AWARD NUMBER: W81XWH-18-1-0796

TITLE: Mechanisms and Efficacy of High-Intensity Variable Training in Patients with Incomplete SCI

PRINCIPAL INVESTIGATOR: T. George Hornby, PT, PhD

CONTRACTING ORGANIZATION: Indiana University School of Medicine
BLOOMINGTON, IN 47401

REPORT DATE: OCTOBER 2019

TYPE OF REPORT: Annual

PREPARED FOR: U.S. Army Medical Research and Development Command
Fort Detrick, Maryland 21702-5012

DISTRIBUTION STATEMENT: Approved for Public Release;
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REPORT DOCUMENTATION PAGE

Form Approved
OMB No. 0704-0188

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1. REPORT DATE	2. REPORT TYPE	3. DATES COVERED
OCTOBER 2019	Annual	30SEP2018 - 29SEP2019

4. TITLE AND SUBTITLE

Mechanisms and Efficacy of High-Intensity Variable Training in Patients with Incomplete SCI

5a. CONTRACT NUMBER
W81XWH-18-1-0796

5b. GRANT NUMBER
SC170299

5c. PROGRAM ELEMENT NUMBER

6. AUTHOR(S)

T. George Hornby, PT, PhD

E-Mail: tghornby@iu.edu

5d. PROJECT NUMBER

5e. TASK NUMBER

5f. WORK UNIT NUMBER

7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES)

Indiana University School of Medicine
TRUSTEES OF INDIANA UNIVERSITY INDIANA UNIVERSITY
IUPUI 980 INDIANA AVE RM 2232
INDIANAPOLIS IN 46202-5130

8. PERFORMING ORGANIZATION REPORT NUMBER

9. SPONSORING / MONITORING AGENCY NAME(S) AND ADDRESS(ES)

U.S. Army Medical Research and Development Command
Fort Detrick, Maryland 21702-5012

10. SPONSOR/MONITOR'S ACRONYM(S)

11. SPONSOR/MONITOR'S REPORT NUMBER(S)

12. DISTRIBUTION / AVAILABILITY STATEMENT
Approved for Public Release; Distribution Unlimited

13. SUPPLEMENTARY NOTES

Background/Readiness: The objective of this proposal is to maximize locomotor outcomes of patients following incomplete spinal cord injury (iSCI) through identification of rehabilitation strategies that maximize recovery. Specific training parameters, such as provision of large amounts of stepping, appears to facilitate locomotor function in patients with iSCI, although other factors may be critical. In this proposed phase II randomized clinical trial, our overarching hypothesis is that the "intensity" of locomotor practice, defined as power output and estimated using cardiopulmonary measures, is critical to maximizing walking outcomes. Performance of high intensity locomotor training increases the cardiovascular and neuromuscular demands, which results in physiological changes that facilitate greater locomotor performance in individuals with and without neurological injury. There are, however, limited data supporting its utility in patients with iSCI. Our recent findings suggest a role for high-intensity stepping training in variable contexts, with gains in peak locomotor capacity as compared low-intensity variable training. Additional changes in cardiopulmonary function and neuromuscular coordination provide a mechanistic rationale for the utility of this strategy. Such changes are likely due to increased central (volitional) activation, and are in sharp contrast to the long-standing notion that high intensity training impairs motor function in neurological injury.

Despite these data, genotypic variations suggest specific caveats related to high intensity training. For example, many patients possess a single nucleotide polymorphism (SNP) variation in the brain derived neurotrophic factor (BDNF) gene that may impact the activity-dependent BDNF expression thought to contribute to neuroplasticity underlying improved performance. This single nucleotide polymorphism (SNP) can influential declarative memory, with recent data suggesting a potential impact on motor recovery after neurologic injury. Our own studies indicate limited BDNF increases in patients with this SNP during high intensity exercise, although the effects of locomotor recovery with repeated high-intensity training is unclear

