Public oral examination for the degree of Doctor of Philosophy

Rehabilitation Science

Dissertation Defense

"Electrical Activation and Analysis Paradigms for Restoration of Breathing"

Michael Sunshine

Thursday, November 5, 2020

3:00pm

Via Zoom

UF College of Public Health and Health Professions
Rehabilitation Science
UNIVERSITY *of* FLORIDA

Doctoral Committee:

David Fuller, PhD

Gordon Mitchell, PhD

Emily J. Fox, PT, DPT, PhD, NCS

Kevin J. Otto, PhD

ABSTRACT

Respiratory insufficiency is a leading cause of death due to drug overdose or neuromuscular disease. We hypothesized that a novel stimulation paradigm using temporal interference (TI) could restore breathing in such conditions. Following opioid overdose in rats, two high frequency (5000 Hz and 5001 Hz), low amplitude waveforms delivered via intramuscular wires in the neck immediately activated the diaphragm and restored ventilation in phase with waveform offset (1 Hz or 60 breaths/min). Epidural TI stimulation robustly activated the paralyzed hemi-diaphragm after chronic spinal cord injury. We conclude that TI stimulation can activate spinal motor neurons after SCI and prevent fatal apnea during drug overdose by restoring ventilation with minimally invasive electrodes.

Further, I investigated how TI stimulation recruits and activates diaphragm motor units. Breathing requires repeated periodic contraction of the diaphragm muscle, which is impaired by neurologic injury or disease. Appropriate motor unit recruitment is essential to produce these repeated bursts without muscle fatigue. Using a custom multi-electrode array, I was able to record numerous diaphragm motor units during endogenous and evoked bursts. TI stimulation recruited motor neurons at similar rates, and in a similar order to endogenous bursts. Additionally, TI stimulation but not square-wave stimulation, recruited more units in the center of the burst resulting in a modulated breath pattern. Collectively, these data suggest that TI stimulation has the potential to restore breathing in conditions of severe hypoventilation.

I then developed a method to assess whole body plethysmography waveforms as these provide information about breathing and related are impaired by injury and disease. Respiratory waveforms vary in timing and amplitude, however, this information is lost with conventional approaches to data analysis. Here I developed an unbiased approach for evaluating the dynamically changing waveforms that typify breathing. The analyses was then validated on a data-set testing a pharmacological rescue to opioid overdose. We conclude that the respiratory waveform cluster analysis developed herein allows for rapid, unbiased assessment of stochastic breathing patterns during hypoventilation. Further, ampakine CX1942 increases breath variability following opioid overdose. This analysis can provide insight into how the neuromotor respiratory system is affected by drugs, disease, or injury.

SELECTED PUBLICATIONS

Sunshine MD, Cassara AM, Neufeld E, Grossman N, Mareci TH, Otto KJ, Boyden ES, Fuller DD. (In Press) Restoration of breathing after opioid overdose and spinal cord injury using temporal interference stimulation. Communications Biology, Nature

Sunshine MD, Sutor TW, Fox EJ, Fuller DD. (2020) Targeted activation of spinal respiratory neural circuits. Experimental Neurology. 328:113256

Sunshine MD, Ganji CN, Fuller DD, Moritz CT. (2020). Respiratory resetting elicited by single pulse spinal stimulation. Respiratory Physiology & Neurobiology; 14;274:103339

Streeter KA, **Sunshine MD**, Brant JO, Sandoval AGW, Maden M, Fuller DD. (2019). Reduced wounding and enhanced neurogenesis following spinal cord injury in spiny mice, Acomys cahirinus. Journal of Comparative Neurology.;528:1535–1547.

Streeter KA, **Sunshine MD**, Patel SR, Gonzalez-Rothi EJ, Reier PJ, Baekey DM, Fuller DD. (2019). Mid-cervical interneuron networks following high cervical spinal cord injury. Respiratory Physiology & Neurobiology; 271:103305

Streeter KA*, **Sunshine MD***, Patel SR, Reier PJ, Baekey DM, Fuller DD. (2017). Intermittent Hypoxia Enhances Connectivity of Mid-Cervical Spinal Interneurons. Journal of Neuroscience; 37(35):8349-8362 *Equal Contribution

SELECTED HONORS AND AWARDS

F31-HL145831 Ruth L. Kirschtein Predoctoral Individual National Research Service Award. Title: A new method of spinal stimulation to activate the diaphragm - NHLBI (PI: M. Sunshine)

T32 HD043730 Interdisciplinary Training in Rehabilitation and Neuromuscular Plasticity Pre-Doctoral Training Fellowship (PI: K Vandenborne ,2016-2018; D Fuller, 2018-2019)