Hypothesis/Specific Aims: Our primary hypotheses are that high intensity variable stepping can markedly improve locomotor performance as well as neuromuscular and cardiopulmonary function as compared to lower-intensity training in patients with chronic motor iSCI. We further suggest that genotypic variations in the ability to synthesis activity dependent BDNF may modify the effects of high intensity training. **Specific Aim 1:** Test if high intensity stepping training in variable contexts results in greater locomotor gains as compared to lower intensity interventions. **Specific Aim 2:** Test the effects of these training strategies on neuromuscular and cardiopulmonary airment specific Aim 3: Test the effects of the presence of the BDNF SNP on locomotor improvements in patients following high intensity activities

15. SUBJECT TERMS:
Exercise, Intensity, Locomotion

16. SECURITY CLASSIFICATION OF:			17. LIMITATION OF ABSTRACT	18. NUMBER OF PAGES	19a. NAME OF RESPONSIBLE PERSON
a. REPORT	b. ABSTRACT	c. THIS PAGE			USAMRMC
Unclassified	Unclassified	Unclassified	Unclassified	10	19b. TELEPHONE NUMBER *(include area code)*

Standard Form 298 (Rev. 8-98)
Prescribed by ANSI Std. Z39.18

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1. **INTRODUCTION:** Our **central hypotheses** are that high-intensity stepping training provided to individuals with iSCI will result in greater improvements in locomotor performance both overground and on a treadmill, including improved gait quality/kinematics and improved neuromuscular coordination, as compared to lower intensity interventions. We hypothesize such training can elicit greater improvements in specific impairments that may underlie locomotor function, including improved cardiopulmonary function (i.e., peak aerobic capacity or efficiency), as well as selected impairments that may underlie gait dysfunction following SCI (strength, spasticity). We further contend that the specific genetic variations, particularly the potential presence SNP of the BDNF gene, may alter the rate of locomotor gains in patients with incomplete SCI. To test these hypotheses, we intend to perform a prospective, assessor-blinded, randomized clinical trial (RCT) to evaluate the effects of ***intensity*** of rehabilitation training applied in patients with chronic (> 1 yr) motor incomplete SCI. In this phase II RCT, 64 ambulatory patients with motor incomplete SCI will be allocated to 30 sessions of *high-intensity stepping training* or *low-intensity stepping training* applied over 8 weeks (2 months). Assessments will be performed prior to, and every 4 weeks of training, with a 2-3 month follow-up examination. We will address 3 specific aims

2. **KEYWORDS:** *Exercise, locomotion, intensity, neurotrophins, growth factors, single nucleotide polymorphism.*

3. **ACCOMPLISHMENTS:** *The PI is reminded that the recipient organization is required to obtain prior written approval from the awarding agency Grants Officer whenever there are significant changes in the project or its direction.*

   - **What were the major goals of the project?**

A copy of the proposed timeline from the clinical protocol is provided to improve clarity of the SOW. The specific aims are described below and will be performed simultaneously (vs consecutively) throughout the proposed clinical trial. Accordingly, the SOW is organized as described for the entire projects and associated activities, with brief recapitulation of the Specific Aims.

Specific Aim 1: Test if high intensity stepping training in variable contexts results in greater locomotor gains as compared to lower intensity locomotor interventions.

Specific Aim 2: Test the effects of these training strategies on neuromuscular and cardiopulmonary impairments.

Specific Aim 3: Test the effects of the presence of the BDNF SNP on locomotor improvements in patients following high-intensity activities.

The activities will be performed by the key personnel on the projects, including Dr. T. George Hornby (TGH), Dr. Flora Hammond (FH), Dr. Susan Perkins (SP) and Dr. Marzieh M. Ardestani (MMA). Consultant Dr. Brian D. Schmit (BDS) will assist as needed**.**

	Year 1				**Year 2**				**Year 3**				**Year 4**			
	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4
Pre-Clinical Trial Activities																
a. Ensure IRB approval (IU and HRPO) prior to subject recruitment																
i. Obtain IRB approval at IU (months 1-2); responsible personnel: TGH/FH/MMA																
ii. Obtain IRB approval at HRPO (months 2-3); responsible personnel: TGH/FH/MMA																

iii. Resubmit HRPO revsions to IRB documentation to IU IRB (months 3-4); responsible personnel: TGH/FH/MMA																	
b. Develop subject recruitment materials																	
i. Hard-copy and web-based recruitment materials developed submitted to IU/HRPO (months 1-3); responsible personnel: TGH/MMA																	
ii. In-person education of study goals, objectives, and patient eligibility recruitment to local hospitals (MD and allied health) (months 1-3); responsible personnel: TGH																	
c. Hiring and training of clinical staff																	
i. Develop SOP for training activities applied to patients (1st month); responsible personnel: TGH/MMA																	
ii. Hiring/training of PT staff to deliver training activities to research participants (months 2-3); responsible personnel: TGH/MMA																	
Clinical Trial Activities																	
Activities include as follows, with targeted enrollment in each year identified. a. Subject enrollment (TGH/FH/TBD PT) b. Recruitment/ training/data collection and analyses include initial participant evaluation, baseline, post-training and follow-up data collection(TGH/MMA/TBD PT) c. Data reduction and analyses(TGH/MMA/TBD PT) d. Data management/ storage (TGH/MMA/TBD PT)																	
i. 1st year enrollment (target: 15 subjects)		4	4	5													
ii. 2nd year enrollment (target: 20 subjects)					5	5	5	5									
iii. 3rd year enrollment (target: 20 subjects)									5	5	5	5					

iv. 4th year enrollment (target: 5 subjects)													3	2		
Data Management and Statistical Analyses (TGH/TBD PT/Perkins																
a. Collaboration with data management team on data completeness and quality, including initial management plan (months 1-3) and yearly and final meetings (months 10-12; months -12 of year 4)																
b. Perform statistical analyses of primary (SP) and secondary outcomes (TGH/MMA)																
Dissemination																
a. Presentation at national conferences (TGH/MMA																
b. Manuscript preparation (TGH/MMA/FH/SP)																

- **What was accomplished under these goals?**

. Ensure IRB approval (IU and HRPO) prior to subject recruitment

- *Obtain IRB approval at IU (months 1-2); responsible personnel: TGH/FH/MMA –* ***submitted July 2018, Approved January 9 2019.***
- *Obtain IRB approval at HRPO (months 2-3); responsible personnel: TGH/FH/MMA –* ***submitted February 17, 2019, resubmitted on 4/10 after follow-up email indicating Program Director received the email but Mr. Piccioni did not.***
- *Resubmit HRPO revsions to IRB documentation to IU IRB (months 3-4); responsible personnel: TGH/FH/MMA*
- ***Proposal approved by HRPO on Sept 12, 2019.***

b. Develop subject recruitment materials

- *Hard-copy and web-based recruitment materials developed submitted to IU/HRPO (months 1-3); responsible personnel: TGH/MMA -* ***ongoing***
- *In-person education of study goals, objectives, and patient eligibility recruitment to local hospitals (MD and allied health) (months 1-3); responsible personnel: TGH–* ***Initially started in last 18 days between approval and date of report due.***

c. Hiring and training of clinical staff

- *Develop SOP for training activities applied to patients (1st month); responsible personnel: TGH/MMA –* ***ongoing***
- *Hiring/training of PT staff to deliver training activities to research participants (months 2-3); responsible personnel: TGH/MMA -* ***ongoing***

- **What opportunities for training and professional development has the project provided?**
  - *Nothing to report*
- **How were the results disseminated to communities of interest?**
  - *Nothing to Report.*
- **What do you plan to do during the next reporting period to accomplish the goals?**

- *If this is the final report, state "Nothing to Report."*
- *Describe briefly what you plan to do during the next reporting period to accomplish the goals and objectives.*

4. **IMPACT:** *Describe distinctive contributions, major accomplishments, innovations, successes, or any change in practice or behavior that has come about as a result of the project relative to:*
   - **What was the impact on the development of the principal discipline(s) of the project?**
     - *Nothing to Report. (HRPO approval on 9/12/19*
   - **What was the impact on other disciplines?**
     - *Nothing to Report. (HRPO approval on 9/12/19)*
   - **What was the impact on technology transfer?**
     - *Nothing to Report.*
   - **What was the impact on society beyond science and technology?**

5. **CHANGES/PROBLEMS:** *The Project Director/Principal Investigator (PD/PI) is reminded that the recipient organization is required to obtain prior written approval from the awarding agency Grants Officer whenever there are significant changes in the project or its direction. If not previously reported in writing, provide the following additional information or state, "Nothing to Report," if applicable:*
   - **Changes in approach and reasons for change**
     - *No changes in approach.*
   - **Actual or anticipated problems or delays and actions or plans to resolve them**
     - *Delays associated with HRPO approval as indicated above (loss of email transmission during Winter/Spring 2019, and delays in HRPO approval processing thereafter.*
   - **Changes that had a significant impact on expenditures**
     - *Limited ability to recruit/test/train participants*
   - **Significant changes in use or care of human subjects, vertebrate animals, biohazards, and/or select agents**
     - *N/A*
   - **Significant changes in use or care of human subjects**
     - **N/A**
   - **Significant changes in use or care of vertebrate animals.**
     - **N/A**
   - **Significant changes in use of biohazards and/or select agents**

- **N/A**

6. **PRODUCTS:** *List any products resulting from the project during the reporting period. If there is nothing to report under a particular item, state "Nothing to Report."*

   - **Publications, conference papers, and presentations**

     - **Journal publications.** *Nothing to report.*
     - **Books or other non-periodical, one-time publications.** *Nothing to report.*
     - **Other publications, conference papers, and presentations.** *Nothing to report.*

   - **Website(s) or other Internet site(s)**
     Nothing to report..

   - **Technologies or techniques**
     Nothing to report.

   - **Inventions, patent applications, and/or licenses**
     Nothing to report.

   - **Other Products**
     Nothing to report.

7. **PARTICIPANTS & OTHER COLLABORATING ORGANIZATIONS**

   - **What individuals have worked on the project?**

     Provide the following information for: (1) PDs/PIs; and (2) each person who has worked at least one person month per year on the project during the reporting period, regardless of the source of compensation (a person month equals approximately 160 hours of effort). If information is unchanged from a previous submission, provide the name only and indicate "no change."

Name:	*Thomas George Hornby*
Project Role:	*PI*
Researcher Identifier (e.g. ORCID ID):	*3147-3818*
Nearest person month worked:	4
Contribution to Project:	*Contributed to all aspects of proposal, including IRB approval, protocol/project development, assistance with equipment set-up, programming*
Funding Support:	

Name:	*Marzieh Ardestani*
Project Role:	Co-I
Researcher Identifier (e.g. ORCID ID):	*N/A*
Nearest person month worked:	4
Contribution to Project:	*Contributed to all aspects of proposal, including IRB approval, protocol/project development, assistance with equipment set-up, programming*
Funding Support:	

Name:	*Christopher E. Henderson*
Project Role:	Co-I
Researcher Identifier (e.g. ORCID ID):	*N/A*
Nearest person month worked:	4
Contribution to Project:	*Contributed to all aspects of proposal, including IRB approval, protocol/project development, assistance with equipment set-up, programming*
Funding Support:	

Name:	*Statistical assistance (Allie Tenet)*
Project Role:	*PI*
Researcher Identifier (e.g. ORCID ID):	*3147-3818*
Nearest person month worked:	6
Contribution to Project:	Development of randomization codes, REDCAp files for testing/training
Funding Support:	

- **Has there been a change in the active other support of the PD/PI(s) or senior/key personnel since the last reporting period?**
  - *Nothing to report*

- **What other organizations were involved as partners?**
    - *Marquette University – Brian Schmit, Co-I (no work on human subjects to be reported there)*
        - **Organization Name: Marquette University**
        - **Location of Organization:** *USA*
        - **Partner's contribution to the projec**t
            - **Financial support;** *N/A*
            - **In-kind support** *: N/A*
            - **Facilities**: N/A
            - **Collaboration** *N/A*
            - **Personnel exchanges** *N/A*
            - **Other.**

8. **SPECIAL REPORTING REQUIREMENTS**
    - **COLLABORATIVE AWARDS:** *N/A*
    - **QUAD CHARTS:** *Attached*
9. **APPENDICES:** *N/A*

ADDITIONAL NOTES: N/A